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TOPIC OF INTEREST - "TOXICOLOGY - I"

GENERAL ARTICLE

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TOXICOLOGY - I

PHARMACOLOGIC PRINCIPLES OF TOXICOLOGY

***Suganthi S. Ramachandran**
****Ramachandran Thiruvengadam**

Abstract: *Understanding pharmacological principles (pharmacokinetics and pharmacodynamics) are of paramount importance in making therapeutic decisions in the management of poisoning. While the array of poisonous substances that affect human health may be diverse ranging from drugs to household chemicals, they all abide by the core principles of toxicokinetics and dynamics. Knowledge of these principles will aid in decisions about monitoring time for an asymptomatic patient or optimizing therapeutic strategies like gastric decontamination, enhanced elimination, or administration of an antidote for a poisoned patient. This review discusses these toxicological principles and their clinical relevance in managing a poisoned patient.*

Keywords: *Poison, Toxicokinetics, Toxicodynamics, Poisoning.*

"What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison." - Paracelsus, 1538 AD

Xenobiotics are chemicals that are foreign to the human body, such as pharmaceutical drugs, household, agricultural and industrial chemicals, plant toxins and animal venom.[1] Poison is any substance that is harmful to living organism. The fundamental difference between pharmaceuticals and other poisons is that drugs are designed to be beneficial to the human body at specific doses and are toxic beyond those doses, while a poison does not benefit the human at any dose.[2] The human body has well-evolved biochemical pathways that can handle these substances up to a physiological limit (pharmacokinetics). These substances, in turn, alter the physiological processes in the humans (pharmacodynamics).[1] Understanding these principles is essential in making diagnostic and therapeutic decisions while managing poisoning episodes in humans. This review briefly describes the toxicokinetic and toxicodynamic changes that occur in poisoning and how understanding these principles can aid in the management of poisoning.

Toxicokinetics

Pharmacokinetics studies the course of a drug in the body and encompasses absorption, distribution, metabolism and excretion (ADME) (Fig.1).[3] Toxicokinetics is its toxicologic counterpart. The concentration-time plot of an orally ingested drug, pharmacokinetic parameters measured and their quantitative mathematical relationships are provided in Box 1 and Fig.2. The toxicokinetic model relies on the serial measurement of blood concentrations over a period. It helps in determining the systemic exposure of the poison. Though pharmacokinetic models are well-characterized during clinical drug development,

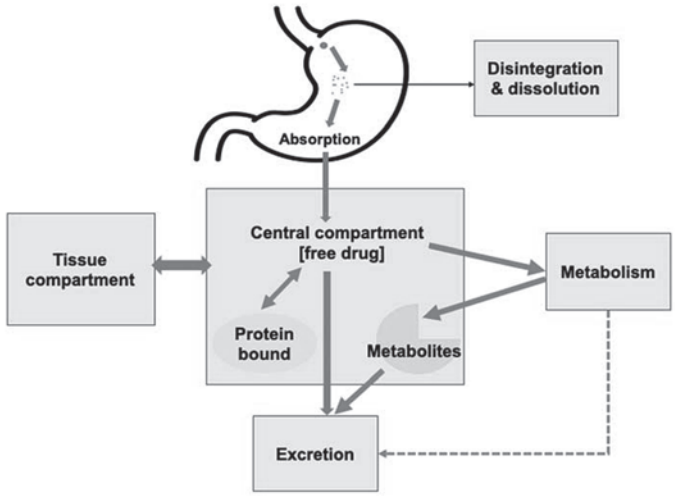

Fig.1. Schematic representation of ADME (Absorption, distribution, metabolism and excretion) process of an orally ingested

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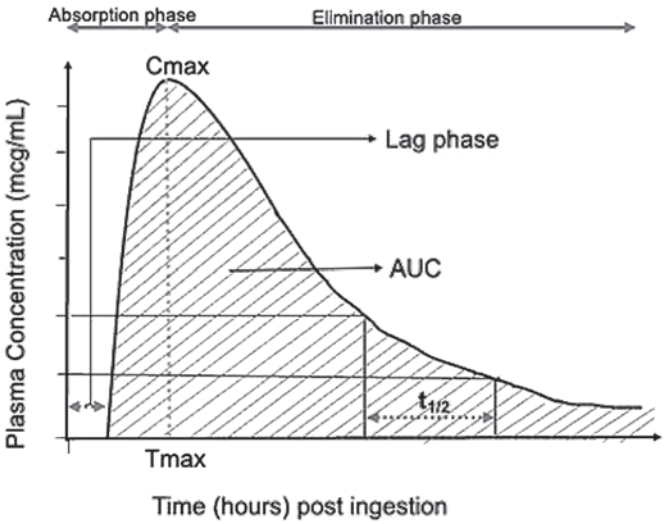

Fig.2. Concentration time-plot of single-dose administration of an orally ingested drug. The shaded area represents AUC (Area under the time curve)

constructing toxicokinetic models remains a challenge due to large inter-patient variability. This section explains the toxicokinetic processes and how they would be affected by overdose or toxicity.

Absorption

Poisons enter the human system through various routes, including ingestion, inhalation, skin contact or injection. Absorption describes how poison reaches blood circulation from the site of exposure. Most commonly, it occurs by passive diffusion for lipid-soluble small molecules. Some molecules require carrier-mediated transport via either facilitated diffusion or active transport. The factors influencing absorption are dosage form, physico-chemical properties of molecules, molecular size, pH of stomach and intestine, the metabolic activity of intestinal cells, and blood flow to the organ.[3] An unionized, lipid-soluble, small molecular size molecule can readily cross the plasma membrane. Various factors that influence absorption during poisoning are discussed below.

Toxicological perspectives

a. Formulation: Formulation determines the rate of absorption of the poison. Unlike solid formulations, which must be disintegrated and dissolved to be absorbed, liquid formulations are readily absorbed. In yellow oleander poisoning, the bioavailability of cardenolides is high in patients who ingest crushed seeds than in those who ingest whole seeds and thus, experience more cardiotoxicity.[4] Controlled release preparations, by their nature, would cause delayed absorption of the active constituents. Ingestion of large number of pills may form pharmacobezoars, that lead to erratic absorption leading to multiple peaks.[5]

b. Route of exposure: Oral ingestions are the most common route of exposure to poisons. Other routes are

Box 1. Basic Pharmacokinetic parameters and their mathematical relationships

Cmax: It is the peak concentration that is achieved after single dose administration. It denotes the point at which absorption and elimination are at equilibrium.

Tmax: The time taken to achieve peak concentration (Cmax)

Area under curve (AUC) of concentration time plot is calculated from the concentration-time curve by series of blood samples drawn post ingestion. It provides an estimate of rate and extent of systemic exposure in the body. It can be calculated manually by trapezoidal rule.

Bioavailability (F): It is calculated by dividing the AUC of oral exposure to AUC of the drug administered intravenously. **$F = AUC_{oral} / AUC_{IV}$**

AUC = Dose X F/CL (CL is total body clearance**)**

Volume of distribution (Vd): The apparent volume that is available for the molecule to be distributed in the body. It is a theoretical volume and is estimated by total dose administered in the patient divided by the steady state plasma concentration of the drug. **Vd = Dose/Css (steady state plasma concentration)**

Clearance (CL): The volume of plasma cleared by the drug per unit time. It can be estimated using the bioavailable dose and AUC **(CL = F X Dose/AUC)** or from the elimination half-life (t1/2) and Vd (**CL = 0.693 X Vd/t1/2).**

Half-life ($t_{1/2}$): The time taken by the plasma concentration to reduce to it's half, if a drug follows first order kinetics. The elimination half-life varies proportionally with the Vd, and inversely with clearance as follows: **$t_{1/2}$ = 0.693 X Vd/CL.** The elimination half-life is an important parameter to infer changes in the clearance.

inhalational, dermal and parenteral. The toxicity invariably changes with the route of exposure. Elemental mercury by oral ingestion is virtually non-toxic; however, by inhalation, it causes devastating effects on the respiratory and central nervous systems (CNS).[6] In contrast, organophosphates being highly lipid-soluble compounds, are readily absorbed by all routes and produce toxicity.

c. Gastrointestinal (GI) transit time: Some poisons that prolong the GI transit time like substances with anticholinergic activity (Datura, tricyclic antidepressants, and opioids), might prolong the absorption and contribute to multiple peaks in the time-concentration profile of themselves and co-ingested poisons. The Cmax and Tmax of the drugs are delayed (Box 1).[2]

d. Saturation of transport proteins: Some drugs require transport proteins to enter cells. For example, gabapentin and methotrexate require amino acid and folate transporters respectively. In overdoses, saturation of these proteins reduces the absorption of these drugs.[3] However, this advantage is offset if there is prolonged GI transit time, giving more time and interface for these drugs to be absorbed.

e. Influence of intestinal/ gastric pH: For poisons that are weak acids or bases, pKa and pH of the medium determine the absorption rate.[3] pKa is the pH at which the molecules are at equilibrium in their ionized and unionized forms. If the pH of the medium is lower than the pKa of an acidic compound, their unionized form predominates and easily gets absorbed through the plasma membrane. If the pH of the medium is higher than pKa, poisons exist more in ionized form and get trapped in such medium (ion trapping). Though it is not followed in practice, theoretical knowledge is that GI decontamination might be helpful even in acute intravenous overdoses of morphine because a weak base gets trapped in its ionized form in the highly acidic gastric pH and gets concentrated in the stomach.[7]

Clinical relevance*:* Absorption of poison determines the onset of clinical toxicity. It is a common practice to observe any asymptomatic individual with an alleged history of poisoning, for at least six hours with absorption kinetics in mind.[8] The observation period would extend to at least 24 hours in case of sustained or delayed release preparation or in case of physiological circumstances that may delay absorption. After stabilization, the next step in the management of a poisoning patient is to prevent any further absorption of the poison. Common GI decontamination procedures for oral exposure are gastric lavage or administration of activated charcoal (Table I). It is futile for poisons with rapid absorption like alcohol and poisons that cause local tissue damage (corrosives poisoning). Single dose activated charcoal would be suitable for patients presenting within one hour of ingestion of poison with immediate absorption, whereas multiple-dose charcoal or whole bowel irrigation would be preferred in cases of controlled/ sustained release products.[9]

Distribution

The absorbed poison in circulation distribute to various tissues in the body. The distribution of the molecules to tissues depends on the blood flow to the organ, plasma protein binding and blood tissue partition coefficient of the compound.[3] Depending on their relative distribution in the body, a drug could follow single-compartment or multi-compartment distribution kinetics. If a small, lipid-soluble molecule gets evenly distributed in the whole body, it is said to follow the single compartment distribution. A drug that follows two compartment model would initially distribute to the organs with high perfusion like the liver, kidney and heart (central compartment) and later, slowly distributes to peripheral tissue compartments (skeletal muscle, adipose tissue, and skin). The drug would be in equilibrium in both compartments. Whenever the concentrations in the central compartment reduce, drugs tend to redistribute from the peripheral compartment. The compartments are rather functional than anatomical ones.

Toxicological perspectives

a. Movement of poison from one compartment to the other

The toxicity produced by a poison could be either because of its predominant presence in the central or peripheral compartment. Lithium causes CNS toxicity only in chronic poisoning.[10] In acute poisoning, despite high plasma concentrations, its rapid distribution to extracellular fluids and high renal clearance makes it insufficient to equilibrate with the toxic compartment (brain). However, in chronic poisoning, lithium is available in the central compartment for a prolonged time to equilibrate with the brain, manifesting as CNS toxicity.[10]

b. Influence of blood pH

Many poisons cause metabolic acidosis or alkalosis which in turn affects the conventional drug distribution of basic or acidic poisons. In these situations, altering the blood pH might ameliorate toxic features. For instance, tricyclic antidepressants (TCAs) poisoning is well known for its cardiovascular toxicity due to sodium ion channel blockade. This toxicity is by virtue of the drug

concentration in the central (blood) compartment. Serum alkalization ionizes the drug and pushes them into the tissue compartment (increase Vd), thereby causing a fall in free concentration of the drug and acute toxic effects.[11]

c. Plasma protein binding

Acidic substances bind albumin, and basic compounds predominantly bind alpha-1 acid glycoprotein.[3] Other hormonal drugs bind to their respective hormone-binding globulins. Plasma protein binding has two major implications. First, drugs with high plasma protein binding like phenytoin, valproate and indomethacin are restricted to the vascular compartment and their volume of distribution would be low. Second, free drugs unbound to plasma proteins can alone elicit a pharmacological response.[3] At therapeutic doses, the binding capacity of the drugs is linear; the increase in dose will not affect the fraction of the unbound drugs. However, in drug overdoses, the saturation of these protein binding sites occurs, leading to high toxic free drug concentrations. Free drug concentrations may increase during pathological states like hypoalbuminemia. Phenytoin toxicity occurs at therapeutic doses in critically ill patients.[12]

d. Volume of distribution (Vd)

It is the apparent volume available for the molecule to be distributed in the body (Box 1). Suppose if the Vd of a drug is 5L, it means that the drug is distributed primarily in the vascular compartment. If the Vd of the drug is high (>1L/kg body weight), such as in digoxin, the drug is widely distributed across the body tissues making the plasma concentration too low (<10% of the drug in the body). Such drugs require a loading dose to attain steady state concentrations quickly.[3]

Clinical relevance: Drug redistribution plays a crucial role in determining the clinical course of the patient as well as in deciding on the elimination of the poison. Atropine maintenance infusion for organophosphate poisoning is titrated according to individual patients to account for the rebound, that occurs due to redistribution of the poison from adipose tissue.[13] Acute severe iron poisoning typically exhibits a deceptive clinical recovery phase after six hours due to redistribution of iron to reticuloendothelial cells. Drugs with a high volume of distribution (>1 L/kg) and high plasma protein binding (>90%) are not amenable to extracorporeal treatment like hemodialysis and the converse is true (Table I).[14] The rapid action of chelation therapy for heavy metal poisoning also relies on the redistribution of poison from the peripheral toxic to the central compartment. Alkalinization is beneficial for both weak bases like tricyclic antidepressants (increased Vd) and weak acids like aspirin and chlorophenoxy herbicides (decreased Vd) as their toxic compartments are different.[11]

Metabolism

Any poison that enters the human body undergoes biotransformation. While liver is the principal site for metabolism, other organs involved are the kidney and lung.[3] Metabolism mostly occurs in two phases: phase 1 reactions (oxidation, reduction, or de-esterification) are mediated by the cytochrome P450 (CYP) system; phase 2 reactions are conjugating steps with glucuronide, sulphate, or acetylation moieties.[3] During phase 2, non-polar lipid-soluble molecules are converted into water soluble polar molecules, which helps in the easy elimination of drugs. During phase 1 reactions, mostly, active molecules are converted to inactive metabolites resulting in detoxification. Some parent compounds are converted to their active metabolites (e.g., organophosphate).[13] Rarely prodrugs (inactive compounds) are converted to active drugs (e.g., enalapril).[3]

Toxicological perspective

a. First pass metabolism: All ingested products are absorbed from the gastrointestinal tract, enter the portal circulation to reach liver and undergo metabolism (first-pass effect) and only a fraction of the parent drug reaches as such into the systemic circulation [bioavailability (Box 1)].[3] At drug overdoses, metabolizing enzymes saturate, leading to increased bioavailable dose as reported for drugs like verapamil and diltiazem. Verapamil bioavailability is usually <30% due to its high hepatic clearance. At overdoses, it has been noted to increase by 2 fold.[15]

b. Capacity-limited metabolism: Drugs that are metabolized enzymatically get saturated easily at overdoses. Most drugs at therapeutic doses follow first-order or linear kinetics, i.e., a constant fraction of the drug is eliminated per unit time, and the half-life remains constant.[3] For a drug with linear PK, we would expect that a 2-fold increase in dose would result in an equivalent increase in systemic drug exposure. Most of the drugs we use belong to this category. At drug overdoses, due to enzyme saturation, the kinetics of elimination changes from first to zero order kinetics (non-linear kinetics), where a fixed amount of drug is metabolized per unit time independent of the concentration. It means that increases in drug exposure are not linearly related to increases in administered doses. Classical example would be phenytoin

exhibits marked saturation of metabolism at concentrations in the therapeutic range. A slight increase in ingested dose produces a disproportionate rise in blood concentration resulting in acute toxicity. Other drugs that follow non-linear kinetics are salicylates, theophylline and ethanol.[3] For poisons that have more than one metabolic pathway (e.g., paracetamol), the fraction of dose that is metabolized by each of them determines the clinical toxicity. Paracetamol is primarily metabolized by hepatic glucuronidation and a small fraction undergoes N-hydroxylation by CYP2E1, leading to the formation of toxic metabolite [N-acetyl-p-benzoquinone imine (NAPQI)]. At therapeutic doses, NAPQI is neutralized by hepatic glutathione conjugation.[16] In cases of poisoning, this toxic metabolite accumulates in large amount and overwhelm the glutathione stores, causing liver injury. Some compounds produce toxic metabolites that have opposite effect to that of parent compound. Meperidine causes CNS depression while nor-meperidine, its metabolite causes CNS excitatory effect.[17]

c. Flow-limited metabolism*:* For drugs that undergo extensive metabolism by multiple pathways in the liver, the blood flow to the organ becomes the rate-limiting factor and is said to follow the flow-limited metabolism. Examples of such drugs are nitrates, propranolol, verapamil and diltiazem.[3] They have very high first-pass metabolism and therefore, have poor bioavailability (<30%).[3] Patients having hypotension and shock have decreased organ perfusion leading to increased bioavailable doses of these drugs and subsequent toxicity. Measures taken to correct hypotension enhance the clearance of these drugs.[18]

Clinical relevance

Risk assessment of any poisoning would be incomplete without the knowledge of metabolism. The nature and severity of toxicity and duration of action of the poisons depend on the rate of metabolism and formation of toxic metabolites. Substances, even when ingested in typically non-toxic doses, might turn poisonous when the liver functions are compromised due to conditions like liver cirrhosis.[2] Theoretically, for poisons that follow non-linear kinetics, enzyme induction should be a useful strategy. However, it is not attempted due to the limitation of its usefulness in the acute setting as the induction takes at least 36-48 hours.[2] Preclinical studies have shown that CYP enzyme inhibition by cimetidine, mitigated the toxicity of paracetamol, but it did not translate in human studies.[19] Understanding metabolism is important for choosing specific antidotes for the poisons. Fomepizole inhibits alcohol dehydrogenase, which inhibits the formation of toxic metabolite formaldehyde in methanol poisoning. N-acetyl cysteine, a thiol-reducing agent, is the antidote for paracetamol poisoning to neutralize NAPQI-mediated toxicity.[3]

Excretion

It is the process of eliminating the poison from the body. Mainly, it occurs via the renal or biliary route.[3] The lung is the route of elimination for gaseous compounds. Renal excretion occurs by either glomerular filtration or active secretion from proximal tubules. The molecular size, plasma protein binding of the poison, and amount of blood flow to the glomerulus would influence the clearance of the drug by glomerular filtration.[3] Low molecular size unbound drugs get easily filtered by the glomerulus. Active secretion of poisons from tubules is transporter-mediated via P-glycoprotein and organic anion/cation transport polypeptide protein (OATP/OCTP).[3] These are saturable at overdoses and lead to a shift from linear to non-linear kinetics. Also, if the poison is toxic to the excreting organ, it tremendously impairs the clearance of the drug.[2] Various poisons and toxins are known to cause acute kidney injury like aminoglycosides. The urinary flow rate and pH determine the passive tubular reabsorption of certain poisons from the tubules.[9] Hence, alteration of pH remains a useful strategy to promote the elimination of poisons. Some drugs like sulphonamides, carbamazepine excreted by the biliary route can be reabsorbed via enterohepatic circulation and can lead to unpredictable multiple peaks and prolonged elimination half-life of the drugs.[2]

Clinical relevance

Prevention of accumulation of toxic metabolites and their enhanced elimination is yet another goal in poisoning management. Urinary pH manipulation provides a useful strategy (Table I). Forced diuresis and urinary alkalinization are recommended for acidic drug poisonings like salicylate and phenobarbital poisoning. In the corollary, urinary acidification increases the excretion of basic compounds. But it is not done in clinical practice for two reasons-first, the efficacy is modest and second, acidification alters the distribution kinetics of many compounds unfavourably. Multiple-dose charcoal is recommended for drugs undergoing enterohepatic circulation. Examples of such drugs are carbamazepine, dapsone, quinine and theophylline.

Prediction of toxicity from blood concentrations

The concentration of poisonous substances can be estimated from biological fluids like whole blood, serum/plasma, or urine. Blood levels are closely correlated with

Table I. Strategies aimed at modifying toxicokinetics of poisons

Strategies	Poison for which it is recommended	Remarks
a) Decrease absorption		
Forced emesis by ipecac	Non-specific	Currently not in use as the risk outweighs the benefit (prolonged vomiting and electrolyte abnormalities)
Gastric lavage	Non-specific	Should be done within one hour of the presentation; not recommended in hydrocarbon poisoning as it can lead to aspiration pneumonitis.
Activated charcoal (1g/kg) - single dose oral	Non-specific	Preferred over gastric lavage. Effective if done within one hour of ingestion; not recommended in corrosive/ heavy metal poisoning.
Activated charcoal (1g/kg) - multiple-dose (e.g. 1 g/kg every 4 hours)	Drugs with enterohepatic circulation (ibuprofen); prolonged absorption	Can cause transient constipation, occasional bowel obstruction (controlled release formulations, carbamazepine, theophylline)
Whole bowel irrigation (~2L/hour oral isotonic solution like polyethylene glycol until the rectal effluent is clear)	Large ingestion of controlled release formulations	Can cause mild electrolyte and acid-base abnormalities
b) Alter drug distribution (Redistribution from toxic compartment)		
Serum alkalinization e.g., sodium bicarbonate infusion	Tricyclic antidepressants, salicylates, chlorophenoxy herbicides	Can cause hypercarbia and electrolyte abnormalities
c) Alter metabolism		
Prevent the formation of toxic metabolites. (inhibit alcohol dehydrogenase by fomepizole or ethanol)	Methanol, ethylene glycol	Ethanol may cause dysphoria
Glutathione donators (e.g., N-acetyl cysteine) - increased metabolic deactivation, methionine	Paracetamol, paraquat	-
d) Enhance elimination		
Urinary alkalinization (target urinary pH > 7.5)	Weak acids (pKa 3.5-7.4) With significant renal excretion (Phenobarbitone, salicylates)	Effective for drugs that have low protein binding and small Vd

Strategies	Poison for which it is recommended	Remarks
Hemodialysis	Molecular weight <500 D;water soluble; poor plasma protein binding (Lithium, ethylene glycol aminoglycosides)	Procedural complications
Hemoperfusion	Adsorbed by activated charcoal Poor plasma protein bound	Procedural complications
Plasmapheresis	Lipophilic and highly protein bound	Procedural complications
Chelation	Desferrioxamine for iron; succimer for lead, arsenic and mercury	Anaphylactoid reactions
Lipid resuscitation therapy or Intravenous lipid emulsion therapy	Local anesthetic systemic toxicity	Potential risk of allergy to animal sources of lipids Requires monitoring of serum lipid levels

the toxic effects of some drugs like lithium, lead, cyclosporine, phenytoin, and carbamazepine.[8] However, it is not established for many drugs and poisons. The concentrations estimated during the absorption and distribution phases vary considerably because the amount and time of ingestion are inaccurate in poisoning cases. Many times, the peak concentration is delayed. The Rumack Matthew nomogram used for predicting liver toxicity from paracetamol poisoning, considers blood levels measured post four hours of ingestion.[16] On the other hand, concentrations estimated during the elimination phase provide valuable information regarding the clearance of the drug. Thus, serum concentrations of many poisonings are mostly done during this phase. The results of assays should be cautiously interpreted to account for preanalytical errors like sample collection methods, timing, storage, transport, and inherent errors in the assay.[8] Measurement of concentration is of limited use in some poisonings, where the effects are predominantly local (acid or alkali poisoning) or the toxic response can be easily measured (ECG for cardiotoxicity; blood glucose for glucose-lowering drugs). These concentrations are useful in clinical management only if it can be reasonably correlated with toxicodynamics and clinical outcomes.

Toxicodynamics

Toxicodynamics is the toxicological counterpart of pharmacodynamics which deals with the study of the interaction of the poison with the biological target to produce its toxic response. These occur by interacting with ion channels, enzymes, or proteins. Interactions could be competitive or non-competitive and reversible or not reversible. Organophosphates bind acetylcholinesterase enzyme irreversibly to produce cholinergic toxicity and are amenable to treatment by oximes only when administered before the ageing of the enzyme occurs.[13] Certain poisons that affect biochemical pathways, such as uncoupling of oxidative phosphorylation and free radical damage are not limited by any physiological limit and the toxic effects accumulate over time depending on the amount of exposure (e.g., paraquat & phosphine poisoning).[2] The degree of response is also affected by the tolerance developed for some effects. Benzodiazepines induced sedation develops tolerance whereas drugs causing cardiotoxicity by sodium channel blockers do not.[2] Poisons that cause extended interference with normal physiology determine the onset of clinical toxicity. Rodenticides (superwarfains) exhibit delayed coagulopathy till the available clotting factors are depleted.[2]

Concept of median lethal dose (LD50)

Toxicodynamic characteristics are quantified by dose-response plots. During animal toxicity studies, the dose-response relationship is studied at an organism level by gradient dose-response curve or at the population level by quantal dose-response curve.[20] The relative safety of the drug is determined by a measure called therapeutic index. It is derived from measuring ED50 and LD50 from the quantal response curve. ED50 is the median effective dose that produces desired response in 50% of the population. LD50 is the median lethal dose that causes mortality in 50% of the population. Therapeutic index= LD50/ED50. The higher the ratio, the safer the drug. It ranges from 2 to more than 100. The fallacy of calculating LD50 using the median dose can be appreciated in Fig.3.Now-a-days, toxicologists prefer a margin of safety

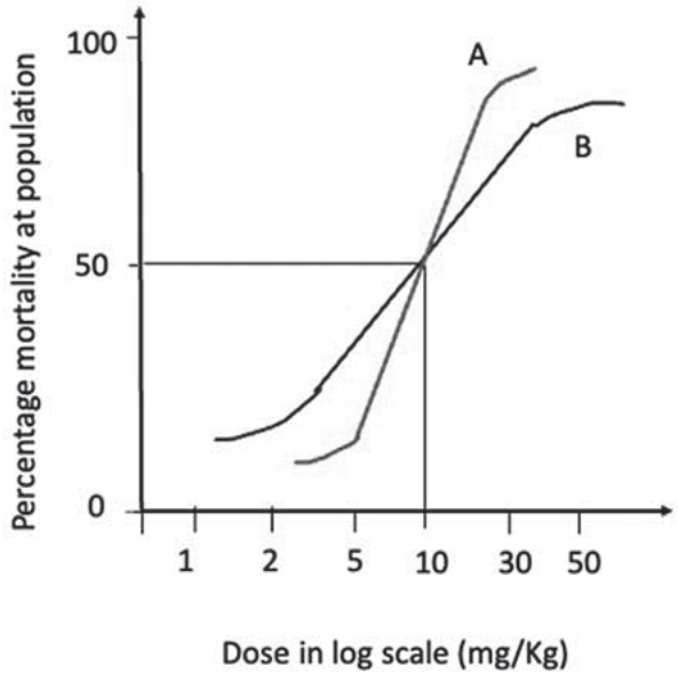

Fig.3. Dose-response curves of Toxicant A and Toxicant B. Even though the median LD 50 is the same, the slope of the curve is steep for toxicant A, compared to toxicant B. Hence a greater number of animals experience mortality at half the LD50 dose for toxicant A

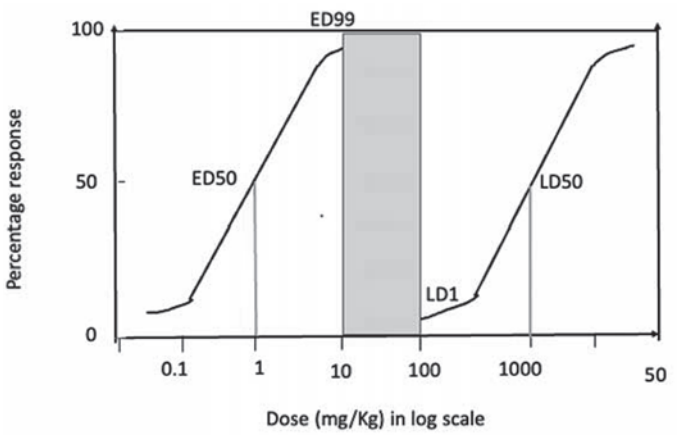

Fig.4. Dose-response curves of a drug denoting the ED50, ED99, LD1, LD50, and margin of safety of a drug. The shaded area represents the margin of safety of the poison

derived using ED99 and LD1 (Fig.4).[20] The wider the margin, the safer is the drug.

Conclusion

The toxicological principles determine various aspects of clinical management of poisoning. The toxicological characterization of various poisons is an evolving field with much to learn about the newer poisons, that are infrequently encountered by humans. An in-depth understanding of these principles by the treating physicians has the potential to improve the clinical outcomes of patients affected by the poisoning.

Points to Remember

- ***Pharmacokinetics deals with the study of movement of drug in the body; describes absorption, distribution, metabolism and excretion processes and toxicokinetics describes the changes occurring in overdose setting.***
- ***Pharmacodynamics involves the study of interaction of drug with its biological target to produce therapeutic effect. The toxicological counterpart is toxicodynamics.***
- ***The relative safety of the drug is determined by therapeutic index, which is derived from measuring ED50 and LD50 from the quantal response curve. ED50 is the median effective dose that produces desired response in 50% of the population. LD50 is the median lethal dose that causes mortality in 50% of the population. Therapeutic index= LD50/ED50. The higher the ratio, the safer the drug,***
- ***A sound knowledge of these toxicokinetic and toxicodynamic principles help in predicting the clinical course and optimize the therapeutic strategies of a poisoned patient.***

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CLIPPINGS

Association Between Screen Time Exposure in Children at 1 Year of Age and Autism Spectrum Disorder at 3 Years of Age - The Japan Environment and Children's Study

This cohort study aimed to examine the association between screen time in children at 1 year of age and the development of autism spectrum disorder at 3 years of age.

A total of 84/030 mother-child dyads were analyzed using data derived from a large birth cohort study conducted in Japan. These children were born to women recruited between January 2011 and March 2014 and data were analyzed in December 2020. The study was conducted by the Japan Environment and Children's Study Group in collaboration with 15 regional centers across Japan.

The outcome variable, children diagnosed with autism spectrum disorder at 3 years of age, was assessed using a questionnaire administered to mothers of the participating children.

The prevalence of children with autism spectrum disorder at 3 years of age was 392 per 100/000 (0.4%) and boys were 3 times more likely to have been diagnosed with autism spectrum disorder than were girls. Among girls, however, there was no association between autism spectrum disorder and screen time. The study concluded that among boys, longer screen time at 1 year of age was significantly associated with autism spectrum disorder at 3 years of age. With the rapid increase in device usage, it is necessary to review the health effects of screen time on infants and to control excessive screen time.

Kushima M, Kojima R, Shinohara R, et al. Association Between Screen Time Exposure in Children at 1 Year of Age and Autism Spectrum Disorder at 3 Years of Age:* The Japan Environment and Children's Study. *JAMA Pediatr. 2022;176(4):384–391. doi:10.1001/jamapediatrics.2021.5778

TOXICOLOGY - I

APPROACH AND INITIAL MANAGEMENT OF A CHILD WITH TOXIN INGESTION

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Abstract: *Traditional medical school teaching lists out various etiological factors of diseases as congenital, traumatic, infective and neoplastic, etc. Toxin ingestion is an important addition to this. Unlike other diseases, literature on toxicology is very much limited to only case reports, anecdotal experiences and few case series. In other disease groups, literature is robust with randomised controlled trials, systematic reviews and meta-analyses and prospective case series. Toxicology in pediatric age group is different from that of adults, since toxin exposure is accidental most of the times and present as emergency with no history of ingestion. The onus is on the pediatrician to suspect, if not suspected and managed at the appropriate time, the outcome gets adverse. Initial steps in approach and management are modified in the context of toxin ingestion as airway, breathing, circulation, decontamination, examination for toxidrome, focused history and glucose estimation. It is also important to be cognizant about the medicolegal aspects of poisoning. In this article, a few pertinent questions are raised and answers are sought to understand the various aspects of toxicology.*

Keywords: *Poisoning, Toxicology, Medicolegal.*

Poisoning causes a significant proportion of accidental deaths (25%) in children in India. A study from Vellore revealed 63.1% poisonings were contributed by chemicals and plant poisons and the remaining were drug related.[1] One should remember the fact that the pattern of poisoning in children widely differs because of exploratory nature of ingestion of common household substances especially in children younger than six years, unlike in older children and adolescents.[2] The possibility of associated trauma or medical illness must be recognized and addressed before initiation of decontamination.[3]

Box 1. Questions raised to analyse a suspected toxicological emergency in PED

1. When to suspect poisoning?
2. What are the resuscitative measures?
3. Any specific management in PED?
4. Decontamination procedures - when and what?
5. Are there any clues as for the toxin ingested?
6. Is there an antidote available and is it required?
7. What other supportive management?
8. What are the medicolegal implications?
9. Is there a role for toxicology screen?
10. What are the resources available to guide management?
11. What are the preventive measures?

When a child is brought to pediatric emergency department (PED) in a critical condition like seizures without any obvious clues, the following questions should be answered after taking care of airway, breathing, circulation and seizure control (Box 1). A systematic approach to analyse and prioritize an emergency situation is to raise a series of questions and attempt to answer. A case scenario approach is adapted to make it interesting.

1. When to suspect poisoning?

In a child with altered consciousness, one should consider intoxication (toxin ingestion or poisoning) as the fourth 'I' after considering the common three causes, such as injury, infection and inborn errors of metabolism (IEM). Toxin exposure should also be considered in children presenting with respiratory distress, unexplained metabolic acidosis, seizures or with a confusing clinical picture.[4]

Case vignette 1: Four years old healthy child had lunch with mother in the noon. Later, mother left for some work

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Box 2. Features that raise strong suspicion of poisoning

a) Unsupervised child

b) Previously well child with sudden deterioration Cyanosis in the back ground of stable cardiorespiratory status.

d) No specific pattern of symptoms like fever, cough, breathlessness or headache, altered mental status previously

e) An unobserved period with no environmental clues or external injury.

in the field leaving the boy at home under the indirect supervision of neighbour. When mother returned home at 7 pm, the boy was lying at door step and was in altered mental status. There was no clear history about what happened between noon to 7 pm as the neighbour was busy with her household work. When he was brought to PED, he was irritable but pain responsive and was localizing. Respiratory rate (RR) was 40/minute. There was good respiratory effort, with air entry equal on both sides and there was no noisy breathing. Pulse rate was 120/ minute, well felt and BP was 90/60mm Hg. His SpO2 was 80% in room air. When child was given O2 through non-rebreathing mask, there was no increase in SpO2. Tongue and lips appeared bluish. There was no clubbing. On examination of cardiovascular system (CVS), there was tachycardia and no murmur. Blood sample was in chocolate brown color (Fig.1.).

Features pointing to a strong suspicion of toxin ingestion in this child are listed in Box 2.

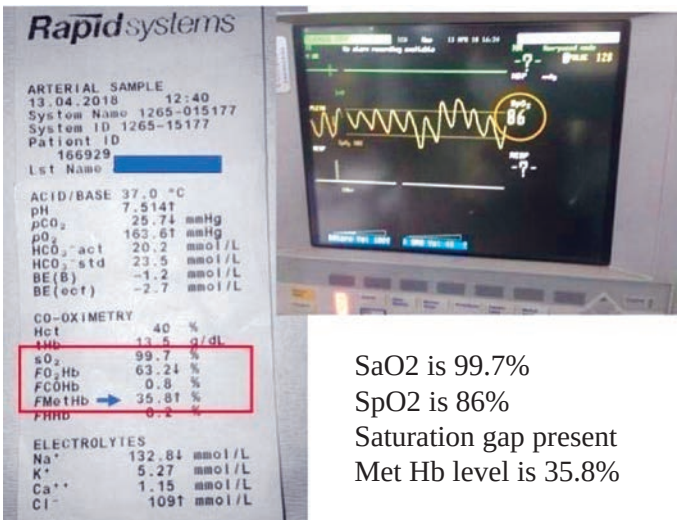
Sudden onset of altered mental status is commonly caused by five conditions a) Unidentified injury, b) seizures (witnessed or un-witnessed), c) intracranial bleed, d) envenomation and e) poisoning.

Some of the poisoning which mimic certain diseases are given in Table I.[5] The clue is the lack of prodromal illness or preceding symptoms for the disease.

2. What are the resuscitative measures?

3. Any other specific management along with resuscitation in the PED?

Toxin ingestion also can present with shock, altered mental status, seizures or respiratory distress/failure.[6] Laboratory abnormalities observed commonly in toxin ingestions are metabolic acidosis, hypoglycemia, electrolyte imbalance, coagulation abnormalities and acute hepatic impairment. Various physiological derangements and related biochemical disturbances need to be corrected as early as possible in ED itself, which are listed out in Box 3.



SaO2 is 99.7%
SpO2 is 86%
Saturation gap present
Met Hb level is 35.8%

Fig.1. Methemoglobinemia and ABG showing saturation gap

Blood in the first container is chocolate brown coloured, compared to mother's blood for control, which is red. ABG reading shows saturation 99.7% and methemoglobin level 35.8%. Pulse oximeter showing a reading of 86%. Child with methemoglobinemia probably due to some accidental drug ingestion

Box 3. Various physiological derangements and related biochemical disturbances

1. Altered mental status
2. Shock
3. Respiratory distress/failure
4. Seizures
5. Arrhythmia
6. Hypoxia
7. Hypoglycemia
8. Acidosis

Table I. Poisons which mimic certain diseases

Symptoms and signs	Possible toxins	Differential diagnosis
Non-ketotic hypoglycemia	Ethanol	MCAD deficiency, GSD
Acute liver failure	Paracetamol, rodenticide	Infective causes like viral hepatitis
Hyperglycemia, ketosis, CNS depression	Theophylline, salicylate	Diabetic ketoacidosis
Hyperthermia, tachypnea, sudden onset of symptoms	Salicylate	Pneumonia

MCAD-Medium chain acyl coA dehydrogenase; GSD-Glycogen storage disorder

a) Altered mental status (AMS) is a common presentation in a child with toxin ingestion which may range from drowsiness, irritability to deep coma. Grading the AMS by AVPU scale or Glasgow coma scale (GCS) will be helpful in deciding the need for any immediate intervention and periodic re-examination will help in assessing the trend. Hypoglycemia and hypoxia are frequent and correctible causes that lead to AMS. Both can be measured by 'point of care' testing.[7]

Box 4 lists the possible differential diagnoses, after excluding hypoglycemia and hypoxia.

Any child with GCS < 8 or rapidly declining GCS or pain-responsive (P) or unresponsive (U) in AVPU scale needs to be admitted in PICU for airway monitoring and support. In addition, traumatic brain injury should be suspected to be a comorbidity or may be a close differential diagnosis.

Case vignette 2: An adolescent girl returned from school at 4 PM. When mother (single parent) returned from work at 9PM, she found her daughter unconscious, convulsing and vomiting reddish fluid.

Box 4. Drugs that cause AMS

1. Antihistamines: E.g. - Chlorpheniramine,
2. Psychiatric drugs: Antidepressants like tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs)
3. Sedative hypnotics: Barbiturates, benzodiazepines, opiates
4. Anticonvulsants: Carbamazepine, phenytoin
5. Recreational drugs: Alcohol
6. Cholinergics: Organophosphates, carbamates

When the child was brought to the ED, she was suspected to have a variceal bleed with status epilepticus. After stabilizing ABC, she was intubated and ventilated. She was found to have hyperglycemia, high anion gap metabolic acidosis (HAGMA) and reddish urine (Fig.2). After few hours of analysis, a possibility of antituberculous

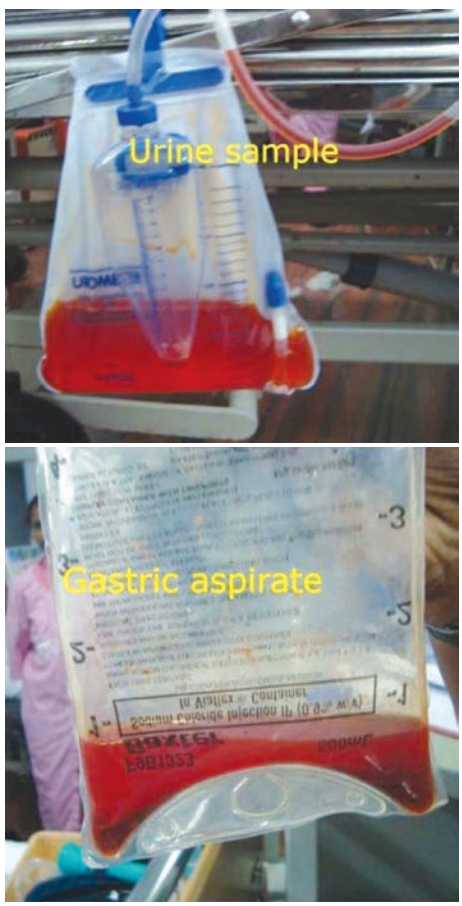


Fig.2. Both urine sample and gastric aspirate showed red color because of rifampicin

Courtesy: Dr.Anitha and Sharada Mehta Hospitals, Chennai

Table II. BP and heart rate changes due to toxins

Hypotension and bradycardia	*Hypotension and tachycardia*	*Hypertension and tachycardia*
Beta blockers	Beta agonists - theophylline, salbutamol, terbutaline	Sympathomimetics - amphetamines, theophylline, ephedrine, pseudoephedrine
Calcium channel blockers (CCBs)	Alpha adrenergic antagonists - Phenothiazines, TCAs, hydralazine	Anticholinergics-antihistamines, TCAs
Cardiac glycosides - Oleander, digoxin, *Cleistanthus collinus* (oduvanthalai in Tamil)		Central hallucinogens - LSD
Cholinergics, - organophosphorus compounds (OPCs)		Envenomations - scorpion sting
CNS depressants (here depressed level of consciousness will be profound)		Cholinergic agents thyroxine

drug poisoning was suspected. Team realized that INH caused seizures and rifampicin caused reddish vomitus and urine. Treated with IV and oral pyridoxin and supportive management and child recovered. Serum sample sent confirmed the presence of INH later.

INH caused seizures and HAGMA and rifampicin caused the reddish discoloration of urine.

b) Shock: Many toxins can cause hemodynamic instability. Management depends on the underlying pathophysiology.

- Fluid loss due to vomiting or diarrhea can lead to hypovolemic shock.
- Vasodilatory shock can occur in iron poisoning. So in addition to fluid bolus, vasoactive agents may be needed.
- Some toxins affect the heart rate and rhythm in addition to shock. They need to be managed accordingly (Table II).[8]

Resuscitation of shock

- Initial fluid management
- Before giving beyond first bolus one should ensure that it is not cardiogenic shock, as due to beta blockers, CCB, TCA
- Iron poisoning may cause vasodilatory shock needing vasoactive agents such as norepinephrine

c) Respiratory distress or failure: Another common critical disturbance seen in poisoning is respiratory distress or failure (Table III). Respiratory failure can occur in a child with toxin ingestion due to various mechanisms such as central nervous system (CNS) depression or weakness of respiratory muscles, direct damage to the lung parenchyma causing pulmonary edema, aspiration pneumonia or acute respiratory distress syndrome (ARDS) and final end result is hypoxia and/or hypercapnia.

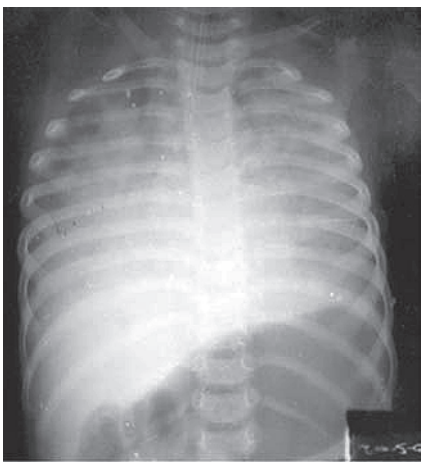


Fig.3. CXR of the child with ARDS

Case vignette 3: Eighteen months old boy, consumed kerosene and brought to ED after 2 hrs, comatose with irregular respiration and shock. Managed with IV fluids, inotropes, ventilation. Developed ARDS, pneumothorax and finally died after 5 hrs (Fig.3).

Management

- Treatment for fever and acidosis.
- Oxygen through appropriate devices

Table III. Respiratory distress and failure

Fast breathing/ Effortless tachypnea (due to metabolic acidosis or hyperventilation due to respiratory centre stimulation)	*Respiratory distress or failure*
Isoniazid	1. Aspiration pneumonia: Kerosene and other hydrocarbons
Salicylic acid	2. Corrosive poisoning: Stridor and distress
Iron	3. Pulmonary edema, secretions: OPC, scorpion sting
	4. Peripheral respiratory failure: Snake envenomation
	5. Central respiratory failure: CNS depressant drugs

- Non-invasive respiratory support (NIV): High Flow nasal cannula (HFNC), Bilevel Positive Airway Pressure (BIPAP)
- Invasive ventilation. Securing the airway and endotracheal intubation may be needed early even before gastric decontamination in a child with depressed mental status because of the high risk for aspiration and related complications. [9]
- Other supportive management: Antibiotics, vasoactive agents, management of pulmonary edema, anti-venom
- Extracorporeal membrane oxygenation (ECMO)

  In some situations, administration of antidotes such as naloxone is indicated along with resuscitative measures, when there is circumstantial evidence of opioid intoxication.[10]

Case vignette 4: Six weeks old baby, had crying spells. A sleepy grandmother administered some liquids (thinking as gripe water) in the night. Baby developed soft stridor and respiratory distress within ½ hour and brought to ER. Lips and tongue showed necrotic white tissue suggestive of corrosive poisoning.(Fig 4.) Later confirmed that grand mother gave the child toilet cleaning acid kept in the bottle by mistake.

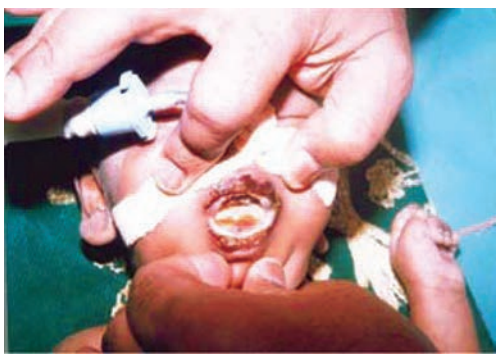


Fig.4. Corrosive ingestion causing necrotic white tissue like appearance of the lips and tongue

d) Seizures

Some toxins can cause seizures. Whenever a child presents with afebrile seizures, toxin ingestion should be considered as a fourth 'I' next to injury, infection, inborn errors of metabolism. An approach to a child with seizures due to toxin ingestion is shown in the algorithm (Fig.5). Checking glucose levels is mandatory.

Management

- Initial management is same as for any child presenting with status epilepticus, such as stabilization of ABC and administration of initial two doses of benzodiazepine (lorazepam) followed by phenobarbitone or levetiracetam
- Phenytoin is contraindicated in toxin induced seizures.[11]
- If hypoglycemia or hypocalcemia is identified it should be managed accordingly.

e) Arrhythmias

- An acutely ill child is to be monitored with pulse oximeter and cardiac monitor in the ED, for arrhythmias. Point of care laboratory tests such as arterial blood gas analysis can identify the presence of metabolic acidosis.
- Symptomatic bradycardia, heart block, supraventricular tachycardia or ventricular tachycardia are some of the arrhythmias that can develop in childhood poisoning involving oleander seeds, digoxin, beta blocker, calcium channel blocker, tricyclic antidepressants (TCA). Recreational drugs like cocaine should be suspected in adolescents. These rhythm disturbances can be managed with the help of a cardiologist.[12]

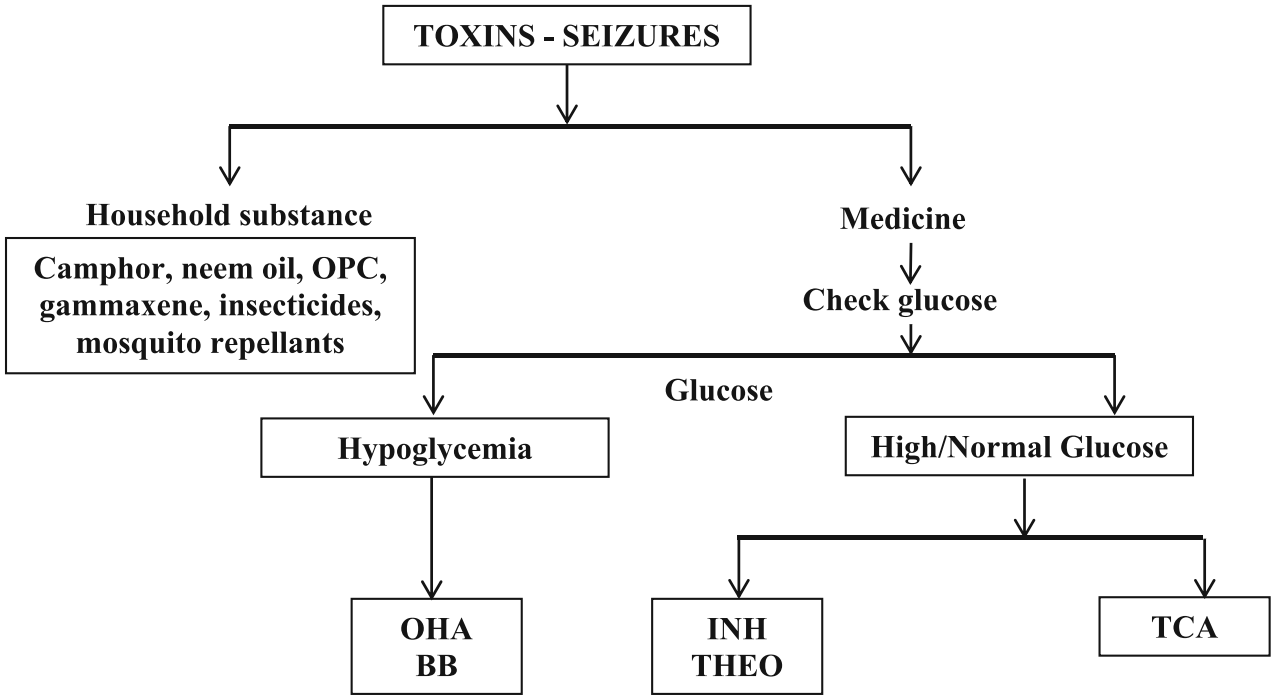


Fig.5. Approach to a child with toxin ingestion and seizures

OHA - oral hypoglycemic agents, BB - beta blockers, THEO - theyophylline

f) Hypoglycemia

In every child with AMS or convulsions, CBG has to be checked immediately and should be connected and monitered in ED itself without any delay. Common causes are hypoglycemic agents, insulin, quinidine, beta blockers, ethanol, etc.

g) Hypoxia

- When both the peripheral saturation or pulse oxymetry saturation (SpO2) and arterial oxygen saturation (SaO2) are low it is true hypoxia, which may be due to central or peripheral respiratory depression wherein a child would need respiratory support.
- If it is due to aspiration pneumonia as in hydrocarbon ingestion or pulmonary edema, it is managed with non invasive ventilatory (NIV) respiratory support and start antibiotics wherever required.
- When there is saturation gap or discrepancy between, SpO2 and SaO2, it indicates presence of abnormal hemoglobins (Hb) such as methemoglobin, they cannot be managed with oxygen or respiratory support alone and can be managed with specific antidotes such as IV methylene blue.

h) Acidosis

- Once acidosis is identified in the child who has effortless tachypnea as in isoniazid, salicylate or TCA poisoning, adequate ventilation has to be ensured and sodium bicarbonate is administered as infusion.

4. Decontamination

Decontamination includes GI decontamination which consists of gastric lavage, activated charcoal administration and whole bowel irrigation, whereas skin decontamination, and eye irrigation are other practices. Advanced methods of extracorporeal removal also helps which is life-saving.

- Gastric lavage is generally found to be useful only within one hour of ingestion. In a country like ours, the patients reach the health care services very late, it can be still considered with appropriate safety measures. An aggressive decontamination may be life-saving when situations with ingestion of sustained release preparations, enteric coated tablets, large quantity ingestion as happens in adolescents, highly toxic drugs like CCB, drugs that delay gastric emptying such as aspirin and anticholinergic agents,[13] when children reach health facility late. One should employ this procedure safely using 12-14 sized nasogastric (NG) tube without causing any injury or airway compromise with proper monitoring. If there is depressed level of consciousness or weak airway reflexes, it should be performed after intubation, preferably with a cuffed tube. It is contraindicated in poisoning due to corrosive and hydrocarbon and also

Box 5. Poisonings where AC is not useful. (mnemonics – PHAILS)

- Pesticide
- Hydrocarbons
- Alcohol
- Iron
- Lithium
- Solvents such as dichloromethane (DCM), also known as methylene chloride, toluene, xylene, glue or lighter fuel and white spirit

in the presence of coma with an unprotected airway. Parents should be educated not to induce vomiting.

Activated charcoal (AC): Administration of AC is a very useful decontamination procedure, but less frequently used. Activated charcoal which is not an expensive preparation, should be available in every ED. It is safe as long as there is no depressed mental status or ileus. In older children, they can consume it with fruit juice in a cup or it can be given through a nasogastric tube after the completion of gastric lavage. Charred bread or charcoal tablets are not equivalent to the efficacy of AC. It is not useful in the following situations (Box 5).

Table IV. Toxidromes

Organ system	Clinical features	Deemed poison
CNS depressants	Drowsiness, stupor, coma, bradycardia, bradypnea, hypotension, miosis	Phenobarbitone, alcohol, benzodiazepines, Opioids (morphine, methadone, fentanyl, oxycodone) Cough syrups with codeine derivates
Serotonin syndrome or toxicity (increased serotonergic activity in the CNS)	Potentially life-threatening condition. Tachycardia, tachypnea, hypertension, diaphoresis,confusion, agitation, coma, tremor, myoclonus, hyperreflexia, trismus, rigidity	MAO inhibitors, SSRI, tramadol, MDMA / ecstasy, amphetamines, lamotrigine.
Myocardial toxins	Brady or tachyarrhythmias, hypotension, cardiac failure or cardiogenic shock	Beta blocker, oleander, CCB, digoxin, TCA
Hepatic toxicity	Raised transaminases, jaundice, bleeding tendency	Paracetamol, rodenticide, paraquat
Corrosives	Drooling of saliva, hoarse voice, stridor, lips and tongue appear red, or white and necrotic, air leak syndrome	Acids, alkalis, detergents, bath room cleaners, button battery
Cholinergics	Fasciculations, salivation, sweating, muscle twitching, hypertension, tachycardia, bradycardia, respiratory distress, miosis, respiratory paralysis, seizures	Organophosphorus poisoning, nerve agents, some anti-lice agents
DUMBBELS (Mnemonics for OPC poisoning)	Diarrhea, urination, miosis, muscle weakness, bronchorrhea, bradycardia, emesis, lacrimation, salivation, sweating	
Anticholinergics	Delirium, tachycardia, dry skin, mucosa, hyperthermia, urinary retention, mydriasis	Antihistamines, TCA, atropinergic drugs, psychoactive drugs
Sympathomimetics	Tachycardia, seizures, hypertension, seizures, mydriasis	Ephedrine, cocaine, amphetamine, theophylline

Knowing toxidrome is very useful in view of the frequent non-availability and limitations of toxin screening. Toxidrome need not be memorised, and should be accessed from books when in need.

- Whole bowel irrigation: This is very useful in iron and lithium poisoning. Should be continued till the rectal effluent is clear.

- Skin and eye decontamination: In OPC poisoning it is a useful procedure. Saline irrigation of eyes, removing the clothes, giving bath or wiping the whole skin will prevent further absorption of toxins.

- Extracorporeal removal:[14] Though extracorporeal therapies (ECT) have been in use for long, they are now increasingly used. They are frequently used in poisoning with salicylates, toxic alcohols and lithium and nearly all poisons. Intermittent hemodialysis also is frequently used. Consideration of ECT depends upon the characteristics of toxins such as molecular mass, volume distribution, protein binding, and risk benefit ratio. Level of evidence for extracorporeal treatment of poisoning is not robust; however, for individual toxins, recommendations are available from the Extracorporeal Treatments In Poisoning (EXTRIP) workgroup.

Urinary alkalinization[15, 16]

- Urine alkalinization means manipulation of urine pH to > or = 7.5 and not diuresis. Urine alkalinisation increases the urinary elimination of salicylate (as first line), chlorpropamide, weedicide like 2,4-dichlorophenoxyacetic acid, some non-steroidal anti-inflammatory drugs (NSAIDs), fluoride, herbicide like methylchlorophenoxypropionic acid (mecoprop), methotrexate, phenobarbital (after AC administration) and tricyclic antidepressants (TCA). This is done in addition to supportive care such as dextrose in chlorpropamide poisoning. Common complication of alkalization are hypokalemia and hypocalcemia, hence close monitoring is for these complications is required during alkalinization.

5. Toxidrome

Toxidrome means toxic syndrome or constellation of clinical features seen due to toxic effects of poisons'.[17] This concept is very useful for rapid detection of toxin and aids in the differential diagnosis. This is categorized based on the system involved or by their pathophysiological effects (Table IV).

Knowing toxidrome is very useful in view of the frequent non-availability and limitations of toxin screening. Toxidrome need not be memorised, and should be accessed from books when in need.

Table V. Antidotes for some common toxins

Toxins	Antidotes
1. Anticholinergics	Physostigmine (not routinely used; used with caution. Sodium bicarbonate (for tricyclic antidepressants)
2. Cholinergics (OPC)	Atropine, P2 AM
3. CNS depressants	Naloxone for opiates Flumezanil for benzodiazepines (Use with caution and not as a routine) Glucose for hypoglycemia Bicarbonate for acidosis Fomepizole and ethanol for methanol
4. Myocardial toxicity	Atropine, orciprenaline for bradycardia Digoxin antibodies (digibind) for digoxin Glucagon for beta blockers Calcium gluconate for CCB
5. Iron	Desferrioxamine
6. Warfarin, rodenticide	Vitamin K
7. Oral antidiabetic	Glucose, octreotide
8. Paracetamol	N acetyl cysteine
9. Methemoglobinemia	IV Methylene blue
10. Isoniazid	Pyridoxine
11. Neuroleptic malignant syndrome	Dantrolene (decreases muscle rigidity)
12. Button battery	Honey/sucralfate for initial few hours to lessen the corrosive effects

6. Antidotes

Antidotes are equivalent to fire extinguishers and they must be universally available, and should be stocked them in the critical care areas. It is a great boon for a handful of life-threatening situations. Every ED should be stocked with antidotes, their expiry dates monitored and replaced in time and there must be a written protocol displayed with details of dose, dilution and side effects of the antidotes for use during emergency (Table V).[18]

Case vignette 6: Seven years old boy, on the way back home, consumed a chocolate like substance kept over a compound wall in the paddy field, despite his sister's objection. In the next one hour, he became unresponsive, with frothing from the mouth.

Findings in ER: Bradycardia, constricted pupils, no muscle twitching or hyper salivation. No seizures or arrhythmia.

Differential diagnosis (DD) for constricted pupils: OPC, opiate, phenobarbitone,clonidine poisoning. He was empirically treated as a case of OPC poisoning. In the next 12 hours, there was no response to treatment and the pinpoint pupils persisted. Next DD was opiate poisoning. Naloxone 0.1 mg/kg was given. Within 2-3 minutes, pupils dilated to 3 mm and he showed response started getting up. Child was managed with naloxone infusion and he completely recovered.

7. Supportive management needed later, based on the system(s) involved

After the initial few hours following resuscitation and stabilization, specific systemic symptoms may evolve gradually:

a) Pure respiratory clinical features: Persistent cough, respiratory distress, adventitious sounds, CXR showing features of pneumonia, air leak syndrome, whiteout lungs suggestive of acute respiratory distress syndrome and necrotizing pneumonia, may evolve following hydrocarbon ingestion depending on the extent of aspiration

b) Respiratory and CNS signs: Presence of respiratory signs like respiratory distress, oxygen requirement along with altered mental status (AMS) and convulsions indicate the following differential diagnosis.

- Hydrocarbon ingestion with aspiration pneumonia, or empyema can lead to hypoxia and hypercapnia where AMS may be an additional feature
- In addition to the above, miosis, muscle twitching, respiratory paralysis is expected in OPC poisoning
- CNS depressant toxicity with aspiration pneumonia
- Salicylate ingestion with central hyperventilation and later effortless tachypnea due to metabolic acidosis and AMS
- Circulatory disturbances such as bradycardia, cardiac failure or cardiogenic shock are seen in poisoning with oleander, digoxin, oduvanthalai with no other systemic science.

c) Circulatory and CNS signs

- Any child having brady or tachyarrhythmia with convulsions or AMS one should consider belladonna or atropine poisoning or tricyclic antidepressant poisoning.
- Saturation gap: This is the difference between the calculated oxygen saturation (SaO2) from a standard blood gas machine and the reading from a pulse oximeter (SpO2) If it is more than 5%, it shows the presence of abnormal Hb as seen in carbon monoxide poisoning,methemoglobinemia, or sulfhemoglobinemia.[19]

Critically ill child with normal saturation and PaO2 is a peculiar finding seen in two forms of poisoning - cyanide and carbon monoxide (Disturbance of cellular respiration)

Case vignette 7: A previously healthy 4 years old boy came to ER with nausea, vomiting and sudden onset of unconsciousness. No trauma, when last seen an hour before he was eating apricot (Similar situation can occur with improperly cooked, unsoaked and dried tapioca). Within 20 minutes he started vomiting and he became unconscious. At ED he presented with a GCS of 7/15, RR- 28, temp-36.8°C and SpO2 in room air - 99%. On further evaluation, high central venous paO2 of 222 mm of Hg, elevated central venous oxygen saturation and HAGMA were demonstrated suggesting cynaide poisoning.

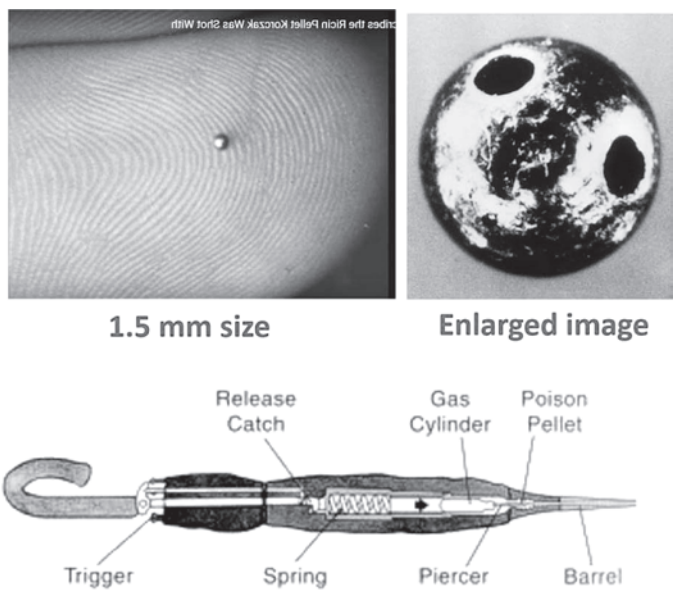


Fig.6. Enlarged image of the pellet containing ricin and the umbrella model used as a gun

Source: Georgi Markov - Wikipedia https://en.wikipedia.org › wiki Georgi_Markov

Ingestion of seeds, fruits or plants containing cyanogenic glycosides (apricot seed, apple seed, tapioca). The pits and seeds of many fruits contain amygdalin - a plant compound that the body converts to cyanide after eating if accidentally seeds are bitten or crushed.

d) Delayed clinical toxicity: This can occur in paracetamol, sustained-release preparations (calcium channel blockers, beta-blockers, lithium), tricyclic antidepressants, oral hypoglycemic agents, paraquat/diquat, warfarin and fat-soluble organophosphate insecticides. Continued monitoring is required in these poisonings to prevent the delayed effects.

8. Medicolegal aspects

In Indian settings, accident register (AR) entry is made in all unknown, suspected or known toxin ingestion followed by written intimation to police authorities so that medical and criminal investigations happen simultaneously. It is useful for the victim and their family in the following way. a) to differentiate toxin ingestion from natural illness, where specific interventions are needed such as - toxicological investigation, identification, antidote administration and specific management which in some aspects different from the standard treatment of a medical illness b) Serial deaths of family members initially considered as natural illness and later suspected as intrafamilial conflict leading to homicidal poisoning happened in certain situation. c) Georgi Markov (01.03.1929 - 11.09.1978) was a Bulgarian dissident writer who was assassinated because of international conflicts between two ruling regimes. Though he was initially admitted with a diagnosis of septic shock, medicolegal investigations and autopsy proved the diagnosis as poisoning by using a micro-engineered pellet containing ricin, (1.70 mms) fired into his leg from an umbrella (Fig.6).[20] Making AR entry will protect the clinician and hence AR entry and police intimation are mandatory. If a patient with toxin ingestion dies while on treatment or brought dead with suspicion of poison ingestion, medical practitioner should intimate the police authorities and not hand over the body to them before police scrutiny.[21]

9. Role of toxicology screen

Toxicology screening to identify unknown poisons is not widely employed in our country. Toxicology screening needed in diagnostic uncertainties, coma of unknown etiology, suspected child abuse or when decision on antidote depends upon the rapid identification of the toxic agent. Heparinized blood, urine (100 mL, first voided), vomitus and gastric lavage contents may be stored for subsequent analysis. Toxicology screening of body fluids is not considered cost-effective and it is also time consuming and in almost all instances the type of poisoning can be suspected based on symptoms and signs. [22]

Urine screening test: Multiple studies in the adult and pediatric populations confirm that the results of a urine drug screen (UDS) rarely change clinical management. Advanced laboratory methods such as gas chromatography/ mass spectrometry (GC/MS) are considered as the "gold standard" in confirming the results of a 'broad spectrum' urine drug screening immunoassay. In a retrospective study of over 300 substances in 160 randomly chosen cases, only three cases were positive for amphetamines wherein overall clinical management was altered based on the results of the rapid comprehensive urine drug screen (RCUDS).[23]

10. Helpful resources in emergency (poison control centres)

Since medicolegal emergencies are less frequent compared to managing medical emergencies, the clinician's expertise in handling toxicological emergencies may be limited. Hence, it is meaningful to seek help from poison information centres. Once the nature of toxin is recognized, then it gets easier to manage with literature search and every pediatrician can document his experience to make it a good supportive reference for the benefit of others.

11. Prevention

Prevention is better than cure.

Practices useful in the prevention of accidental poisoning

- All medicines should be kept in a cupboard and should be locked, to make it inaccessible for kids.
- Parents should not refer to medicines as juice or candy.
- It is preferable to avoid taking medicines in front of children and take care not to leave open medical containers unattended to.
- One should not administer medicines in darkness in order to avoid giving wrong medicines.
- Clear labelling of any chemical substance sold should be made mandatory.
- Child-proof containers will go a long way in preventing poisoning with household drugs or toxic substances.

Practices useful in the prevention of accidental drug overdose

- Better to avoid drugs with higher strength preparations which are likely to end up in toxicity. Among the 26 fatal toxin exposures in pre-school children in the United States in 2001, one third of them were caused by therapeutic errors involving acetaminophen (paracetamol), aspirin, methadone, morphine and oxycodone.[24]
- Careful calculation and counterchecking with a second person is safer in drugs with narrow therapeutic margins such as aminophylline, digoxin, etc.
- Drug infusions like morphine or insulin infusion should be meticulously calculated and rate of infusion should be regulated.
- Drugs such as fentanyl with erratic absorption and serious side effects should be carefully handled and monitored e.g Fentanyl dermal patch.
- Care taker should keep all potential poisons out of the reach for children - preferably locked storage.
- Food storage containers or water bottles should not be used to store poisonous substances.

Points to Remember

- ***In preschool children, toxin exposure is more likely to be accidental and mainly household substances.***
- ***In children, toxin exposure may be occult and unwitnessed, hence it should be considered as an important differential diagnosis in all pediatric emergencies, where cause is not obvious***
- ***In adolescents, it is mostly intentional***
- ***Resuscitation is the most important step in the management of a critically ill child with poisoning. This takes priority over identifying the toxin as well as decontamination***
- ***Toxidrome is the constellation of clinical features seen in a child with poisoning, which is more useful than toxicology screening***
- ***Activated charcoal administration is a useful decontamination procedure except in few poisonings such as hydrocarbon, iron, pesticides or corrosives***
- ***Antidotes should be stocked in every emergency department.***
- ***Poison information Centres play a great role in guiding the clinicians in managing the poisoned child and to get excellent outcome***

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CLIPPINGS

How are granulocytes for transfusion best used? The past, the present and the future.

This review presents current evidence regarding use of granulocytes for transfusion in patients with severe neutropenia. Robust randomized trial data are lacking and trials conducted so far have shown no clear benefit.

Granulocyte transfusions continue to be used in clinical practice, predominantly for treatment of refractory infection in the setting of severe neutropenia. There is biological plausibility for effectiveness in these patients with deficiencies of neutrophils, either as a consequence of disease or treatment. However, there is a chequered history of conducting and completing interventional trials to define optimal use, and many uncertainties remain regarding schedule and dose. Practice and clinical studies are severely limited by the short shelf life and viability of current products, which often restricts the timely access to granulocyte transfusions.

In the future, methods are needed to optimise donor-derived granulocyte products. Options include use of manufactured neutrophils, expanded and engineered from stem cells. Further possibilities include manipulation of neutrophils to enhance their function and/or longevity. Granulocyte transfusions contain a heterogeneous mix of cells, and there is additional interest in how these transfusions may have immunomodulatory effects, including for potential uses as adjuncts for anti-cancer effects.

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TOXICOLOGY - I

DECONTAMINATION IN POISONING

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Abstract: *Decontamination is the initial step in the management of any poisoning or toxin exposure and is considered vital. Knowledge and training in all modalities of decontamination can improve the outcome of exposed victims. Decontamination is the removal of harmful substances from the victim's body. The objective of decontamination is to ensure that the toxic component (chemical, biological, radiological) is no longer in direct contact with the victim. It can be categorized into, (1) Surface decontamination (skin, eye), (2) Gastrointestinal decontamination after ingestion of a substance. This article will focus on the importance, decision process and various methods of decontamination.*

Keywords: *Decontamination, Poisoning, Toxin exposure.*

Decontamination plays an important part in the early management of patients with toxic ingestion. The goal is to diminish the absorption of toxic substances, thereby reducing the systemic effects. Decontamination also helps to lower exposure among health care personnel during hospital treatment and transportation.

Principles of decontamination in children are similar to those for adults, but in practice it is more challenging. The anatomical variations, physiological needs and vulnerabilities of children require health care personnel to be more cautious during decontamination. Decontamination is fraught with hazards and should be done only when indicated.

Challenges in children

Understanding how children differ from adults in necessary for safe decontamination (Box 1).

Box 1. Toxin ingestion in children vs adults

- Children being non-verbal are unable to give us a reliable history, making us to completely dependent on the caregiver's version.
- Children react to unknown people or environment by becoming more anxious and inconsolable which makes the initial assessment difficult.
- The skin in children is more permeable, resulting in more absorption directly or from clothing.
- Removing clothing during decontamination to prevent further dermal exposure and immediate measures to prevent hypothermia are of paramount importance. Privacy should always be maintained while decontamination, especially for older children.
- Children tend to dehydrate faster due to toxin induced vomiting and diarrhea, as they have less body fluid reserve. Hence signs of early shock need to be assessed carefully.

To decontaminate or not?

Risk assessment should be done only after initial assessment and stabilization of the child.[1] It is described as a "distinct cognitive process through which the clinician attempts to predict the likely clinical course and potential complications for the individual patient at that particular presentation".[2]

Risk assessment features are[2]

- Identification of the substance and dose ingested
- Time since ingestion
- Present clinical status
- Toxidromes pertaining to the substance ingested

Surface decontamination (skin) should be done in all cases of suspected dermal poisoning. Treating physician and health care personnel must wear appropriate PPE during the decontamination process.

Gastrointestinal decontamination should only be done if the victim has ingested a significant toxic amount of the

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substance. The substance and dose ingested may not always be known. Patient presents either with symptoms and signs of toxicity (if ingested dose is reaching the toxic dose) or patients remain asymptomatic (dose was not sufficient enough to cause toxicity). If the history does not correspond to the victim's clinical presentation, then the risk assessment needs to be revisited.[3]

The decision to decontaminate and treat depends on initial assessment, progression of symptoms and re- evaluation. The risk assessment strategies give us clues to diagnose and manage toxic ingestions as every case scenario is distinctive. Hence the knowledge and experience of the treating physician plays an important role in decision making.

Toxidromes

Toxidromes for common poisoning in children are shown in Box 2.

General management

Initial stabilization of the patient is of prime importance before decontamination and specific management in poisoning.

Box 2. Toxidromes for common poisoning

1. Organophophorus compounds (Pesticides, insectides)

Bronchorrhea, lacrimation, bronchoconstriction, urination, bradycardia, arrhythmia, hypotension, Tachycardia, hypertension (nicotinic symptoms), GI hyperactivity, miosis, restlessness, ataxia, seizures

2. Sedatives/hypnotics: (Benzodiazepines, barbiturates)

Hypothermia, respiratory depression, bradycardia/ hypotension, CNS depression

3. Corrosives: (Caustic soda, bleach, household chemicals)

Oral ulcerations and pain, drooling of saliva, facial puffiness, dysphagia, vomiting, abdominal pain

4. Hydrocarbons: (Turpentine oil, kerosene, paint, cleaning solutions, spot remover)

Coughing/choking, wheeze, hypoxia, pulmonary edema due to chemical pneumonitis, vomiting, diarrhea, seizures, coma

5. Camphor

Seizures, restlessness, delirium, confusion, nausea, vomiting

Airway, breathing and circulation must be maintained in patients suspected to have systemic poisoning.

If airway assessment shows hypoxia, supplemental oxygen must be started. If any signs of airway compromise or apnea are present patient needs emergency intubation and mechanical ventilation.

Indications for intubation in a poisoning victim:

- Corrosive poisoning (early intubation by an experienced personnel in the presence of voice change or stridor)
- Bronchorrhea - organophosphorus poisoning
- CNS depression - opioids, barbiturates
- Seizures
- Aspiration
- Hypercarbia (CNS depressants)

Maintenance of blood pressure and tissue perfusion may require volume correction - IV fluids (10 ml/kg in shock), administration of vasopressor agents (if not responding to initial fluid therapy). After each bolus, patient should be reassessed for improvement.

Intra venous dextrose (2 to 4 mL/kg of a 25% solution for children) should be given in case of hypoglycemia.[4]

I. Surface decontamination

(1) Dermal decontamination

Various toxins can cause systemic toxicity following dermal absorption (Box 3).[5] Patients exposed to liquids, aerosols, or solids will require skin decontamination.[6] Exposure to gases or vapor does not require decontamination usually - however needs changing of clothes. Most of these dermal poisoning substances are corrosive agents capable of causing burns (even up to full thickness). When a victim is suspected to have dermal exposure, decontamination should begin immediately. The victim should disrobe with assistance and should be done safely with proper protective measures. It is appropriate to wash the victim thoroughly with water (if available decontamination shower). Importance should be given to prevent hypothermia.

(2) Ocular decontamination

Ocular exposure to a chemical in children needs timely irrigation of the affected eye with copious amount of a safe irrigating solution. Any delay in decontamination has

Box 3. Toxins - dermal absorption

Aniline dyes
Camphor
Dinitrophenol
Hydrofluoric acid
Organophosphate insecticide
Nerve agents
Nitrobenzene
Organic mercury
Phenol
Thallium

significant effect on the outcome and prognosis of the injured eye.[7] Commonly available preparation of 0.9% Normal saline having a pH ranging from 4.5 to 6 is used for ocular decontamination. Ringers Lactate solution can also be used as an alternate due to its closer to neutral pH of eye.[8] Ophthalmologic consultation is needed for all ocular exposures.

II. Gastrointestinal decontamination

Gastrointestinal decontamination (GID) is the removal of toxic substances from the GI tract to decrease absorption or to increase the elimination. Before decontamination the possible risks must be considered, as the procedure in itself can cause dangerous side effects.

GID is defined under the following components:

(1) Gastric Evacuation : Gastric lavage remains the mainstay. Syrup of ipecac, once used as an emetic is no longer recommended.

(2) Administration of adsorbent : Activated charcoal (AC).

(3) Intestinal evacuation : Whole bowel irrigation (WBI).

(4) Enhanced elimination : Multidose activated charcoal (MDAC), hemodialysis, hemoperfusion, urine alkalinisation.

1. Gastric evacuation: Gastric lavage is a method of stomach emptying that is used to decrease passage of toxic substances to the intestines thereby preventing further absorption.[9] Gastric lavage was first described in 1822 mainly for opium poisoning. In late 90s gastric lavage was the method of choice for all types of poisoning. Further studies revealed the harmful effects of lavage which introduced the changes in its usage. Lavage should be used only if there is significant toxic ingestion due to significant evidence of side effects like aspiration, laryngospasm and esophageal perforation caused by the procedure. Lavage is found useful when performed within 1-2 hours of ingestion.[10] There is no published evidence demonstrating that gastric lavage changes patient outcome. Routine use of lavage must not be incorporated into patient care, administration of activated charcoal and supportive care have shown better outcome.[11]

Indications

- Significant level of toxic ingestion
- When benefits outweigh the risks

Contraindications[12]

- Unprotected airway
- Caustic ingestion (due to risk of exacerbating any esophageal or gastric injury)
- Hydrocarbon ingestion (due to higher risk of aspiration)
- Patients at risk of gastrointestinal hemorrhage or perforation (recent surgery, coagulopathy)

Procedure

Gastric lavage was performed using Ewald tube (large lumen soft red rubber tube) since 18th century. Its use is obsolete now, as studies revealed its deleterious effects are more when compared to nasogastric tubes (NG).

NG tube or Ryle's tube are available in different sizes according to age group. Available from size 8-20, made of nontoxic, nonirritant polyvinyl chloride (PVC) catheter.

Level of consciousness and gag reflex should be assessed before insertion of NG tube as airway management remains the priority. During lavage, the patient should lie in the left lateral decubitus position and in Trendelenburg position to reduce risk the aspiration. The oral route is preferred for intubated patients, nasal route for conscious victims. Size is calculated by adding 16 to patient's age in years and dividing it by 2 (Table I).[12]

Table I. Age appropriate size of the NG tube

Age group	Size of NG tube (Fr)
Neonate	6-8
1-5 years	8-10
>5 years	8-14

Size = (16+patient age in years) / 2.

The approximate length of NG tube to be inserted is calculated by measuring the distance from mouth to mid-epigastrium, allowing for the natural curve of the oropharynx.

After insertion, tube placement is confirmed by withdrawal of gastric contents. It can also be reconfirmed by auscultation over epigastrium after insufflation with 10-20 cc of air. NG tube aspirate can be sent for toxicological analysis along with blood and urine samples. Lavage can be done by repetitive instillation (10-20 mL/kg) of NS (maximum 300 mL) and aspiration of small aliquots. Lavage is continued until the aspirated solution is clear of any particulate matter.

Complications

- Aspiration pneumonia
- Esophageal or gastric perforation
- Laryngospasm, hypoxia
- May propel the toxins that were to be removed past the pylorus, potentially facilitating systemic absorption and decreasing the effectiveness of activated charcoal[13]
- Increases the vagal tone and precipitates bradyarrhythmias.
- Water intoxication, hypothermia.

2. Administration of adsorbent: Activated charcoal (AC) a fine, black, odorless and tasteless powder, has been used an effective adsorbent of many substances. It is pharmacologically inert and non- absorbable substance. AC prevents absorption of the toxic substance in the gastrointestinal tract, thereby decreasing its systemic absorption. Once it was referred to as 'the universal antidote', but further studies explaining its complications have limited it usage. Administration of AC is benefited when given within 1 hour of ingestion, while the toxin still remains in the stomach and the recommended dose is given in Table II.[14]

Administration

Available as powder form that can be mixed with water to form a slurry. It can be given through NG tube if present. Since it is poorly palatable, flavoring with juice, chocolate milk, or ice cream can also be done to improve the compliance but reduces its efficacy.

Certain toxins do not bind to charcoal; hence AC is not beneficial in the following toxins:

Table II. Recommended dose of activated charcoal

Age	Dose
Up to 1 year	10-25 g or 0.5-1.0 g/kg
1-12 years	25-50 g or 0.5-1.0 g/kg
Adolescents and adults	25-100 gm

- Corrosives
- Cyanide
- Ethanol/methanol/glycols
- Eucalyptus and essential oils
- Fluoride
- Hydrocarbons
- Metals - including lithium, iron compounds, potassium, lead
- Mineral acids - Boric acid

Contraindications

- Depressed airway reflexes, late presentation (more than 2 hours)
- Need for endoscopy - AC is likely to impair visibility during endoscopy
- Presence of intestinal obstruction (absolute contraindication) or concern for decreased peristalsis (relative contraindication)

Complications

- Emesis
- Aspiration
- Intestinal obstruction - bezoar formation
- Intestinal perforation

3. Intestinal Evacuation: Whole Bowel Irrigation involves ingestion of large amounts of Polyethylene Glycol (PEG) solution orally or through NG tube. It helps in removal of unabsorbed toxins from GI tract by causing its rectal expulsion. WBI is mainly recommended for substances not bound to AC[15] and toxic ingestions of sustained-release or enteric-coated drugs and who present more than 2 hours after drug ingestion. WBI is continued until the rectal effluent is clear. Radiographic studies may be useful in some circumstances (iron ingestion) to confirm the absence of residual toxin. The recommended dose of PEG for WBI is given in Table III.

Table III. Recommended dose of WBI

Age	Dose
9 months to 6 years	500 mL/hr
6 to 12 years	1000 mL/hr
Adolescents and adults	1500 to 2000 mL/hr

Indications

- Iron ingestion >60 milligrams/kg with opacities on abdomen X-ray.
- Life-threatening ingestions of diltiazem, verapamil, lithium, lead.
- Slow-release potassium ingestion.
- Symptomatic arsenic ingestion.

Contraindications

Ileus, bowel obstruction or intestinal perforation, clinically significant GI hemorrhage, hemodynamic instability and intractable emesis.

Complications

- Nausea, vomiting, cramping and bloating
- Patients with vomiting and an unprotected airway are at risk of aspiration
- WBI may interfere with AC when administered concurrently

(4) Multidose activated charcoal (MDAC)

MDAC is also called as 'gastrointestinal dialysis' is used in toxins that undergo extensive enterohepatic / enteroenteric circulation. It comprises of giving repetitive doses of AC every 1 to 2 hours.

Dose

Initial dose: 1 gm/kg

Repeat dose: 0.5 gm/kg every 2 hours

Indications for MDAC

Poisoning with life threatening amounts of following substances: Carbamazepine, dapsone, phenobarbital, quinine, theophylline, digoxin, salicylates

Likely to be effective in the following: Anticholinergics, sodium valproate, thyroid hormone

Table IV. Enhanced elimination

Treatment	Substance
Hemodialysis	Multidose activated charcoal Iron Diltiazem Verapamil Lithium Lead Slow release Potassium Arsenic Lithium Ethylene glycol Methanol salicylate Theophylline Sodium valproate (in severe overdose)
Hemoperfusion	Theophylline Phenobarbital
Urinary alkalization	Phenobarbital Salicylates

Urinary alkalization

It is mostly used in case of significant salicylate poisoning.[16] For moderate to severe salicylate poisoning (serum pH less than 7.4 and urine pH less than 6.0), urine alkalinisation should be initiated early with bicarbonate therapy. A slow bolus of bicarbonate-dextrose-potassium solution is started at the rate of 1-2 mEq/kg for an hour.[17] This is prepared by taking 500 ml of 5% dextrose solution and adding 40 mEq of sodium bicarbonate (8.4%). To prevent hypokalemia, 10-20 mEq of potassium (7.45%) is added.[17] Further dose is titrated based on serum and urine pH (Table IV).

Complications

- Alkalosis
- Vomiting, diarrhea
- Abdominal discomfort
- Gastrointestinal bleeding
- Hyperkalemia

Conclusion

The incidence of poisoning in children is on the rise. Obtaining a reliable history with prompt identification of toxidromes plays a vital role in the decision making process. Initial stabilization with airway management when needed, taken precedence over decontamination. Decision to decontaminate and the method used depend on time of presentation, toxin ingested and symptoms on arrival. It is important to look out for the possible complications and take the necessary precautions.

Points to Remember

- ***Initial patient stabilization and airway management is of prime importance.***
- ***Early and timely decontamination improves patient outcome.***
- ***Reliable history and toxidrome identification helps in decision making process.***
- ***Method of decontamination depends on risk assessment strategies.***
- ***Possible side effects of decontamination process must be kept in mind.***

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CLIPPINGS

COVID UPDATE

In India, from 3 January 2020 to 4:36pm , 4 November 2022, there have been 44,658,365 confirmed cases of COVID-19 with 530,479 deaths, reported to WHO. As of 30 October 2022, a total of 2,196,382,882 vaccine doses have been administered.

TOXICOLOGY - I

COMMON DRUG POISONING IN CHILDREN

***Jayakrishnan MP**

Abstract: *Poisoning due to drug ingestion is becoming more frequent because of wide availability. It is an emergency seen at different levels of practice: office practice, hospital practice and intensive care units. No other area in medicine is so demanding with respect to precision, urgency and practicality. Sudden development of the problem and rapid course of events complicate the decision making. Lack of information about poisoning often delays the diagnosis in an emergency. The drugs used by adults must be kept safely out of reach of children in closed containers as these drugs are some of the common causes of poisoning. Antidepressants, selective serotonin reuptake inhibitors, Tricyclic antidepressants are some of the causes for poisoning and older generation sedating antihistamines can produce substantial toxicity due to anticholinergic and sedative effects. Acetaminophen is the most commonly used antipyretic drug. When significant toxic dose is ingested, N-acetylcysteine is a specific antidote. Poisoning due to sedative hypnotics can result in cardiorespiratory depression. Good supportive care can save most of the patients. Antipsychotics can result in toxicity due to overdose, idiosyncrasy or drug interactions. Ingestion of cardiovascular drugs like antiarrhythmics and antihypertensives are relatively less common but the toxcicity can be associated with significant morbidity and mortality. Iron ingestion is becoming more common due to increasing use of prenatal iron. Vomiting is the most prominent clinical feature of iron toxicity.*

Keywords: *Antidepressants, Selective serotonin reuptake inhibitors, Tricyclic antidepressants, Antihistamines, Calcium channel blockers, Antihypertensives, Antipsychotics, Dapsone, Iron, Isoniazid, Oral hypoglycemic agents, Paracetamol, Thyroxine.*

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Poisoning is a frequent reason for emergency room visit in children and should be considered as a differential diagnosis whenever there is a diagnostic dilemma. Over the last few years drugs are increasingly involved due to accidental ingestion in preschool children or intentional use in adolescents or due to therapeutic over dosage.[1] Some of the common drugs involved in poisoning are discussed in this review.

Antidepressants

The commonly used antidepressants are selective serotonin reuptake inhibitors (SSRI - fluoxetine, sertraline, paroxetine, citalopram). Tricyclic antidepressants (TCAs - amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, imipramine) are less commonly used for treatment of depression, but they are used for other indications like enuresis and ADHD.

SSRI

Generally, SSRI toxicity is not associated with serious toxicity in accidental ingestions. Doses up to 30 times the daily recommended dose are not associated with significant symptoms.[2] Clinical features include sedation, tachycardia, prolongation of QT in ECG and serotonin syndrome (altered mental status, seizures, autonomic instability, fever, hyperreflexia, tremors and clonus). Citalopram is the most toxic among them.

Evaluation: ECG should be taken to look for QRS widening or QT prolongation, serial ECGs monitoring is needed if abnormal. If serotonin syndrome suspected, creatine kinase, liver and renal function tests are to be done.

Treatment: ABCs need to be taken care of during treatment followed by activated charcoal for decontamination. Seizures are treated with benzodiazepine. If QTc is prolonged, watch for torsades de pointes and magnesium sulphate infusion is used if torsades de pointes observed. Bicarbonate infusion is used, if QRS widening is present.

TCA

TCA in doses exceeding 10-20 mg/kg can cause significant toxicity in children.[3] Cardiac arrhythmias and CNS symptoms like lethargy, coma and seizures are the

predominant features. Symptoms start within 1-2 hours of ingestion and serious toxicity manifests within 6 hours. Anticholinergic toxidrome with delirium, mydriasis, dry mucous membranes, tachycardia, hyperthermia and urinary retention can occur. Sinus tachycardia, widening of QRS complex, ventricular ectopics and arrhythmias can occur. ECG showing QRS duration >100 ms and R wave in aVR ≥3 mm are predictors of serious toxicity.

Treatment: Initial management includes addressing the ABCs and activated charcoal for decontamination. Frequent ECGs in the first 6 hours is helpful. Sodium bicarbonate infusion is the antidote and is started if the QRS duration is ≥110 ms or if there is ventricular arrhythmias or hypotension. Multiple boluses of sodium bicarbonate 1-2 mEq/L are infused to keep the QRS <110 ms. Seizures are treated with benzodiazepines. Phenytoin is generally contraindicated in seizures caused by toxins.

Antihistamines

Antihistamines of the H1 type are commonly prescribed in children for allergic disorders. Based on the sedative effect, there are two types of antihistamines, which are sedating and lesser sedating.

Examples of sedating type: Cyproheptadine, pheniramine, dexchlorpheniramine, promethazine, diphenhydramine, dimenhydrinate, doxylamine, trimeprazine and brompheniramine. Apart from H1 receptor blockade, they also have alpha adrenergic, anticholinergic and serotonergic effects.

Clinical features of poisoning of sedating antihistamines include CNS depression, confusion, delirium or seizures. In overdose, they can also affect cardiac channels resulting in prolongation of QT interval and ventricular arrhythmias. Anticholinergic toxicity features include agitation, hallucinations, fixed and dilated pupils, tachycardia and hyperthermia.

Less sedating antihistamines like cetirizine, loratadine, desloratadine and fexofenadine penetrate the CNS less. Overdose results in dizziness, lethargy, agitation and tachycardia. Anticholinergic and cardiac toxicity can occur with high doses,[4] but less frequently compared with sedating antihistamines.

For all antihistamines: Onset of symptoms is expected between 30 minutes and 2 hours of ingestion. Duration of action: 3 hours to more than 24 hours. All children consumed antihistamine need to be carefully monitored. It can cause serious toxicity and death particularly in those presenting with respiratory distress, seizures or when the dose consumed is more than 3-5 times the recommended dose. In addition to clinical monitoring, repeated ECG recording is important, initially and repeated 4-6 hourly until the child recovers.

Treatment: Initial management includes managing the ABCs and decontamination with activated charcoal.

Repeated monitoring is needed with ECG 6 hourly to look for QT prolongation. Management is mainly supportive as there is no specific antidote. Seizures, dystonia and severe agitation should be treated with benzodiazepines. Children can be discharged after 24 hours monitoring, if they remain conscious and there are no ECG changes.

Antihypertensives

Beta blockers

Beta blocker overdose results in decreased cardiac contractility causing hypotension, bradycardia, heart block, hypoglycemia and bronchospasm in predisposed children. Lipophilic agents like propranolol can cause CNS effects like altered sensorium, coma and seizures. QRS widening and ventricular arrhythmias also can occur. Clinical features manifest within 6 hours of ingestion except with slow release drugs or sotalol.[5]

Evaluation: Requires ECG and hemodynamic monitoring, blood glucose, calcium, electrolytes.

- **Treatment**: ABCs should be stabilized and supportive therapy should be instituted.
- Decontamination should be done with activated charcoal and whole bowel irrigation is continued until the rectal effluent is clear. Further elimination techniques such as multiple doses activated charcoal, hemoperfusion or hemodialysis may be needed in severe cases.
- Supportive management includes benzodiazepines for seizure control, atropine for bradycardia, sodium bicarbonate for QRS widening, magnesium sulfate for QTc prolongation.
- Glucagon is considered as a useful drug, though there are no studies. It should be given after antiemetics as glucagon may induce vomiting and one should watch for side effects of glucagon such as hypocalcemia and hyperglycemia.
- Severe poisoning and refractory cases may warrant high-dose insulin, euglycemia (HIE) treatment.

HIE treatment is a simple way to augment cardiac contractility and does not need invasive monitoring. It can cause profound hypokalemia and hypoglycemia which can worsen the cardiotoxicity. Potassium and glucose should, therefore, be checked before initiation of high-dose insulin, euglycemia. In general, 1 U/kg of regular insulin bolus along with 0.5 g/kg dextrose intravenously (IV) is administered. Intravenous dextrose bolus should not be given if the glucose level is more than 400 mg/dL. Glucose should be monitored every 30 mins initially to maintain strict glycemic control (glucose 100 to 200 mg/dL) by starting 10% dextrose infusion and IV dextrose boluses, as needed.

- Supportive treatment with vasoactive agents may be needed, as inotropic effect of HIE treatment may be delayed up to 15 min to 60 min. Phosphodiesterase such as inamrinone and milrinone increase the cAMP and may prove beneficial.

Calcium channel blocker (CCB)

CCB targets the L-type voltage-gated calcium channels, leading to significant bradycardia, hypotension, conduction disturbances and escape rhythms. Sometimes nifedipine causes hypotension and reflex tachycardia. Examples of CCB include verapamil, diltiazem and dihydropyridines (e.g. amlodipine, nifedipine). Depending on the type of drug, decreased cardiac contractility and negative chronotropy may be associated with decreased peripheral vascular resistance. Hyperglycemia can occur in severe CCB poisoning and this is a differentiating feature from poisoning due to beta blockers.[6] Onset of symptoms will occur soon after ingestion, except with slow release preparations.

- **Treatment** : ABCs should be stabilized and supportive therapy should be started. Activated charcoal and WBI are used in slow release preparations.
- Specific therapy with calcium infusion either as calcium gluconate or chloride. Increased extracellular concentration of calcium will promote calcium influx via unblocked L type calcium channels, but responses are variable, suboptimal and transient.
- IV fluid therapy should be carefully administered with bedside monitoring.
- Glucagon, epinephrine and amrinone can be used as supportive management whenever needed.
- High dose insulin-glucose infusion. (This therapy is discussed in detail in another article in the same issue).
- Lipid emulsion therapy may be useful in lipid soluble CCB poisoning like verapamil and diltiazem. Lipid emulsion infusion can sequester intensely lipophilic drugs such as verapamil and diltiazem and thus reduce their volume of distribution. Treatment includes initial bolus of 1.5 ml/kg of 20% lipid emulsion followed by 0.25 to 0.5 ml/kg/min over 30 minute. Anticipate adverse effects of therapy which include acute pancreatitis, ARDS, and fat overload syndrome inducing hepatosplenomegaly, seizures, fat embolism and coagulopathy.

Children with refractory CCB poisoning should be shifted to cardiac ICU centre early, so that advanced hemodynamic interventions like transvenous pacers, intra-aortic balloon pump, or extracorporeal membrane oxygenation can be used when necessary.

Clonidine

Clonidine is a centrally acting alpha-2 agonist. This action results in decreased sympathetic outflow resulting in lethargy, miosis, bradycardia, hypotension and apnea. Early after ingestion, hypertension may be present.

No definite toxic dose is established. Even a single tablet can cause toxicity in children.[7] Toxic effects generally occur within 30 minutes to 4 hours after overdose and usually resolve within 24 to 72 hours.

Treatment: Minimal role for GI decontamination due to small quantity itself causing toxicity and rapid onset of symptoms. Naloxone in high doses may be effective in respiratory suppression. Bradycardia is treated with atropine and other supportive measures.

Antipsychotics

Antipsychotics are classified as typical and atypical. Typical antipsychotics have predominant D2 receptor antagonism and examples include haloperidol, droperidol, thioridazine and chlorpromazine. Atypical agents have less D2 antagonism and include drugs like clozapine, quetiapine and risperidone.

Toxicity with both groups can result in sedation, tachycardia and QT prolongation.[8] Phenothiazines like thioridazine can cause QRS widening.

Treatment: Supportive care is the mainstay including stabilizing ABCs. Seizures and dystonia are managed with benzodiazepines. Maintenance of normal potassium, magnesium and calcium are important in QT prolongation. Bradycardia may require atropine or pacing.

Dapsone

Dapsone is a commonly used drug in the treatment of dermatologic conditions like Hansen's disease, acne vulgaris and immune thrombocytopenia purpura. Peak level after oral ingestion is 2-6 hours and in toxic ingestion half-life may be 2-4 days.

In acute poisoning, dapsone induces methemoglobinemia and hemolytic anemia.[9] Methemoglobin has iron molecule in the ferric form, which lacks the ability to bind oxygen. Whatever ferrous form that remains will have an increased affinity for oxygen and this will result in shift of oxygen dissociation curve to left. This will further reduce the oxygen delivery to tissues.

Initial symptoms of poisoning include lethargy, vomiting, headache, breathlessness and cyanosis. This can progress to irritability, hypotonia, ataxia, extrapyramidal symptoms, seizures and coma. The patient may present with central cyanosis and the pulse oximetry reading typically low, in the eighties, with no improvement on administering oxygen. The PaO_2 is normal, when the pulse oximeter reading shows a low value. Clinical cyanosis, no improvement after O2 administration, pulse ox reading showing SpO2 hovering around 75-80%, but normal arterial saturation in ABG (because SaO2 is calculated from PaO2 which is normal here) should raise the suspicion of methemoglobin. The blood is chocolate brown in colour and if dropped on a piece of blotting paper, it will remain brown as it dries. In contrast, normal deoxygenated blood on exposure to air will absorb oxygen and turn red.

Co-oximeter measurement of methemoglobin can quantitate the percentage of methemoglobin. Cyanosis manifests at levels around 5-10%. At 20-30%, moderate symptoms like nausea, vomiting, fatigue, breathlessness, tachycardia, anxiety, dizziness and confusion occur. Levels more than 40% are associated with severe presentation like seizures, coma, arrhythmia and death.

Treatment: Gastric lavage should be done if the patient presents within 1 hour of ingestion. Activated charcoal can be administered. Multiple dose activated charcoal (0.5 g/kg 4-6 hourly for 4 doses) may be effective in severe poisoning as there is enterohepatic recirculation of dapsone which can result in recurrence of symptoms. Whole bowel irrigation may be tried in severe cases.[10]

Methylene blue, IV in the dose 1-2 mg/kg over 5 minutes is the antidote of choice in severe cases. This can be repeated every 2-4 hours to a maximum of 7 mg/kg. One should estimate serum G6PD levels, before starting methylene blue as it can lead to hemolysis in the presence of G6PD deficiency. In toxin ingestion causing methemoglobinemia, IV ascorbic acid is not found to be useful.

Iron salt poisoning

Iron preparations

Elemental iron in different preparations are ferrous gluconate 12 %, ferrous sulphate 20% and ferrous fumarate 33%.[11] Carbonyl iron and iron polysaccharide complex preparations have not been reported to cause serious toxicity.

Toxic dose: Ingestion of <20 mg/kg is usually asymptomatic. Ingestion of 20-60 mg/kg has low potential to cause toxicity. Ingestion of > 60 mg/kg can cause serious toxicity.

Table I. Clinical features and course

Phase	Organ system involved	Onset of symptoms	Clinical and lab features
1	Gastrointestinal	0-6 hours	Vomiting/hematemesis Loose stools, abdominal pain, irritability, lethargy
2	Apparent stabilization (Severe toxicity: this phase is absent; direct progression to phase 3)	6-48 hours	Symptoms subside, metabolic acidosis in those with severe toxicity
3	Mitochondrial toxicity	12-48 hours	Shock, acidosis, coma, seizures, hyper/hypoglycemia, coagulopathy, acute tubular necrosis
4	Hepatic necrosis	12-96 hours	Jaundice, coagulopathy, encephalopathy
5	Gastric scarring	2-4 weeks	GI scarring

The clinical course of poisoning can evolve over a period of time, described in 5 phases (Table I).[11]

Children who do not have any of the phase 1 symptoms can be safely assumed to have no serious toxicity.

Evaluation: Symptoms are generally manifest soon after ingestion and if there are no symptoms in the first 6 hours (except with enteric coated tablets) it is unlikely that significant ingestion has taken place.

Laboratory evaluation: Hyperglycemia or hypoglycemia may be present. Serum electrolytes, renal and hepatic function, prothrombin time (can be prolonged even without liver failure) are other investigations which may be useful.

Serum iron, regular iron formulation: Peak level: 4-6 hrs. post ingestion. Values obtained after 4-6 hours may underestimate toxicity. Enteric coated tablets: 8 hours. Values more than 500 mcg/dL (90mmol/L): serious toxicity.

Abdominal X-ray for visible tablets

Blood gas: Metabolic acidosis predicts serious toxicity

Leucocytosis may suggest significant toxicity

Treatment: Supportive care. Stabilizing the ABCs is the priority over other steps.

Decontamination: Gastric lavage may be useful if iron tablets are visible in stomach in the X-ray. Ideally lavage should be done in 1-2 hours after ingestion, although it may be effective later also if iron is visible in the X-ray. Aspiration, oesophageal or gastric perforation are potential complications.

Activated charcoal administration is not useful.

Whole bowel irrigation (WBI) with nasogastric colonic lavage solution (PEGLEC) 10-20 ml/kg/hr until rectal effluent is clear. Contraindicated in bowel obstruction.WBI is indicated if abdominal X-ray reveals tablets and estimated intake is >60 mg/kg. Rarely, iron tablets adherent in the stomach wall may have to be removed by endoscopy or gastrotomy.

Antidote: Deferoxamine

Indications: Clinical toxicity, acidosis, coma, seizures. Iron visible on abdominal X-ray. Serum iron concentration is >500mcg/dL (90mmol/L).

Concentration 60- 90 mmol/L or symptomatic (persistent vomiting or diarrhea, abdominal pain, hematemesis).

Significant symptoms like altered consciousness, shock, acidosis or worsening symptoms. A fall in serum bicarbonate is a surrogate marker of systemic poisoning.

Dose: 10 mg/kg/hour initially and increase to 15mg/kg/hr IV in 1-2 hours. If oliguria or anuria develops hemo or peritoneal dialysis may become necessary.

End point of chelation therapy: Significant poisoning usually requires therapy for 12-16 hours. Treatment should be continued until the child is asymptomatic, acidosis is resolved, serum iron is <60 mmol/L and urine colour has returned to normal. Generally treatment is not required for more than 24 hours. Hypotension can occur during the initial part of deferoxamine infusion. ARDS has been reported following prolonged infusion of deferoxamine.

Isoniazid (INH)

Isoniazid, is a potential source of toxicity in children. Acute toxicity manifests as altered mental status or seizures which can progress to status epilepticus associated with high anion gap metabolic acidosis and hyperglycemia. Seizures most commonly manifests within 30 minutes of ingestion, but the onset can be delayed up to 2 hours. Dose more than 20mg/kg can result in toxicity. Clinical features are primarily related to CNS toxicity, with tachycardia, tachypnea and fever as associated features. The possibility of ingestion is suggested by history of anti-tuberculosis treatment in the child or any other family member. Pink discoloration of urine due to rifampicin, which is marketed as a combination with INH, is a clue to INH poisoning in a child with unexplained CNS symptoms.

Patients requiring assessment: Ingestion of more than 20 mg/kg of isoniazid, ingestion of unknown quantity, intentional intake and symptomatic children.

Children with no features of toxicity for 6 hours after ingestion are unlikely to develop serious symptoms.

Treatment: Control of seizures, airway stabilization, respiratory support and shock correction are priority over decontamination.

GI decontamination: There is limited role for gastric lavage and activated charcoal. INH is rapidly absorbed from stomach and patients become symptomatic with CNS involvement usually within 30 minutes of ingestion. As there is a chance of aspiration of stomach contents, gastric lavage and activated charcoal are indicated only in patients who present within 1-2 hours of ingestion.

Control of seizures: Intravenous benzodiazepine like lorazepam and pyridoxine are used to control seizures. Lorazepam is given in the dose of 0.05 to 0.1 mg/kg IV; doses may be repeated every five minutes up to 10 mg total over 20 minutes. Pyridoxine[12] is given in the dose of 70 mg/kg (maximum dose 5g) with repeat doses if there is

Table II. Stages of paracetamol toxicity

Stage	Time after ingestion	Characteristics
1	30 min - 24 hours	Nonspecific symptoms: Anorexia, nausea, vomiting, malaise Lab tests normal except paracetamol levels
2	24 - 48 hours	Resolution of earlier symptoms; right upper quadrant abdominal pain and tenderness; elevated liver enzymes (aspartate > alanine), increased INR
3	3 - 5 days	Peak enzyme elevations; liver failure, multi organ-system failure, death or recovery begins Liver enzymes can be very high with values in thousands IU/L
4	4 days-2 weeks	Resolution of liver function abnormalities

persistence of seizures. In general serious toxicity occurs if >70 mg/kg and the antidote pyridoxin is given weight by weight, hence the pyridoxin dose is 70 mg/kg. Though intravenous preparation is ideal, when not available, intramuscular and oral pyridoxin crushed and given through NG tube can bridge the gap of dose. Oral and IM pyridoxin are equally effective and life saving. Phenytoin is not only effective in controlling seizures, but as a principle not preferred in toxin induced seizures. Phenobarbitone 20 mg/kg may be tried in refractory seizures. Other supportive management includes ventilatory support and bicarbonate to correct acidosis.

Oral hypoglycemic agents

Sulphonyl ureas, the most common drugs used in type 2 diabetes, can cause hypoglycemia following ingestion. Can cause prolonged and severe hypoglycemia after poisoning. In toddlers, ingestion of a single sulfonylurea tablet can lead to significant toxicity.[13] Hypoglycemia develops within 6 hours of ingestion but can be delayed up to 16-18 hours. Severe hypoglycemia can develop after overnight fasting in these children. Metformin overdose can result in lactic acidosis.

Children requiring assessment: All children with deliberate self-poisoning or significant accidental ingestion, any symptomatic child and acute ingestion of unknown quantity needs repeated assessment.

Treatment: Symptomatic hypoglycemia is treated with IV glucose. Frequent monitoring of glucose level is important and if 2 or more glucose bolus is required, octreotide should be started in the dose of 1 mcg/kg IV or 1-2 mcg/kg s/c every 8 hours. In refractory hypoglycemia the initial bolus of octreotide is followed by a continuous infusion of 1 mcg/kg/hr (maximum 25mcg). The infusion should not be ceased during the time of night time fasting. Patients who require IV glucose and/or octreotide should be monitored until there is euglycemia for at least 8 hours when off all therapy.

Paracetamol

Paracetamol overdose is a very common indication for emergency room visit in children. Overdose results in hepatotoxicity. Even therapeutic dosing has been associated with toxicity in certain conditions like malnutrition, starvation and post-operative state.[14]

A small portion of the amount of ingested paracetamol is metabolised by the hepatic cytochrome P450 enzyme CYP2E1 to *N* -acetyl-*p* -benzoquinone-imine (NAPQI). NAPQI produced after ingestion of nontoxic doses of paracetamol is immediately detoxified by glutathione. But in poisoning, glutathione stores are depleted and the excess free NAPQI causes hepatocellular necrosis.

Patients requiring assessment : Acute ingestion of >150 mg/kg, ingestion of unknown quantity, repeated supra therapeutic dosing > 90mg/kg/day on consecutive days, deliberate self-poisoning and symptomatic child.

Clinical course: Four stages of toxicity have been described, based on clinical and laboratory evaluation (Table II).

Management

Laboratory evaluation

Serum level of paracetamol, liver, renal function tests, prothrombin time with INR. SGOT and INR are the earliest and most sensitive tests in paracetamol liver toxicity.

Management principles involve GI decontamination with activated charcoal and administration of N-Acetyl cysteine (NAC). NAC is most effective if administered within the first 8-24 hours of ingestion.

Activated charcoal : 1g/kg (maximum 50g) for patients who present within 4 hours of ingestion.

NAC: If paracetamol level is not available, NAC can be started if the history is suggestive of acute ingestion >150 mg/kg, ingestion of unknown quantity, repeated supra therapeutic dosing > 90 mg/kg/day on consecutive days or in cases of deliberate self-poisoning. In symptomatic children with suspected poisoning also NAC can be started. Malnutrition, acute febrile illness and chronic use of CYP450 enzyme inducing drugs like rifampicin and isoniazid are associated with increased risk of hepatotoxicity. There are no definite guidelines regarding indication to start NAC with a lower amount of paracetamol ingestion in such cases. For single acute ingestions within 24 hours of ingestion, the Rumack-Matthew nomogram can be used by plotting the paracetamol level and start treatment with NAC if the value is above the treatment line (lower line).

NAC can be given either by oral or intravenous (IV) route, both having equal efficacy. IV infusion is indicated if there is intolerance to oral route, intestinal obstruction, persistent vomiting, GI bleed, altered mental status or liver failure.

Oral route: 140 mg/kg loading dose followed by 17 doses of 70 mg/kg every 4 hours.

IV route: Diluted in 5% dextrose.150 mg/kg over 1 hour; 50mg/kg over next 4 hours, 100 mg/kg over next 16 hours

Paracetamol level (if available) and SGOT concentration should be measured at completion of NAC course. NAC should be continued if SGOT is more than normal or paracetamol level is > 10 μg/ml.

King's college criteria for liver transplantation after paracetamol overdose is given below.

Single criterion: Arterial pH <7.3 after achieving hemodynamic stability or all the following 3 criteria: PT> 100seconds, creatinine >3.3 mg/dL and grade 3 or 4 hepatic encephalopathy.

Thyroxine

L-thyroxine ingestion is generally not associated with symptoms in children, unless the dose ingested is more than 3 mg. Clinical features include nervousness, insomnia, mild tremor, fever, hypertension and loose stools. Massive overdose can result in severe life threatening features like cardiac arrhythmias, seizures and respiratory failure. Symptom onset may be delayed by 6 hours-11 days, as L-thyroxine has to be converted to free T3 for symptoms to manifest. Symptom onset is within the first 24 hours when preparations containing T3 alone are taken.

Children requiring assessment: Ingestion of more than 3 mg L-thyroxine, all children with deliberate self-poisoning or significant accidental ingestion, any symptomatic child and acute ingestion of unknown quantity.

Treatment : GI decontamination with activated charcoal may be useful. Asymptomatic children can then be followed up closely at home for development of symptoms. For tachycardia, tremor and diahoresis propranolol 2 mg/kg/day is effective. In massive overdose, cholestyramine 240 mg/kg/day to reduce absorption of L-thyroxine can be tried. Antithyroid drugs like methimazole or propyl thiouracil are effective in large overdose. In life threatening situations plasmapheresis is reported to be useful.[15]

Points to Remember

- ***Taking care of ABC , activated charcoal ,monitoring with serial ECGs, biochemical investigations and appropriate management are useful in SSRI, TCA, antihistamine and antihypertensive poisoning.***
- ***Dapsone induces methemoglobinemia and hemolytic anemia treated with gastric lavage, multiple AC and methylene blue.***
- ***Ingestion of > 60mg/kg of elemental iron is toxic and treatment includes WBI and deferoxamine.***
- ***Ingestion of more than 20 mg/kg of INH is toxic and treated by control of seizures with benzodiazepine, pyridoxine (1 gm/gram of INH) and phenobarbitone in refractory seizures.***
- ***N- acetylcysteine is indicated in toxic dose (> 150 mg/kg) of acetaminophen ingestion and is effective if given witin 24 hours.***
- ***Advanced elimination techniques, hemodynamic and cardiac support measures like pacing, transplant and bridge therapies are to be considered when available.***

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CLIPPINGS

The role of diazepam in the treatment of nerve agent poisoning

The main site of action of diazepam is at the GABA(A) receptor, although it has been suggested that some of the potentially beneficial actions of diazepam in nerve agent (eg.sarin, soman,tabun, VX) poisoning are mediated through other means. Convulsions may have long-term sequelae in the central nervous system, because of damage by anoxia and/or excitotoxicity.

Studies show that diazepam is an efficacious anticonvulsant in nerve agent poisoning. There is considerable experimental evidence to support the hypothesis that diazepam (and other anticonvulsants) may prevent structural damage to the central nervous system as evidenced by neuropathological changes such as neuronal necrosis at autopsy. In instances of nerve agent poisoning diazepam seems to have been an effective anticonvulsant. Consequently, the use of diazepam is an important part of the treatment regimen of nerve agent poisoning, the aim being to prevent convulsions or reduce their duration. Diazepam should be given to patients poisoned with nerve agents whenever convulsions or muscle fasciculation are present. In severe poisoning, diazepam administration should be considered even before these complications occur. Diazepam is also useful as an anxiolytic in those exposed to nerve agents.

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TOXICOLOGY - I

ANTIEPILEPTIC DRUGS POISONING

***Sheeja Sugunan**

Abstract: *Antiepileptic drugs are common drugs involved in poisoning, both accidental and intentional. Decontamination and serum level estimation are often useful in management. Though there are no specific antidotes except flumezanil, many children can be saved by early diagnosis and supportive management. Paradoxically some anticonvulsant drugs can cause seizures. Whenever children on anticonvulsant drugs are admitted with altered mental status, neurological disturbances like ataxia or even seizures, poisoning with antiepileptic drugs should also be considered as differential diagnosis.*

Keywords: *Antiepileptics, Phenytoin, Phenobarbitone, Sodium valproate, Carbamazepine.*

It is one of the common accidental poisonings seen in children. Tablets are available both as blister packets and also in bottles with 100-150 tablets. In children presenting with unexplained altered sensorium, seizure, nystagmus, extrapyramidal signs and conduction abnormalities antiepileptic drug poisoning should be considered. The history of ingestion of the drug may not be readily available. Whenever toxin ingestion is suspected one should enquire about the availability and any missing number of antiepileptic drugs at home. In case of intentional poisoning always suspect multiple drug ingestion; all such cases should be admitted and evaluated even if asymptomatic and the said drug dose appears to be less than the toxic dose.

Phenytoin

Mechanism of action

Phenytoin blocks voltage-sensitive sodium channels. This leads to a delay in neuronal electrical recovery from inactivation. It selectively blocks the neurons that are firing at high frequency.

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Pharmacokinetics

It is a weak acid with erratic gastric absorption. Phenytoin precipitates in the acid environment of the stomach. Peak blood levels are usually attained 3-12 hours after single dose ingestion, but absorption can be extended up to two weeks. Ninety per cent of phenytoin is bound to plasma proteins, only the free unbound phenytoin has biological activity. Phenytoin undergoes enterohepatic circulation - metabolised in the liver and is excreted in the bile as an inactive metabolite, which is then reabsorbed from the intestinal tract and excreted in the urine.

Clinical features

There is a good correlation between drug level and dose. Symptoms of phenytoin poisoning depend on the dose ingested and drug level (Table I). Duration of symptoms cannot be predicted by drug level. Oral overdose mainly leads to neurological toxicity while parenteral overdosage causes cardiac toxicity. Rapid IV administration causes cardiac arrhythmias due to the propylene glycol contained in the formulation and not due to the phenytoin itself.

Neurological manifestations are mainly concentration dependent. Symptoms can range from mild nystagmus to ataxia, slurred speech, vomiting, lethargy, seizure, coma and death. Phenytoin over dosage at high doses can cause paradoxical seizures.[1] Toxicity mainly depends on the level of unbound phenytoin. Hence, toxicity may be more in those with malnutrition, chronic liver disease, kidney disease with hypoalbuminemia, etc.

Table I. Symptoms against the drug level in eptoin toxicity

Drug level	Symptoms
<10mg/L	Side effects rare
10-20mg/L	Occasional horizontal nystagmus
20-30mg/L	Nystagmus
30-40mg/L	Ataxia, slurred speech, tremor, nausea, vomiting
40-50mg/L	Lethargy, confusion, hyperactivity
>50mg/L	Coma, seizures

Toxic dose

Any child who has ingested >20 mg/kg or more than 10 mg/kg above daily ingestion should be assessed. 10-20 mg/L is the therapeutic level at which side effects are rare; some may show occasional horizontal nystagmus.

Investigations

- ECG (particularly if IV dose received) at admission and after 6 hours.
- Serum phenytoin concentration.
- Liver and renal function tests, blood gas, electrolytes (in severe cases)

Treatment

All symptomatic children and in whom the amount ingested is not known should be admitted and observed for 24 hours, and can be discharged if symptom-free with normal ECG and normal sensorium.

In children, who present with severe symptoms, maintain airway, breathing and circulation. Manage shock and arrhythmias according to standard treatment protocols. Gastric lavage and whole bowel irrigation are not routinely recommended for phenytoin poisoning as it rarely offers any advantage over activated charcoal and can result in complications especially due to aspiration.

Activated charcoal 0.5-1gm per kg may be given if the airway is intact or protected. As the drug undergoes enterohepatic circulation, activated charcoal may be repeated after 6 hours to help in excretion. This is also considered as gastrointestinal dialysis. Activated charcoal can cause vomiting, aspiration and electrolyte disturbance. Hence, monitor for constipation and loss of bowel sounds in children who are treated with activated charcoal.

Dialysis and hemoperfusion: Traditionally it was considered that haemodialysis is not useful as the drug is mainly protein bound. The Extracorporeal Treatments in Poisoning (EXTRIP) Work group has now concluded that phenytoin is moderately dialyzable. It may be considered in patients in whom a prolonged coma is present or expected. It's use may also be considered in patients with prolonged incapacitating ataxia. Intermittent HD is the preferred modality of treatment, hemoperfusion is an acceptable alternative.

In patients with pre-existing hypoalbuminemia, albumin transfusion may help bind the drug in plasma and limits its entry into CNS.

Benzodiazepines

It usually produces mild to moderate central nervous system depression. Deep coma requiring mechanical ventilation is rare.

Pharmacokinetics

Benzodiazepines can be short (<12 hr), intermediate (12-24 hr) or long acting (>24 hr). They are rapidly absorbed in the gastrointestinal tract, with peak plasma concentrations occurring 30 to 90 minutes after ingestion. It is primarily metabolised in the liver. Drugs that interact with CYP enzymes may prolong the half-life of most benzodiazepines. Almost 70% of diazepam administered is excreted unchanged in the urine.

Clinical features

Most patients present with increased sleepiness. Impaired mental status, drowsiness, slurred speech, ataxia and coma can also occur. The examination may reveal decreased deep tendon reflexes, nystagmus, paradoxical stimulation and hypothermia

Admission criteria

All symptomatic children should be admitted. If asymptomatic needs to be observed for 24 hours.

Management

Appropriate supportive care to maintain airway, breathing and circulation should be given if needed.

Activated charcoal is not routinely recommended as the risk often outweighs the benefit.

Hemodialysis has no role in benzodiazepine poisoning.[2]

Antidote: Flumazenil acts as a nonspecific competitive antagonist at the benzodiazepine receptor that can reverse benzodiazepine-induced sedation. The risks associated with the use of flumazenil, often outweigh any potential benefits for most patients.[3] It is contraindicated in intentional overdose as it can precipitate seizures in withdrawal. Flumazenil is also associated with seizures in patients with a prior seizure history or a mixed overdose. Flumazenil can be safely administered to non-habituated users of benzodiazepines. Most pediatric poisoning come under this group.

Indications for flumazenil include: Accidental or iatrogenic poisoning, patients with severe respiratory depression, who would otherwise require mechanical ventilation.

Initial dose: 0.01mg/kg IV over 15 seconds (max.0.2 mg)

Discharge

Patients can be discharged if asymptomatic for 24 hours post-ingestion.

Carbamazepine

It may be associated with prolonged or delayed onset of symptoms. There is a reasonable correlation between serum carbamazepine concentration and clinical symptoms.

Pharmacokinetics

Carbamazepine is a sodium channel blocker. It is absorbed slowly and distributed erratically following oral administration. It is lipid-soluble and hence enters the brain rapidly. It can paradoxically cause seizures characterized by stimulus-sensitive multifocal myoclonus. EEG may reveal a burst-suppression pattern, with bursts containing only generalized spikes accompanying myoclonic activity.

Carbamazepine is metabolized primarily in the liver by oxidative enzyme, conjugated with glucuronic acid and finally excreted in the urine. Carbamazepine enhances the metabolism of phenytoin and can decrease its blood level, while INH and Erythromycin inhibit the hepatic metabolism of carbamazepine. It induces a cytochrome P-450 system and increases the metabolism of other antiepileptic drugs.

Clinical features

It can have neurological, cardiovascular and anticholinergic effects. CNS symptoms include ataxia, nystagmus, drowsiness, coma and seizures. Patients may present with tachycardia, hypotension or life-threatening arrhythmias (heart block, widening of QRS, ventricular fibrillation). Other symptoms include urinary retention, decreased bowel motility, dry mouth and sinus tachycardia

Admission criteria

All symptomatic children and children with ingestion of an unknown quantity of the drug must be admitted. If the quantity ingested is known, ingestion of >20mg/kg warrants admission. Observe for a minimum of 8 hours. Longer observation will be needed in children with a history of ingestion of sustained release formulations.

All children with life-threatening or potentially life-threatening signs and/or symptoms are admitted to ICU and monitored for arrhythmia or QRS widening.

Investigations

- ECG monitoring.
- Complete blood count, renal and liver function tests and electrolytes should also be checked. Long-term carbamazepine use may be rarely associated with agranulocytosis, thrombocytopenia, and aplastic anaemia.
- Blood levels: Ingestion of 50 mg/kg or more of the drug is associated with significant toxicity. There is a reasonable correlation between drug level and symptoms (Table II). As carbamazepine absorption varies, the serum concentration may not peak for as long as 24-72 hours. With controlled-release formulation, levels may continue to rise until 4 days after ingestion.

Management

Appropriate supportive care should be provided to maintain airway, breathing and circulation. Children may require fluid resuscitation for hypotension or hypovolemia with 20 mL/kg of normal saline / balanced electrolyte solution such as plasmlyte.

Consider activated charcoal (0.5-1g/kg) especially in children with massive ingestion (>50mg/kg). Ensure that the airway is protected. Multidose-activated charcoal (2-4 hourly) may be indicated in children with large ingestions, provided bowel sounds are present. Gastric lavage may be helpful if performed within 1 hour of ingestion.

In ingestion of extended-release formulations, whole bowel irrigation may be done with polyethene glycol (balanced electrolyte solution) lavage solution at 25 ml/kg/hr (adolescents 1.5-2L/hr). Whole bowel irrigation can be complicated with ileus and complete bowel obstruction.

Table II. Symptoms against drug level in carbamazepine poisoning

Drug level (mg/L)	**Drug level**	**Symptoms** (mmol/L)
5-12	20-50	Therapeutic range
10-20	40-85	Nystagmus, sedation, ataxia
20-40	85-170	Horizontal and vertical nystagmus, coma
>40	>170	Respiratory depression, seizures, cardiac arrhythmia

Benzodiazepines should be used to terminate seizures that are not self-resolving. Sodium channel blocking anticonvulsants (e.g. phenytoin, sodium valproate) are relatively contraindicated.

Dialysis

Carbamazepine is moderately dialyzable. High-efficiency haemodialysis and charcoal hemoperfusion have a similar effect. Peritoneal dialysis is not useful. Indications for extracorporeal treatment include.[4]

- Refractory seizure (recommended)
- Life-threatening dysrhythmias (recommended)
- Prolonged coma or respiratory depression requiring mechanical ventilation (suggested).
- Persistent toxicity with rise in concentration or persistently elevated concentration despite using multidose-activated charcoal (suggested).

Dialysis should be continued till clinical improvement is apparent or serum carbamazepine concentration is below 10 mg/L. In pediatric patients use of continuous veno venous hemodiafiltration (CVVHDF) has been reported especially in unstable patients.

A patient may be discharged once symptoms subside and his blood level is less than 4-8mg/L. Patients who were previously on long-term treatment can be discharged once a therapeutic level is attained.

Sodium valproate

It is a commonly used anti-epileptic drug with varied neurological actions. It is used for both generalized and partial seizures. It is available in tablet (immediate-release or enteric coated), syrup and intravenous formulations.

Pharmacokinetics

Sodium valproate is absorbed rapidly from the gastrointestinal (GI) tract. It is highly plasma protein bound and has a half-life of 8-20 hours in most patients. Peak plasma levels may be attained within 4 hours in standard preparations, while in enteric-coated preparations it may take 8-12 hours.

It is metabolised in the liver, initially mainly by glucuronidation. It undergoes further metabolism with oxidation and involves cytochrome P450 enzyme.[5]

Pathophysiology

Valproate causes inhibition of beta-oxidation of fatty acids resulting in mitochondrial injury. It decreases tissue carnitine levels which also causes mitochondrial dysfunction in liver cells resulting in micro-vesicular steatosis. It can lead to cerebral oedema associated with ischemia and herniation. This occurs due to the presence of toxic metabolites like 2-EN-VPA in the brain. Valproic acid causes urea cycle dysfunction leading to the accumulation of ammonia. Valproic acid can also inhibit carnitine which is a co-factor for long-chain fatty acid metabolism

Clinical features

Symptoms usually manifest within 4 hours for standard release preparations, while it may be delayed up to 12 hours for enteric-coated preparations. Bone marrow suppression may occur 3-5 days after massive ingestion.

Acute overdose usually presents with encephalopathy, electrolyte abnormalities such as hypernatremia, elevated transaminase levels, hyperammonemia, and hepatoxicity. Severe over dosage can cause hypotension, respiratory depression, metabolic acidosis, cerebral oedema and valproate-related hyperammonemia encephalopathy which may progress to coma and death if not treated aggressively. Sodium valproate dose response relationship is described in Table III.

Investigations

- ECG monitoring.
- Blood glucose, electrolytes, liver function tests, blood gas, ammonia, calcium.
- Serum sodium valproate concentration: Six hourly measurements until concentration returns to normal in patients with altered sensorium. Serum levels may peak late especially if enteric coated sustained release formulations are used.

Table III. Sodium valproate dose response relationship

Drug consumed	Clinical symptoms
< 200 mg/kg	Asymptomatic / Mild sedation
200-400 mg/kg	CNS depression with moderate toxicity
>400 mg/kg	Risk of multi organ system involvement
>1000 mg/kg	Potentially life-threatening, coma, multi-organ failure, cerebral oedema

- Therapeutic range for total valproic acid is 350 to 700 mmol/L (50 to 100 mg/L). More than 6000 mmol/L (850 mg/L) indicates severe poisoning.

Admission criteria

Following children require assessment/admission

- Deliberate self-poisoning.
- >200mg/kg in drug naïve children.
- >50mg/kg greater than the child's normal therapeutic dose if on the regular dose,
- Any symptomatic child.
- Unknown quantity ingestion.
- Non accidental poisoning
- Developmental age inconsistent with the reported mode of access and ingestion of the drug (non-accidental poisoning likely).

Management

Appropriate standard supportive care to maintain airway, breathing and circulation to be provided. IV fluid resuscitation with 20 mL/kg normal saline in patients with hypovolemia or hypotension should be given.

Ensure adequate glucose intake as inadequate glucose intake may lead to gluconeogenesis which may cause endogenous protein catabolism thus contributing to hyperammonaemia. Manage hypoglycaemia and dyselectrolytemia when present.

Benzodiazepines should be administered if there is a seizure due to valproate toxicity.[6]

Activated charcoal 1g/kg single may be given if >200 mg per kg ingestion.[7] As both enteric coated tablets and extended-release tablets are available charcoal may be given up to 4 hours after ingestion. If child is drowsy secure the airway with intubation before giving activated charcoal. Charcoal can be repeated if >500mg/kg ingestion or if blood levels show a rising trend.

Dialysis

Valproic acid is moderately dialyzable. Recommended indications for extracorporeal treatment include[8]

- Valproic acid concentration>1300 mg/L (9000 μ mol/L)
- Cerebral oedema,
- Shock

Suggested indications for dialysis include

- Ingestion >1g/kg,
- Valproic acid concentration >900 mg/L (6250 μ mol/L),
- Need for mechanical ventilation due to respiratory depression,
- acute hyperammonaemia,
- pH <7.15.

Stop dialysis when there is a clinical improvement or serum concentration is between 50 and 100 mg/L (350 -700 μ mol/L). Intermittent haemodialysis is preferred. Hemoperfusion and CRRT are acceptable alternatives. After cessation of dialysis rebound elevation in valproate level can occur, but this generally doesn't lead to clinically significant toxicity.

Carnitine: The use of carnitine is not supported by robust evidence but because of its reasonable biological basis and low risk of harm, it may be used in patients with symptomatic acute valproate poisoning. Carnitine may alter the generation of potentially toxic metabolites. Serum ammonia levels must be measured simultaneously. When serum ammonia levels start decreasing, coma and acidosis resolve and L-carnitine therapy can be stopped.

Indications for using carnitine

- Cerebral oedema
- Significant Metabolic acidosis
- Hyperammonaemia
- Hepatotoxicity

Dose 100 mg/kg loading dose IV followed by 50 mg/kg q8th hourly

Oral carnitine at a dose of 100 mg/kg q6th hourly may be also considered in asymptomatic children with acute overdosage.[7]

Naloxone: There have been reports of using opioid antagonist naloxone in the dose range of 0.8 mg to 2 mg to reverse central nervous system depression in some cases of valproate poisoning. It may be useful in chronic valproate poisoning.[6,9]

Intravenous L Arginine: It is not a standard treatment for valproic acid poisoning. It may be considered in moderate to severe hyperammonaemia without haemodialysis access, persistent hyperammonaemia despite dialysis or hyperammonaemia with life-threatening cerebral oedema.[10]

Dose 250 mg/kg loading over 2 hours followed by 250mg/kg /day maintenance infusion.

Discharge

All children should be observed for a minimum of 6 hours for immediate release preparations and a period of 12 hours for sustained release preparations. Children with moderate to severe symptoms, ingestion of >400mg/kg or persistent symptoms beyond 6 hours need admission, evaluation and management.

At discharge ensure the period of observation is complete with normal GCS and normal ECG.

Phenobarbitone

Phenobarbitone is a commonly used antiepileptic drug.

Pharmacokinetics

Phenobarbitone is a long-acting, polar drug that is slowly absorbed and slowly redistributed. Part of it is metabolised to inactive compounds and part excreted unchanged in the urine. Barbiturates easily cross the placenta and are excreted into breast milk. It is also a hepatic enzyme inducer which can induce the metabolism of other drugs.

Pathophysiology

Barbiturates act on the GABA-A receptor and increase the amount of time the chloride ion channel is open.[11] This increases the affinity of the receptor for GABA. Even in the absence of GABA it can increase the chloride influx and cause significant CNS depression.

Admission

Following children requires assessment/admission

- Children with deliberate self-poisoning
- >5mg/kg in drug-naive children
- >10mg/kg greater than the child's normal therapeutic dose if on a regular dose
- Any symptomatic child
- Acute ingestion of an unknown quantity
- Chance of non- accidental poisoning

Clinical features

Children usually present with features of central nervous system depression like lethargy, slurred speech, respiratory depression, and coma. Large ingestion can mimic brain death. It may also cause hypotension and arrhythmias.

Investigations

ECG at admission and repeat after 6 hours

Phenobarbitone serum levels

- >175-258mmol/L: may cause toxic effects
- >345-650mmol/L: Potential to be lethal[12]
- Therapeutic range for anticonvulsant activity is 10-25 mg/L. Serum concentrations of >50 mg/L may induce coma and concentrations > 80 mg/L may be fatal.

LFT, RFT, Blood gas, electrolytes (in symptomatic patients)

Management

Treatment is mainly supportive as there is no specific antidote.

Appropriate supportive care to maintain airway, breathing and circulation to be provided. IV fluid resuscitation with 20 ml/kg normal saline in patients with hypovolemia or hypotension. Patients with severe respiratory depression may require endotracheal intubation and mechanical ventilation.

Multidose-activated charcoal 1g/kg every 6 hours via NG tube after securing the airway has been found to increase phenobarbitone elimination and shorten the duration of coma.[12] Ensure the presence of bowel sounds before repeating the dose.

Dialysis

Haemodialysis and hemoperfusion may be used in severe cases. Hemoperfusion even though more efficacious than haemodialysis, is associated with a higher incidence of complications. Intermittent HD is preferred for severe barbiturate poisoning. Hemoperfusion and CRRT are acceptable alternatives.[13] Indications for dialysis include

- Fluid refractory shock
- Stage IV coma
- Persistent toxicity symptoms.
- Renal failure or pulmonary oedema.
- Respiratory depression requires mechanical ventilation.

Multiple-dose activated charcoal treatment should be continued during extracorporeal treatment (ECTR) provided bowel sounds are present. It may be stopped when clinical improvement is apparent.

Urinary alkalinization is not recommended as multidose-activated charcoal is considered superior as it does not increase renal clearance significantly.

Points to Remember

- ***Anticonvulsants are the common drugs involved in poisoning.***
- ***In the presence of altered mental status, nystagmus, extrapyramidal signs and conduction abnormalities suspect antiepileptic drug poisoning.***
- ***Serum level estimation will be useful in the management.***
- ***Some anticonvulsant poisoning may paradoxically present with seizures.***
- ***There are no antidotes for anticonvulsant poisoning except benzodiazepines.***

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NEWS AND NOTES

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TOXICOLOGY - I

POISONING DUE TO DRUGS AND TOXINS CAUSING CARDIOTOXICITY

***Rameshkumar R**

Abstract: *Though cardiovascular toxicities due to drugs and substances constitute a small percentage of all poisoning, prompt identification and management are warranted to reduce the mortality. In the pediatric emergency room, a systematic approach and stabilization of airway, breathing and circulation, along with supportive care, takes priority over the search for a specific antidote. All healthcare workers should be apprised of the National / Regional Poison Center contact numbers. This article discusses the common drugs and substances causing cardiac toxicity and their management in children.*

Keywords: *Children, Drugs, Substance, Cardiotoxicity, Management, Beta blocker, Calcium channel blocker.*

Cardiovascular system (CVS) poisoning due to drugs and substances in children constitutes a small percentage of all poisoning presentations.[1,2] It causes serious complications, including a high mortality risk. The medications more often cause cardiotoxicity compared to other substances, namely plants. Children's curiosity and readily exploring nature frequently exposes them to potentially serious drugs and plant-related poisoning, both outside and inside the home. In particular, even a single dose of beta-blockers (BBs) and calcium channel blockers (CCBs) can present with cardiac toxicity. This article discusses the basic pharmacology/ pathophysiology, risk factors, approach and management of clinically important drugs and toxins listed in Box 1.

Box 1. Cardiotoxic drugs and potentially toxic plants

1. Beta-blockers (BBs)
2. Calcium channel blockers (CCBs)
3. Anticancer drugs
4. Cardiac steroids
5. Tricyclic antidepressants (TCA)
6. Common oleander and yellow oleander

Pharmacology / Pathophysiology / Toxicokinetic [1-3]

Normal physiology of cardiac myocyte

Cardiotoxic xenobiotics produce their effects by affecting the complex mechanisms regulating contractility, cardiac output, peripheral vascular resistance and cardiac conduction system. The autonomic system primarily acts via adrenergic receptor activity. Adrenergic xenobiotics affect the signaling pathways that alter the autonomic tone, including the interactions between adrenergic receptors (alpha and beta), G-protein complexes, and cyclic adenosine monophosphate (cAMP) synthesized by the enzyme adenylate cyclase. The beta-1 receptor agonists increase heart rate and exert an inotropic effect and beta-2 receptor activation increases heart rate and, to a lesser extent, exerts inotropy, but primarily leads to the relaxation of smooth muscle. Beta-3 receptor agonism leads to lipolysis and thermogenesis. In the periphery, alpha-1 receptor activation leads to vasoconstriction. Alpha-2 receptors are found in both presynaptic and postsynaptic locations. Presynaptic alpha-2 agonism leads to negative feedback, decreasing the release of norepinephrine and thus resulting in bradycardia and hypotension, whereas postsynaptic alpha-2 agonism, similar to alpha-1, leads to vasoconstriction. The cardiac myocyte and vascular smooth muscle tone function depend on the influx of calcium across voltage-dependent L-type calcium channels.

Beta-blockers (BBs)

BBs competitively antagonize cardiac beta-1 adrenoceptors, which generally increase cAMP production, phosphorylation, and opening of L-type calcium channels. Thus, BBs reduce the facilitation of calcium entry into cardiomyocytes, leading to negative chronotropic and inotropic effects. Hence, they have a "direct depressant action" on the myocardium, leading to conduction delays,

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bradycardia, and reduced contractility with no or little effect on peripheral vasculature. Specific BBs, namely labetalol and propranolol in toxic doses, also antagonize voltage-gated sodium channels and can be associated with a higher mortality risk than other BBs.

Except for sustained-release preparations, BBs are readily absorbed, with peak absorption occurring within one to four hours when ingested. Propranolol, the most lipophilic BB, can easily cross the blood-brain barrier and lipid cell membrane and hence may cause seizures in a toxic dose. The liver excretes BBs except for atenolol, carteolol and nadolol which are excreted by the kidney.

Calcium channel blockers (CCBs)

CCBs directly inhibit voltage-gated calcium channel (L-type) opening and calcium influx into the myocardium and vascular smooth muscle cells. Calcium influx in the myocardium initiates excitation-contraction coupling, sino-atrial (SA) node depolarization, and maintains vascular and gastrointestinal tract (GIT) smooth muscle tone. CCBs also reduce insulin secretion by inhibiting L-type calcium channels in pancreatic islet cells, leading to hyperglycemia and decreased cardiac glucose utilization. Hypotension following CCBs toxicity is multifactorial and results from negative inotropy, negative chronotropic effects, and peripheral vasodilatation. Severe cardiac toxicities are commonly seen with CCBs like verapamil and diltiazem. The delayed onset and prolonged duration of toxicity are because of ongoing GIT absorption. Dihydropyridine CCBs such as amlodipine and nifedipine mainly affect the vascular smooth muscle and overdose leads to vasodilatory shock with reflex sinus tachycardia.

At higher doses, CCBs clearance slows due to a change in hepatic metabolism from first-order to zero-order kinetics. Among CCBs, verapamil has a strong affinity for both myocardium and vascular smooth muscle. Diltiazem has a similar effect as verapamil but has less vasodilation and more potent effects on chronotropic action. Dihydropyridines (Nifedipine, amlodipine, felodipine, isradipine, nicardipine and nimodipine) are potent vasodilators but have lesser effects on cardiac pacemaker activity and myocardial contractility.

TCAs and anticancer drugs

The exact mechanisms of antipsychiatric (TCAs) and anticancer drugs-induced cardiac toxicity remain unclear, and it is proposed to be multifactorial (production of reactive oxygen and nitrogen species, inflammation, lipid peroxidation, apoptosis of cardiomyocytes and interstitial fibrosis). TCAs have many other mechanisms of action: blockade of the potassium channels and sodium channels, alpha-adrenergic activity, and inhibition of biogenic amine reuptake, antihistamine, and anticholinergic properties. The mortality is usually due to cardiac and neurotoxicity. In particular, understanding anthracycline-induced cardiac toxicity is crucial to plan for effective cardioprotection.

TCAs are generally rapidly absorbed from the gastrointestinal tract (GIT). The overdose results in decreased GIT motility and delayed absorption because of inherent anticholinergic effects. TCAs have a long elimination half-life as these drugs are largely bound to the plasma protein and are highly lipid-soluble. After significant first-pass hepatic metabolism, TCAs are excreted by the kidney. The acid-base abnormality (metabolic or respiratory acidosis) may potentiate the toxicity due to the large unbound fraction of TCAs levels.

Cardiac glycosides and cardioactive steroids (CAS)

All cardiac glycosides possess a steroid nucleus with an unsaturated lactone at the C17 and at least one glycosidic residue at the C3 position. Digoxin is the only cardiac glycoside used for medicinal purposes with a narrow therapeutic index. It is mainly used to increase cardiac inotropy but also affects the vascular smooth muscle and sympathetic nervous system. Cardiac glycosides cause an increase in intracellular sodium and a decrease in intracellular potassium by reversibly inhibiting the Na-K-ATPase. The increase in intracellular sodium prevents the Na-Ca antiporter from expelling calcium from the myocyte, which increases intracellular calcium and augments cardiac inotropy. Cardiac glycosides also increase vagal tone, which leads to decreased SA and AV node conduction. It causes premature contraction and dysrhythmias by delayed after-depolarization due to excessive intracellular calcium and shortens repolarization of the atria and ventricles by decreasing the myocardium refractory period, thereby increasing automaticity.

Cardioactive steroids (CAS) are medically important substances historically used for conditions like “dropsy” and edema. They are available in several plants, namely oleander, lily of the valley, and common milkweed plant. The acute ingestion of cardiac glycoside-containing plants causes toxicity, similar to digoxin poisoning, which causes reversible inhibition of the Na-K ATPase pump resulting in an increase in intracellular sodium and a decrease in intracellular potassium resulting in hyperkalemia. Most cardiac glycosides have a narrow therapeutic index

and half-life ranging from 30 to 40 hours, but this may get altered when consumed in toxic doses. The kidney primarily excretes it. Cardiac toxicity may be delayed up to 8 to 12 hours of exposure. The enteric bacteria, *Eubacterium lentum (Eggerthella lenta)* inhibits digoxin absorption. Antibiotics that may inhibit the growth of these bacteria in the GIT may cause increased absorption of digoxin.

Risk factors

- Age at time of exposure (below four years)
- Female
- Total cumulative dose
- Class of drugs - heart failure is common with anticancer drugs like anthracyclines (Doxorubicin, Daunorubicin, Epirubicin, Idarubicin), alkylating agents (Ifosfamide), antimetabolites (5-Fluorouracil - myocardial ischemia), monoclonal antibody (Trastuzumab), small molecule-targeted therapies (Sunitinib).
- Concomitant therapy (such as radiation therapy)
- Cardiac disease
- Elevated cardiac biomarkers levels
- Time to presentation after ingestion (the later the presentation, the poorer the outcome)

Initial stabilization - Toxicology approach [1,2,4,5]

Healthcare workers, in particular, working in the pediatric emergency room should be aware and familiar with the general management of the poisoned child. Younger and undernourished children (less than six years) can be severely affected by very little exposure to toxic substances due to low body mass and an immature metabolism. Most of the symptoms develop within six hours of ingestion/exposure. If no symptom develops within six hours, it is unlikely that the child will develop signs of toxicity after this time, especially with TCA. Certain medications have proven to be fatal, even with the ingestion of small amounts (Box 2).

Box 2. Medications proved to be fatal even in small doses

1. Beta-blockers
2. Calcium channel blockers (the minimal potential fatal dose per body weight is 15 mg/kg for Nifedipine, Verapamil, and Diltiazem)
3. Cardiac glycosides (Minimal acute potential toxic dose is > 4 mg in a child)
4. Tricyclic antidepressants(The minimum potential fatal dose is reported as 15 mg/kg for Amitriptyline, Imipramine, and Desipramine)
5. Antimalarials (The minimum potential fatal dose per body weight is 20 mg/kg for both Chloroquine and Hydroxychloroquine)

The patient's airway, breathing, and circulation should be stabilized first, followed by a secondary assessment with a focused history and physical examination as per advanced pediatric life support guidelines. Meticulous attention to history, vital signs and physical examination help to recognize the toxidrome or illness pattern of a child's suspected poisoning. The systematic approach and meticulous supportive care are cornerstones in managing most children with known / unknown poisoning. Contacting the National / Regional Poison Center is a helpful strategy to improve the clinical outcome of the patients.

Airway stabilization (A): If required, rapid sequence intubation (RSI) is usually a good approach. Other approaches, such as delayed sequence intubation (DSI), awake intubation (for patients with caustic injury), and apneic oxygenation, may be considered on a case-to-case basis.

Breathing stabilization (B): Noninvasive ventilation methods such as high flow nasal cannula (HFNC), bi-level or continuous positive pressure ventilation (Bi-PAP/ CPAP)if respiratory efforts are adequate and intubation and mechanical ventilation if there is poor effort or altered level of consciousness.

Circulation stabilization (C): Most pediatric cardiotoxicity patients have unstable circulation / cardiac status and pose a unique challenge in management. Patients often have rate and rhythm abnormalities, in addition to evidence of abnormal perfusion. Hence, continuous cardiac and saturation monitoring is essential.

Simultaneous to stabilization of A, B, C, focused attention to neurological status (Disability), mucus membrane, skin (Exposure) and bedside capillary blood sugar measurement are paramount in the management of any patient in the emergency room.

Gastrointestinal decontamination

Initially, most patients require the best possible supportive care more than any other specific treatment. The methods include gastric lavage, activated charcoal,

and whole bowel irrigation.[6] Decontamination procedures are discussed in detail in another chapter in the same issue.

Management[2,4-6]

Beta-blockers (BBs)

- In general, lipid-soluble BBs are more toxic than water-soluble BBs because of their quinidine-like effects.
- Airway protection is vital as central nervous system (CNS) depression can occur.
- Premedication with atropine is necessary as airway manipulation can cause vagal stimulation, which might further aggravate/worsen existing bradycardia.
- Seizure: benzodiazepines are the first line of treatment.
- Bronchospasm: Treated with supplemental oxygen and inhaled bronchodilators.
- Cardiac toxicity: Prompt recognition of QRS widening and prolongation of QTc interval is crucial.
- Administer sodium bicarbonate (i.v. 1 mEq/kg, maximum single dose 50 mEq; flush with normal saline before and after infusion) - for QRS widening. Ensure adequate ventilation to avoid hypercarbia.
- Magnesium sulfate (i.v. 25 to 50 mg/kg) - for QTc prolongation and in polymorphic ventricular tachycardia.
- Glucagon: indicated in BBs toxicities, presenting with bradycardia and hypotension. For infants and children - loading dose, i.v. 0.05 mg/kg followed by continuous infusion of 0.05 to 0.1 mg/kg/hour. For adolescents, loading dose, i.v. 5 to 10 mg, followed by continuous infusion of 1 mg to 5 mg/hour. Premedication with antiemetics may be required as glucagon induces vomiting. Even though no human studies prove its effectiveness, glucagon is used along with other treatment modalities. Many toxicologists prefer to use HIE (high dose insulin euglycemia) based on case series and clinical experience. Monitor and treat the other possible side effects, namely hypocalcemia and hyperglycemia.
- Another option for hypotension is high-dose insulin euglycemia: refractory to basic supportive care including fluid, atropine, and Glucagon. A detailed description is provided in the CCBs section. Monitor and treat hypokalemia and hypoglycemia. Based on the clinical findings and hemodynamic parameters, adrenaline, isoprenaline and phosphodiesterase inhibitors (milrinone) can be started and titrated to achieve clinical stabilities.
- Enhanced elimination techniques (multiple doses of activated charcoal, hemodialysis, or hemoperfusion) are useful in BBs poisoning
- Extracorporeal membrane oxygenation (ECMO), if refractory to the above interventions, may be needed until the xenobiotic effect wears off.

Calcium channel blockers (CCBs) (Table 1)

- In CCBs-induced cardiotoxicity other than dihydropyridines, the electrocardiogram (ECG) abnormalities include sinus bradycardia, variable degrees of atrioventricular (AV) blocks, bundle branch block (BBB), QT prolongation, and junctional rhythms. In dihydropyridine toxicities, normal sinus rhythm is maintained and can cause reflex sinus tachycardia.
- Decontamination procedures should not precede airway, breathing, and circulation stabilization. For detailed text, refer to the decontamination article available in the same issue.
- Atropine: is indicated in a patient with symptomatic bradycardia. But often ineffective in significant CCBs exposure. Pediatric dosing is 0.02 mg/kg i.v., with a minimum dose of 0.1 mg to avoid paradoxical bradycardia.
- Calcium infusion: Rationale: Increased extracellular concentration will promote calcium influx via unblocked (L-type) calcium channels. Nevertheless, the response is variable and suboptimal in severe toxicity. Infusion mitigates the conduction disturbances and shock but is less effective in bradycardia. Because of the serious side effects of high calcium doses, many prefer other treatment modalities after the initial dose. Calcium gluconate is preferable over calcium chloride as gluconate can be administrated via the peripheral or central line. Dose: Infants, children, and adolescents, dose expressed as calcium gluconate: extrapolating adult dose, the usual dose of 1-2 ml/kg to a maximum of 20 ml can be tried over 20 minutes as a single dose [10% calcium gluconate: 90 mg elemental calcium or 4.5 mEq/1g ampoule)]. Monitoring: Calcium levels should be monitored 30 minutes after the infusion.
- Hyperinsulinemic euglycemia therapy (HIET): It has emerged as a potential therapy for severe CCBs toxicity. Insulin has a direct positive inotropic effect. It is indicated in cardiogenic shock due to CCB or BB overdose. HIE improves cardiac myocyte function by enhancing carbohydrate utilization within the myocyte

and via other direct inotropic effects. If initial blood glucose is < 200 mg/dL, give 25 g of dextrose IV before giving a bolus with regular insulin 1 unit/kg IV. Followed by an infusion of regular insulin 0.5 to 1 unit/kg/hr IV drip (max 35 to 100 units/hour), using an infusion pump and dedicated IV line. Simultaneously start glucose infusion at 0.5 mg/kg/hr (D10) and maintain blood glucose (BG) between 100-200 mg/dL. Assess the response clinically and by ECHO. If there is no significant response, increase the insulin drip to 0.5 units/kg/hr every 15 minutes to a max dose of 4 units/kg/hr. These kids should be monitored for hypoglycemia, hyponatremia and hypokalemia and managed accordingly. Dextrose infusion is continued for an average of 18 hours after the insulin infusion is stopped, as dextrose requirements increase when organ perfusion improves.

- Methylene blue: For refractory CCBs toxicity-induced vasodilatory shock. Dose: 1 to 2 mg/kg single injection. The physician should be aware of the bluish discoloration of skin and urine that may ensue (which is transient) hemolysis, methemoglobinemia, and serotonin syndrome in the presence of serotonergic agonists, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs).
- Lipid emulsion Therapy: An oil-in-water emulsion that creates a lipid phase in the plasma and pulls a lipid-soluble drug into the lipid phase in the blood. Intravenous infusion can sequester intensely lipophilic drugs (Verapamil and Diltiazem), reducing their distribution volume. Indication: Only in refractory shock or severe toxicity, unresponsive to conventional treatment options. Dose: Initial bolus of 1.5 ml/kg of 20% lipid emulsion followed by 0.25 to 0.5 ml/kg/min over 30 minutes. The physician should be aware that the infusion can interfere with the analysis of blood glucose and magnesium level. Caution: Acute respiratory distress syndrome (ARDS), acute pancreatitis, interference with vasopressors, and fat overload syndrome inducing seizures, fat embolism, hepatosplenomegaly and coagulopathy in high doses and multiple doses.
- Glucagon: It increases intracellular levels of cyclic AMP. It has minimal effect on mean arterial blood pressure. Dose: Adult: Bolus of 5 to 10 mg over 1 to 2 minutes followed by infusion of 2 to 10 mg/hour. Children: As mentioned above BBs toxicity.
- Based on the clinical findings and hemodynamic parameters, adrenaline, isoprenaline and phosphodiesterase inhibitors (milrinone) can be started and titrated to achieve clinical stability

Extracorporeal membrane oxygenation (ECMO): If refractory to the above interventions, ECMO may be needed until the xenobiotic effect wears off.

Tricyclic antidepressants (TCAs)

- TCAs overdose can cause cardiac toxicity. Blockade of fast sodium channels in myocardial cells slows the action potential and provides a membrane-stabilizing effect. ECG finding: QRS prolongation secondary to prolongation of phase "0" of the myocardial action potential. This effect can lead to heart block and bradycardia. QT prolongation due to potassium channel blockade may potentially cause torsades de pointes. TCAs overdose can also exert a quinidine-like toxic effect on the myocardium that can cause decreased cardiac contractility and hypotension.
- Decontamination procedures should not precede airway, breathing, and circulation stabilization. There is a separate chapter on decontamination available in this issue for details.
- Every effort should be made to minimize the development of acidosis because acidosis may increase cardiac and neurologic toxicity.

Table I. Overview of BBs and CCBs overdose treatment stages[1]

Stage-1	Stage-2	Stage-3
Initial stabilization	Vasoactive infusions	Shock refractory to high dose insulin and 3 or more Vasopressors / Inotropes
- GI decontamination (if appropriate) - Judicious and cautious fluid resuscitation - IV Calcium Calcium - Atropine - Glucagon (in select BBs cases only)	- High-dose insulin - Inotropes - Vasopressors	- Methylene blue - Intravenous lipid emulsion - Mechanical devices (Pacemaker, ECMO)

- Atropine: Indicated in a patient with symptomatic bradycardia. (Details as mentioned above).
- Seizures: Benzodiazepines are the first line of treatment.
- Sodium bicarbonate: Indication: Hemodynamically unstable patients, seizures, and patients with QRS prolongation (more than 100 msec). Dose: bolus of 1 to 2 mEq/kg, titrate to maintain serum pH 7.45 to 7.55, followed with 150 mEq $NaHCO_3$/**L** infusion to maintain targeted pH (4).
- Physostigmine, Type 1A, Type 1C, and Type 3 anti-dysrhythmic agents should be strictly avoided.
- Intralipid emulsion: Should be considered in hemodynamically unstable patients with lipophilic TCAs overdose.
- Enhanced elimination (with dialysis and hemoperfusion) is not effective because of high protein bound and extensive volume of distribution.
- Based on the clinical findings and hemodynamic parameters, adrenaline, isoprenaline and phosphodiesterase inhibitors (milrinone) can be started and titrated to achieve clinical stabilities.

Cardiac glycosides and cardioactive steroids (CAS)

- Cardiac dysrhythmia is the most dangerous and life-threatening manifestation of cardiac glycoside / CAS overdose and can include virtually any type of cardiac dysrhythmia except for rapidly conducted atrial dysrhythmias.
- Multi-dose activated charcoal (MDAC) can be considered in yellow oleander poisoning because cardiac glycosides undergo some extent of enterohepatic or entero-enteric recirculation.
- Antidote: Digoxin-specific antibody antigen-binding fragments (DSFab) (digibind or digifab) is indicated for life-threatening toxicity, including acute ingestion of greater than 4 mg in a child, digoxin concentration greater than 15 ng/mL measured at any time and digoxin concentration greater than 10 ng/mL measured 6 hours after overdose. DSFab can be dosed as follows (infusion over 30 minutes and onset is 20 minutes, with the complete effect seen within 90 minutes):

If the dose of Digoxin ingested is known, but the digoxin level is not known: (0.8 times the ingested dose) ÷ 0.5 = Number of vials of DSFab for an acute overdose.

If digoxin level is known: (Digoxin level (steady state) x Weight (kg)) ÷ 100 = Number vials of DSFab for acute or chronic overdose. (rounded to the nearest vial dosing).[7]

- Each vial is for single use only and contains 40 mg of Digoxin immune Fab protein. As a rule of thumb, each vial is known to bind 0.5 mg of Digoxin.
- DSFab fragments also can be given for poisoning with natural toxins, but the dosing is unclear.
- Response to DSFab or repeat dosing: based on the clinical improvement rather than digoxin concentrations unless the laboratory can measure free digoxin level.
- More recent literature suggests that i.v.calcium administration is safe in treating Digoxin toxicity.[1]
- Atropine: as mentioned above (BBs and CCBs management)
- Temporary pacing (external or transvenous): It is reasonable to attempt temporary pacing in patients with life-threatening bradydysrhythmias as a temporary measure. (caution: attempt of pacing/ cardioversion may induce or worsen the fatal dysrhythmias).
- Other options: Lidocaine and Phenytoin. Dialysis is not helpful in the treatment of digoxin toxicity itself.

Points to Remember

- ***Cardiovascular toxicity in children can cause significant mortality.***
- ***Initial resuscitation (airway, breathing, circulation) is the priority over decontamination.***
- ***In CCBs toxicity, differentiating the negative inotropy vs. low systemic vascular resistance is crucial for selecting appropriate vasoactive therapy (inotropes vs. vasopressors).***
- ***An orderly step-wise approach using all strategies, decontamination, judicious use of fluids, vasoactive therapy, calcium, sodium bicarbonate, magnesium, and high-dose insulin therapy improves the clinical outcomes in BBs and CCBs cardiotoxicity.***
- ***Enhanced elimination (dialysis and hemoperfusion) is ineffective in TCAs toxicity because they are highly protein bound and have extensive volume distribution.***
- ***Hyperinsulinemic euglycemia therapy (HIET) is preferred for severe calcium channel blocker toxicity than high-dose calcium infusion.***

- ***Digoxin-specific antibody antigen-binding fragments (DSFab) are indicated for life-threatening toxicity.***
- ***If refractory to conventional treatments, mechanical support (ECMO / Pacing) should be considered.***

The National Poison Information Centre (24x7) is situated in AIIMS, New Delhi (011 26589391; 011 26593677 and Toll-free number: 1800116117).

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CLIPPINGS

Anxiety and Depressive Symptoms and Disorders in Children and Adolescents With Migraine - A Systematic Review and Meta-analysis

Though it is presumed that children and adolescents with migraine are at risk of internalizing symptoms and disorders, high-level summative evidence to support this clinical belief is lacking. This peer-reviewed search was performed using MEDLINE, Embase, PsycINFO, and CINAHL databases to determine if there is an association between internalizing symptoms and disorders and migraine in children and adolescents. Case-control, cohort, and cross-sectional studies on the association between internalizing symptoms and disorders and migraine in children and adolescents 18 years or younger were eligible.

The primary outcome was migraine diagnosis; additional outcomes included migraine outcomes and incidence. Associations between these outcomes and internalizing symptoms and disorders were evaluated.

The study team screened 4946 studies and included 80 studies in the systematic review. Seventy-four studies reported on the association between internalizing symptoms and disorders and migraine, and 51 studies were amenable to pooling. Meta-analyses comparing children and adolescents with migraine with healthy controls showed: (1) an association between migraine and anxiety symptoms (2) an association between migraine and depressive symptoms and (3) significantly higher odds of anxiety disorders and depressive disorders in those with, vs without, migraine. Twenty studies assessing the association between internalizing symptoms or disorders and migraine outcomes (n=18) or incident migraine (n=2) were summarized descriptively.

In this study, children and adolescents with migraine were at higher risk of anxiety and depression symptoms and disorders compared with healthy controls. It may be beneficial to routinely screen children and adolescents with migraine for anxiety and depression in clinical practice. It is unclear whether having anxiety and depressive symptoms or disorders has an effect on migraine outcomes or incidence.

Falla K, Kuziek J, Mahnaz SR, Noel M, Ronksley PE, Orr SL. Anxiety and Depressive Symptoms and Disorders in Children and Adolescents With Migraine: A Systematic Review and Meta-analysis. JAMA Pediatr. Published online October 31, 2022. doi:10.1001/jamapediatrics.2022.3940.

TOXICOLOGY - I

PESTICIDES POISONING

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Abstract: *Pesticides are chemical compounds used commercially, in agriculture and in households worldwide. They aim at controlling or eliminating insects, animals, fungi and other microorganisms. The major agents within each category of pesticidesare insecticides, rodenticides and avicides, fungicides, herbicides and class classified pesticides. Insecticides include acetylcolinesterase inibitors (organophosphates,carbamates), organoclorides and pyrethroids. Rodenticides and avicides (warfarin and super warfarin, calciferol, sod fluoroacetate, chlorolase, thallium) are used against rodents and birds. Fungicides (pentachlorophenol, thiocarbamates, organomercury compounds , organotin compounds) inhibit fungal growth. Herbicides (124 dichlorphenoxyacetic acid, glyphosate, paraquats and diquat) curtail pest plant species. The class classified pesticides are chloropicrin, arsenic and metal phosphides and have the characteristics of two or more categories of pesticides.*

Keywords: *Pesticide, Poison, Herbicide, Rodenticide, Fungicide, Insecticide, Avicide, Cross classified.*

Each year, approximately 7 million people worldwide experience pesticide poisoning-of which 353,000 die.[1] The major agents within each category of pesticides are as follows.

A. Insecticides

Insecticides are chemicals, naturally occurring, or synthesized, which are used to kill insects. Various categories are listed out in Box 1.

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Box 1. Various categories of pestides

A. Pesticides and insecticides

1. Acetylcholinesterase Inhibitors (ACI) (Organophosphates and Carbamates)
2. Organochlorides
3. Pyrethroid compounds

B. Rodenticides and avicides

1. Warfarin and warfarin derivatives (Super warfarins)
2. Calciferol (Vitamin D)
3. Sodium fluoroacetate
4. Chloralose
5. Thallium rodenticide

C. Fungicides

1. Pentachlorophenol
2. Thiocarbamates
3. Organomercury compounds
4. Organotin Compounds

D. Herbicides

1. 2,4-Dichlorophenoxyacetic acid
2. Glyphosate

E. Cross-classified pesticides

1. Chloropicrin.
2. Arsenic
3. Metal Phosphides

1. Acetylcholinesterase inhibitors (ACI) (organophosphates and carbamates)

- Widely used as insecticides
- Annual worldwide exposure of humans is an estimated 3 million and 10% of whom die
- Organophosphates: Ester derivatives of phosphoric acid - O=P(OR)3.
- Carbamates: Ester derivatives of carbamic acid-HOC (O)NH_2.

Mechanism of toxicity

- Inhibit acetylcholine esterase (AChE) and neuropathy target esterases (NTE)
- Impairment of synaptic transmission
- Symptoms are secondary to choline excess
- Inhibition by organophosphates is irreversible
- Carbamates transiently inhibit AChE

Clinical features

- Cholinergic manifestations:

A common mnemonic is DUMBELS:

- **D**efecation (diarrhea)
- **U**rination
- **M**iosis
- **B**radycardia, bronchorrhoea and bronchospasm
- **E**mesis
- **L**acrimation
- **S**alivation

Patients may present with abdominal cramps, wheezing, diaphoresis and hypotension and cardiac arrhythmias

- Nicotinic manifestations

  Muscle weakness

  Fasciculation

  Tremor

  Muscle paralysis

Further signs are tachycardia, hypertension, pallor and mydriasis.[1]

- Central nervous system manifestations

  Seizures, altered mental status, possibly leading to coma

  Respiratory failure

  Organophosphate induced delayed neuropathy-polyneuropathy one to three weeks post exposure.

  Believed to result from neuropathy target esterase (NTE) inhibition. Characterized by muscle dysfunction and paresthesias. May become a chronic condition.

- Intermediate neurologic syndrome-24 to 96 hours post exposure in up to 40% of patients:

  Depressed deep tendon reflexes, weak neck flexion, respiratory insufficiency, weakness of proximal muscles and signs of cranial nerve involvement.

Investigations and diagnosis[1]

- RBC AChE level: Marker of exposure; correlates well with severity.
- CBC, LFTs and RFTs
- ECG (to rule out arrhythmias)
- CXR (to rule out aspiration secondary to bronchorrhea)

Treatment

- Atropine - 0.02 mg/ kg in children, 1-3 mg IV in adults to resolve the muscarinic symptoms. If no improvements within the first five minutes, atropine dose to be doubled. Atropine dose to be repeated every 20 minutes till the signs of atropinization occurs, (mainly drying up of secretion) then the frequency can be reduced. Severe cases may require large doses for atropinisation.
- Oximes - they reactivate cholinesterase and is used in organophosphate poisoning. It has limited use in carbamate poisoning. It is given as loading dose as slow infusion over 20 mins.

  Pralidoxime: Loading dose - 30 mg/kg IV

  Maintenance dose - 8 mg/kg/hour

  Obidoxime: Loading dose - 4 mg/kg IV

  Maintenance dose - 0.5 mg/kg/hour

- Benzodiazepines for seizures
- Gastric lavage can be given within 2 hours of ingestion

2. Organochlorides

- Previously widely used in developed countries, and still used extensively in developing nations
- Chlorinated organic hydrocarbons (R-Cl).
- Most well-known is probably dichlorodiphenyl trichloroethane (DDT).

Mechanism of toxicity

- Antagonise chloride transport in GABAergic neurons through inhibition of Ca^{2+}/Mg^{2+}ATPase within the CNS resulting in over-stimulation.[2]

Clinical features

- Characterised by CNS over stimulation:

  Seizures, abdominal discomfort, nausea and vomiting, headaches, hyperesthesia particularly in the extremities, face and tongue, hyperactivity, discoordination and dizziness, confusion and myoclonic convulsions.

  Toxic to the liver, kidneys and lungs

  Rhabomyolysis with high doses.[2]

Investigations and diagnosis

- Gas chromatography may be used to detect organochlorides, but may be impractical
- Full neurological examination is necessary
- Organ specific markers such as liver transaminases to detect end-organ damage.

Treatment

- Prevent further absorption and manage the clinical manifestations[2]

  Cholestyramine and sucrose polyester to increase fecal excretion.[3]

  Bowel irrigation at the discretion of a medical toxicologist.

  Activated charcoal may prevent binding, but not adequately studied.[2]

- Aggressive therapy with benzodiazepines or barbiturates for seizures (Phenytoin generally not effective).[2]
- Hemoperfusion shown effective in removing organochlorides from the blood.[2]

3. Pyrethroid compounds

- Derivatives of (1R, 3R)-trans-chrysanthemic acid.
- Extensively used worldwide
- Frequently mixed with other pesticides to increase effective spectrum.
- Currently used in many common household brands, such as mosquito repellants,ant prevention chalk.

Mechanism of toxicity

- Delayed closing of sodium channels during re-polarisation resulting in an inward sodium current lowering action potential threshold.[4]
- At very high levels, acts on GABAergic neurons.
- May further act on protein kinases resulting in additional calcium and neurotransmitter release.
- Directly neurotoxic, particularly in the sciatic and posterior tibial nerves resulting in damage resembling Wallerian degeneration.

Clinical features

- Paresthesias, muscular fasciculation, listlessness, dizziness, fatigue, headache and loss of appetite[5]
- Altered consciousness, seizures and comas at high doses.
- Dysphagia, sore throat, mouth ulcerations, epigastric pain and vomiting when ingested. Aspiration pneumonitis and pulmonary edema may occur.[6]
- Hepatic and renal dysfunction also seen.[6]
- Cardiotoxicity rare, but Intermittent to persistent sinus arrest with escape junctional rhythm observed.[7]
- Leukocytosis may be seen.[6]

Investigations and diagnosis

- Gas chromatography confirmatory only, may not be practical.
- Careful neurological testing required.
- ABG to detect anion gap metabolic acidosis.
- ECG, renal function and liver function testing for end organ damage.
- Blood count for leucocytosis.[6]

Treatment

- Paresthesia treated with vitamin E containing creams or local anesthetic creams.[8]

  Chloride channel agonists for seizures.

  Phenobarbitone is effective at 25% anesthetic dose.

  Higher doses are not effective against seizures.[9]

B. Rodenticides and avicides

Employed against rodents and birds in households and agriculture.

1. Warfarin and warfarin derivatives (Super warfarins)

- Also known as coumarins or colloquially as “rat poisoning”
- Possess anti-coagulative properties

Mechanism of toxicity[10]

- Vitamin K activates the coagulation factors II, VII, IX and X and anticoagulant proteins C and S
- Warfarins inhibit vitamin K_1-2,3 reductase, required for vitamin K re-activation
- Symptoms occur once active vitamin K-dependent factors have become depleted

Clinical features[10]

- Anticoagulant effects within 12-48 hours after ingestion
- Super warfarins are more potent and cause severe symptoms
- Epistaxis, flank pain +/- hematuria, intracranial bleeding, gastrointestinal bleeding, hemoptysis, gingival bleeding, menorrhagia and ecchymosis

Investigations and diagnosis

- CBC, LFT, PT/PTT, blood group and type
- Levels of vitamin K, factors II, VII, IX and X and PIVKA II (protein-induced in vitamin K absence)
- Non-contrast head CT
- Mixing study-distinguishes coagulation factor deficiency from a circulating anticoagulant

Treatment

- If asymptomatic: Observation and PT/PTT taken after 48 hours
- If elevated without bleeding signs: Vitamin K (5-10 mg per day in children and 20 mg per day in adults initially, monitor INR for long-term dose determination)
- If actively bleeding patient:

  Vitamin K_1 IV 2-5 mg at IV infusion rate <1 mg/min

  FFP (15-30 mL/kg)

  May also consider prothrombin complex concentrate (PCC) or recombinant factor VIIa

2. Calciferol (Vitamin D)

- High quantity required for human toxicity
- Important role in calcium and phosphate homeostasis

Mechanism of toxicity

- Calcium and phosphate absorption from the small intestine
- Causes bone to secrete calcium into blood and stimulates renal tubular re-absorption of phosphate.
- Toxicity exerted through hypercalcemic action

Clinical features

- Symptom onset is gradual
- Hypercalcemia, confusion, renal insufficiency, anorexia, abdominal pain, nausea and vomiting, arrhythmias, systemic metastatic calcifications, osteomalacia, lethargy and constipation

Investigations and diagnosis

- CBC, RFT, calcium, phosphorus and ECG

Treatment

- Management targets hypercalcemia
- Mild to moderate hypercalcemia (<3 - 3.5 mmol/L) - no initial treatment
- Severe hypercalcemia (>3.5 mmol/L)-Normal saline infusion

  (200-300 ml/hour or to maintain urine output of 100-150 ml/hour), furosemide, steroids, calcitonin and bisphosphonates as needed

3. Sodium fluoroacetate

- Highly toxic agent
- Lethal dose for humans is 2-10 mg/kg[11]

Mechanism of toxicity[11]

- Impairs a host of metabolic pathways
- Mimics acetyl CoA to enter and halt the tricarboxylic acid (TCA) cycle,
- Hinders metabolic pathways of fatty acids, urea and glucose

Clinical features[11]

- Symptoms onset may be delayed up to 6 hours
- Hypocalcemia, lactic acidosis, nausea and vomiting, abdominal pain, diaphoresis, altered mental status, seizure, coma, reversible renal failure, hypotension and respiratory depression
- Cardiac manifestations: Dysrhythmias
- ECG changes-nonspecific ST segment and T wave changes or QTc prolongation.

Investigations and diagnosis

- CBC, RFT-specifically, repeated calcium levels
- Repeated arterial or venous blood gases and ECG

Treatment

- No antidote exists
- Supportive management
- Any asymptomatic patient ought to be monitored for 24 hours

4. Chloralose

- Used for control of nuisance birds and rodents.

Mechanism of toxicity

- Binds allosteric sites in GABAergic neurons
- Potentiates affinity for the $GABA_A$ receptor resulting in CNS depression.

Clinical features

- Coma, extremity myoclonus, generalized convulsions and tracheobronchial hypersecretion
- Liver injury and rhabdomyolysis may be observed.
- May result in acute heart failure with hypokinesia, ST depression and elevated troponin
- Pulmonary edema also observed.[12]

Investigations and diagnosis

- Confirmed by Gas Chromatography-mass spectroscopy (GC-MS) or ^{1}H-Nuclear Magnetic Resonance (^{1}H-NMR)
- Electrocardiogram, echocardiogram and cardiac blood markers to assess cardiac function
- Chest X-ray to assess lungs for pulmonary edema.
- Liver function testing and measurement of creatine phosphokinase MM (CK-MM) levels to assess liver and monitor for rhabdomyolysis.[12]

Treatment

- Gastric lavage and activated charcoal within first two hours.[12]
- Nitrates and diuretics for pulmonary edema.[12]
- Atropine if no cardiac contraindications may be used with caution for tracheobronchial hypersecretions.
- Benzodiazepines for extremity myoclonus and convulsions.

5. Thallium rodenticide

- Elemental metal (Tl), historically used extensively as a rodenticide
- Continued use as rodenticide in developing countries
- Still used extensively in manufacturing.

Mechanism of toxicity

Substituted in membrane transport proteins and intracellular processes for potassium due to similar diameter. Binds Na-K ATPase with 10x affinity of potassium disrupting Na-K homeostasis.

- Absorbed rapidly and efficiently through mucous membranes.
- Renal excretion.
- Thought to damage mitochondrial membrane by disrupting the sulfhydryl groups.[13]
- May cause insoluble riboflavin complex formation producing riboflavin deficiency via sequestration.
- Associated with axonal nerve damage.

Clinical features

- Initially patients may experience abdominal pain, nausea and vomiting, diarrhea or constipation, sialorrhea and increased thirst.[14]
- Subsequently, patients typically manifest neurological symptoms. Paresthesias, hyperesthesia, hyperalgesia, progressive weakness originating in distal extremities (particularly great toe).[14] Diplopia, nystagmus, changes in colour perception and blindness due to optic neuritis frequently observed.[14]
- Delirium, restlessness, hallucinations and delusions are common, especially in children.[14] Convulsions in severe cases.
- Late (≈2 weeks) manifestations include yellow acneform lesions of the face and icthyotic lesions on the dorsum of the hands and feet and hyperkeratotic lesions of the soles of the feet and palms of the hands.
- Alopecia is a characteristic late manifestation.[14]
- Thallium is hepatotoxic, nephrotoxic and cardiotoxic.[14]

Investigations and diagnosis

- Unexplained neuropathy in the presence of alopecia or skin manifestations
- Urine or plasma analysis for presence of thallium is confirmatory.
- Anemia, leukocytosis, thrombocytopenia, elevated creatinine, elevated LDH, hypokalemia and elevated liver transaminases are frequently seen.[14]

Treatment

- Gastric lavage with activated charcoal within the first four hours of ingestion.
- Oral administration of prussian blue 250 mg/kg daily divided into 3-4 doses.[13] Combine with 5-10% mannitol.
- Charcoal hemoperfustion during first 48 hours.
- Hemodialysis with potassium supplementation for later stages of intoxication.
- Dithiocarbamate and forced potassium dieresis may exacerbate neurological symptoms.[13]

C. Fungicides

Fungicides inhibit fungal growth. Agriculture makes significant use of these compounds.

1. Pentachlorophenol

- Used in wood, leather, toilet paper, agriculture and oil plant products as a preservative and fungicide
- Used throughout the world.

Mechanism of toxicity

- Uncoupler of the electron transport chain
- Prevent phosphate uptake by mitochondria during oxidation of alpha-ketoglutarate.

Clinical features

- Pyrexia along with profuse sweating, tachypnea and weakness, tachycardia, irritability and lethargy.
- Coma and convulsions with severe intoxication.[15]
- Epigastric pain with ingestion.[16]
- Renal failure, liver failure and cardiac failure may occur[15]

Investigations and diagnosis

- One-dimensional thin-layer chromatography of serum is confirmatory.
- Progressive metabolic acidosis, proteinuria and elevated plasma urea.
- Chest X-ray similar to bronchiolitis or pneumonia.[15]

Treatment

- Management of pyrexia, fluid resuscitation, and correction of electrolyte disturbances.
- Exchange transfusion[15] and forced diuresis with furosemide and mannitol[16] shown effective.

2. Thiocarbamates

- Widely used internationally
- Exist in two isomeric forms: S-thiocarbamates and O-thiocarbamates.
- Used in preservation of seeds and seedlings, turf-grass, fruits and vegetables and ornamental plants.

Mechanism of toxicity

- Competes with nicotinamide adenine dinucleotide (NAD+) binding, preventing oxidation of acetaldehyde to acetate.[17]
- Influences vesicular transport within cells causing glutamate release and contributing to basal ganglia lesions.[17]
- Highly toxic to dopaminergic neurons and shown to induce accumulation of copper within the hippocampus and cerebellum, resulting in neurotoxicity. Mitochondrial uncoupling leading to perturbed respiration in dopaminergic and GABAergic neurons.Cellular destruction via the formation of reactive oxygen species

Clinical features

- Irritation of the mucosal surfaces (eyes, nose, throat, etc.).
- Coughing and dyspnea.
- Nausea, vomiting and headache similar to migraines
- Exposure to thiocarbamate solution can cause erythema and burns at higher concentrations and some patients may experience a urticarial reaction
- Epigastric pain with ingestion

Investigations and diagnosis

- Detected by measuring carbon disulfide levels in patients breath.

Treatment

- Supportive care with adequate hydration.

3. Organomercury compounds

- One of the most toxic pesticides
- Major agents-methyl mercury, methoxyethyl mercury and phenyl mercuric acetate

Mechanism of toxicity

- Absorbed through skin, lungs or gut
- Predilection to accumulate in red blood cells and the nervous system

- Long half-life in the human body (45-56 days)

Clinical features

- Metallic taste, numbness and tingling in hands and face, tremor, headache, fatigue, altered mental status, incoordination, slurred speech, loss of proprioception, hearing loss, impaired vision, muscle spasticity or rigidity

Investigations and diagnosis

- CBC, RFTs
- Mercury blood and tissue levels - >5 mcg/dL are diagnostic for acute exposure

Treatment

- Acute poisoning-Succimer , dimercapto succinic acid (DMSA) proves most effective
- Dimercaprol (BAL) exacerbates the neurologic manifestations
- EDTA is inefficacious

4. Organotin compounds

- Used to control blights
- Major agents-triphenyl tin fentin hydroxide fentin chloride and fentin acetate

Mechanism of toxicity

- Limited skin and gastrointestinal absorption
- Irritates skin, eyes and respiratory tract
- Toxic to the central nervous system

Clinical features

- Headache, epigastric pain, nausea, vomiting, dizziness, convulsions, loss of consciousness, photophobia, mental disturbances and glycosuria secondary to blood sugar elevations

Investigations and diagnosis

- Diagnosis relies heavily on clinical history with congruent clinical manifestations.
- CBC, RFTs

Treatment

- No antidote exists
- Chelating agents show no efficacy
- Supportive management only

D. Herbicides

Employed in agriculture, herbicides curtail pest plant species and are frequently formulated with toxic components.

1. 2,4-Dichlorophenoxyacetic acid

- 2,4-dichlorophenoxyacetic acid (2,4-D) used extensively for broadleaf weed control in various plant species.
- Most used herbicide in many developed countries.

Mechanism of toxicity

- Causes disturbance to the hydrophobic phospholipid bilayer in cell membranes resulting in cellular dysfunction and the development of echinocyte formation in erythrocytes.
- Causes disorganisation of the Golgi apparatus, perturbation in the function of microtubules and inhibition of synthesis of complex gangliosides.
- Acts as a false neurotransmitter mimicking acetylcholine.
- Strongly inhibits cytochrome c reductase and succinate dehydrogenase and uncouples the electron transport chain in hepatic mitochondria resulting in cellular damage.[18]

Clinical features

- Nausea and vomiting, confusion, aggression and tachypnoea are common.[19]
- Loss of deep tendon reflex, tachycardia and pyrexia with diaphoresis, vasodilatation and coma are common later signs.[20]
- Chloracne.

Investigations and diagnosis

- Gas chromatography of plasma and urine samples is confirmatory.[20]
- ST depression on ECG with prolonged QT interval and T wave inversion raise suspicion in conjunction with elevations in creatinine phosphokinase.[20]
- Isolated elevation in urea and elevated ALT and AST levels are frequent.

Treatment

- Primarily supportive.
- Alkaline diuresis shown effective.[20]

2. Glyphosate

- One of the most widely used herbicides in the developed world.
- Used in conjunction with plants engineered to be resistant to the chemical
- Molecular formula: $C_3H_8NO_5P$.

Mechanism of toxicity

- Engineered to be minimally toxic to humans and other animals.
- Primary deleterious effect from surfactant.[20] Polyethoxylated tallow amine (POETA) is a common surfactant. Causes membrane disruption and inhibits cellular respiration leading to cellular necrosis.[21]

Clinical features

- Poorly absorbed through the skin
- Hypotension, mental deterioration, abdominal pain diarrhea, nausea and vomiting are common
- Respiratory failure, acute kidney injury, severe acidosis, and cardiac arrhythmias including junctional rhythms with premature complexes, ventricular and supraventricular tachycardias, bradyarrhythmias and atrial fibrillation also seen.[21,22]
- Erosion of the gastrointestinal tract can lead to gastrointestinal hemorrhage.[23]

Investigations and Diagnosis

- Acute kidney injury, hyperkalemia, pulmonary oedema and metabolic acidosis indicative of poor prognosis.[23]
- Gas and high performance liquid chromatography to identify the presence and quantity of glyphosate in the plasma only useful for confirmation.[24]

Treatment

- No specific antidote
- Observed patients for a minimum of 24 hours.
- It is controversial whether haemodialysis is useful.[24]
- Consider gastric lavage and administration of activated charcoal within the first hour of ingestion (limited evidence).[23]
- Refractory hypotension may be treated with intravenous fat emulsion therapy.[23]

3. Paraquats and diquats

- Class: Bipyridyl herbicides
- Sole pesticide that causes severe mucosal burns

Mechanism of toxicity

- Corrosive agents
- Rapidly absorbed once ingested
- Reach most organs through the blood circulation-lungs, heart, kidney and liver are most vulnerable
- Create reactive oxygen species, destroying tissues via lipid peroxidation
- Paraquat accumulates in alveolar cells-necrosis and pulmonary fibrosis ensue

Clinical features

- Symptom onset within 6-12 hours
- Topical exposure: Skin ulceration, erythema and blistering; eye irritation and ulceration
- Inhalation exposure: Throat burns, lung damage and epistaxis.
- Oral ingestion

Small to medium dose (<15 ml 20% solution): Symptoms within days to weeks: Pulmonary fibrosis, nausea, vomiting, diarrhea and failure of liver, heart and kidneys.

Large dose (>15 ml 20% solution): Presents acutely with shock, seizure, acute kidney injury (AKI), confusion and coma, respiratory failure, perforation of viscera, hematemesis, abdominal pain and dysphagia.

- Complaints of "burning" skin carries an increased risk of lethality

Investigations and diagnosis

- Urine or serum paraquat/diquat levels
- CBC, LFTs, RFTs, serial ABG, coagulation profile and blood sugar levels-every 6-12 hours
- Chest X-ray, ECG and potentially OGD

Treatment

- No antidote exists
- Supportive management only

General prognostic guidelines for paraquat ingestion:

- <20 mg/kg-None to moderate symptoms, complete recovery
- 20-40 mg/kg-Death secondary to pulmonary fibrosis within weeks
- >40-50 mg/kg-Death within one to five days secondary to multi-organ failure, cardiogenic shock and corrosion of gastrointestinal tract.

E. Cross-classified pesticides

These pesticides possess characteristics of two or more categories of pesticide.

1. Chloropicrin

- Used widely against plant diseases, insects, and nematodes protecting vegetable, citrus, ad field crops, and ornamental plants
- Also used in the treatment of wood from pests, such as termites.
- Historically used as a rodenticide.

Mechanism of toxicity

- Inhibition of pyruvate dehydrogenase and succinate dehydrogenase.
- Activates endoplasmic mechanisms and chaperone proteins involved with protein misfolding. Misfolding of sulfhydryl containing proteins.[24]
- Shown to cause oxidative damage due to reactive oxygen species.[25]
- Irritation to epithelial surfaces on gross scale.

Clinical features

- Eye irritation, sore throat and headache, shortness of breath, cough other findings include hallucinations, tachycardia and persistent chest wall pain with increased plasma creatinine phosphokinase MM (CK-MM).
- Acute pulmonary edema may be observed in severe cases of inhalation.
- Ingestion of chloropicrin is extraordinarily rare.

Investigations and diagnosis

- Gas-liquid chromatography and GC-MS can be used to detect chloropicrin in exposed tissues, but may not be practical
- Chest radiography indicated to assess for pulmonary oedema.
- CK-MM levels and cardiac function testing to assess for muscle and cardiac damage.[26]

Treatment

- N-acetyl cysteine may be beneficial.[26]
- Continuous irrigation to exposed areas for minimum of 15 minutes.
- Ensure airway patency and treat potential bronchospams with bronchodilators.
- Observe for a minimum of 24-48 hours for possible delayed onset pulmonary oedema.

2. Arsenic

- Inorganic forms - arsenite (AsO_3^{3-}) and arsenate (AsO_4^{3-}) highly toxic[26]
- Chronic exposure to arsenic via deep-water wells poses a public health problem in many countries
- Ingestion of 100-300 mg - high risk of mortality

Mechanism of toxicity[27]

- Binds to red blood cells, which distribute arsenic to multiple organ systems
- Interferes with several enzymes
- Inhibition of gluconeogenesis, glutathione metabolism, glucose uptake and fatty acid oxidation
- Crosses placenta

Clinical features

- Acute toxicity (symptoms within minutes to hours)

  Nausea, vomiting, cholera-like diarrhea, hemorrhagic gastroenteritis, hypotension, tachycardia, dysrhythmias, myocardial ischemia

  Shock, pulmonary edema, acute renal failure, encephalopathy, seizure, dysesthesia.

  Inhalation causes acute hemolytic anaemia, jaundice, abdominal pain, and acute renal failure

- Subacute toxicity (symptoms within 1-3 weeks):

  Headache, altered mental status, sensory and motor neuropathy, QTc prolongation, pancytopenia, cough, alveolar infiltrates, rash, alopecia, periorbital edema and Mees lines

- Chronic toxicity (defined as continued low-level exposure)

  Hyper- or hypopigmented keratosis, Bowen disease, squamous and basal cell carcinoma. Hypertension, fatigue, malaise, leukopenia, anemia, peripheral arterial disease, non-cirrhotic portal hypertension, diabetes mellitus and lung cancer.

Investigations and diagnosis

- CBC, RFTs, abdominal X-ray, ECG, 24-hour urine arsenic levels (collected in a metal-free container)
- Nerve conduction studies
- Urine hCG in premenopausal females

Treatment[23]

- Chelation agents

  Unithiol IV (first-line)-slow infusion of 3-5 mg/kg for 20 minutes every 4 hours

  Dimercaprol (alternatively) - 3-5 mg/kg IM every 4-6 hours

  Once patient stable - switch to an oral chelating agent; either unithiol (4-8 mg/kg every 6 hours) or succimer (7.5 mg/kg every 6 hours or 10 mg/kg every 8 hours)

  Continuous monitoring of the heart is needed

3. Metal phosphides

- Include zinc, aluminium, and magnesium phosphide (Zn_3P_2, AlP and Mg_3P_2 respectively).
- Magnesium and aluminium phosphide used to kill insects
- Zinc phosphide used to control rodents.

Mechanism of toxicity

- Toxicity due to the phosphine produced
- Directly inhibits mitochondrial respiration by disturbing the mitochondrial membrane potential and inhibiting complex IV of the electron transport chain.[1]
- Alters mitochondrial morphology reducing its function thus inhibiting aerobic respiration.[28]

Clinical features

- Typical symptoms include shortness of breath, respiratory pain, headache, light-headedness, nausea, chest tightness or pain, dizziness, eye irritation, sore throat, and cough, nausea and vomiting, abdominal pain decreased level of consciousness and cyanosis.
- Other manifestations include blurred vision, dizziness, dyspnea, apnea, and seizures cardiac arrhythmias (sinus tachycardia, bundle branch block and ST elevation in a brugada pattern) and left ventricular failure resulting in cardiogenic shock.[2]

Investigations and diagnosis

- Electrolyte imbalances, leukocytosis and hyperglycemia.

  Acid-base imbalance (metabolic acidosis or mixed acid-base disturbances)

  Hypomagnesemia and hypernatremia

  Other findings include derangements in liver function tests consistent with hepatotoxicity
- Abdominal X-ray useful in identifying radiopaque zinc phosphide ingestion
- ECG abnormalities shown to be poor prognostic factors.
- Hyperglycemia useful in assessment of severity of intoxication

Treatment

- Gastric lavage may be performed using activated charcoal or potassium permanganate.
- A mixture of coconut oil and sodium bicarbonate has also been reported to be successfully used for gastric lavage.
- Liquid paraffin to accelerate the excretion of phosphine from the GI tract.
- Treatment of hypomagnesemia with magnesium sulphate.[29]

Prevention

- Though most poisonings resulting in hospitalisations are result of suicide attempts, majority of non-intentional poisonings result from occupational exposure.[3]
- Farmers often mishandle pesticides: In developing countries, containers often written in unfamiliar languages. Many farmers are illiterate
- In some areas pesticide poisoning results in more deaths than infectious diseases.[30]
- About 99% of deaths from pesticide exposure occur in developing countries.[4]
- May decrease poisonings by reducing use of pesticides worldwide.[30]
- Pamphlets or leaflets written in local languages with easily recognisable figures may enhance proper handling
- Control of sale of pesticides and expenditures on farmer training may further reduce poisonings.[30]
- A third of all suicides worldwide committed by means of pesticide poisoning.
- Pilot programmes in Sri Lanka and China to curtail pesticide poisoning suicide attempts:
  - Storage of pesticides by farmers in boxes requiring two keys held by two different individuals to open. Underlying factors responsible for individuals attempting or intending to attempt suicide should be addressed.
  - All pesticide poisoning patients to be given a thorough mental health evaluation.

Quick reference

Pesticide category	Pesticide class	Predominant manifestations	Specific antidote	Treatment
Insecticides	Organophosphates and Carbamates	Muscarinic (DUMBELS) Nicotinic CNS	Atropine and oximes	Give atropine - 0.02 mg/ kg in children and 1-3 mg IV in adults. within the first five minutes post infusion, the atropine dose is to be doubled. Keep repeating IV atropine till atropinization occurs and then reduce the frequency. Slowly infuse a loading dose of oximes over a 20-minute period. Pralidoxime: loading dose - 30 mg/kg IV maintenance dose - 8 mg/kg/hour Obidoxime: loading dose - 4 mg/kg IV maintenance dose - 0.5 mg/kg/hour
	Organochlorides	GABAergic overstimulation hepatotoxic, nephrotoxic, pulmotoxic	None	Seizures - benzodiazepines or barbiturates. Activated charcoal. Cholestyramine and sucrose polyester to increase faecal excretion. Hemoperfusion has been shown to be effective. Bowel irrigation may be considered.
	Pyrethoid compounds	Neurological overstimulation and neurotoxicity	None	Skin paraesthesia - wash affected area and use vitamin E containing cream or local anaesthetics. Seizures - phenobarbitone
Rodenticides and avicides	Warfarin and derivatives	Coagulopathy	None	Gastric lavage with activated charcoal if within first hour of ingestion Patients with relatively normal INR and no evidence of acute bleeding may be given vitamin K_1 1-5 mg per day in children and 20 mg per day in adults. Monitor INR every 4 hours during the first 24 hours and then daily thereafter. In patients with acute bleeds give FFP in addition to vitamin K_1 With severe, on-going hemorrhage, slowly administer vitamin K_1 intravenously at less than 1 mg/min in conjunction with FFP and prothrombin complex concentrate (PCC) [alternatively, recombinant factor VIIa in place of PCC may also be considered].
	Calciferol	Hypercalcemia	None	Treatment of hypercalcemia. Mild to moderate hypercalcemia (calcium level mild <3 mmol/L and moderate 3 - 3.5 mmol/L) Severe hypercalcemia (calcium level >3.5 mmol/L) initially infuse normal saline at 200-300 ml/hour and titrate to maintain a urine output of 100-150 ml/hour.

Pesticide category	Pesticide class	Predominant manifestations	Specific antidote	Treatment
				Give furosemide, steroids, calcitonin and bisphosphonates as needed
	Sodium fluoroacetate	Metabolic acidosis, hypocalcemia	None	Gastric lavage, activated charcoal
	Chloralose	CNS Depressant	None	Gastric lavage with activated charcoal within the first two hours. Treatment of pulmonary edema with nitrates and diuretics. Extremity myoclonus and convulsions may be treated with benzodiazepines. Atropine may be used with caution for tracheobronchial hypersecretions.
	Thallium	Neurotocicity, hepatotoxicity, nephrotoxictity, cardiotoxicity Alopecia and dermatological manifestations	Prussian blue	Gastric lavage with activated charcoal. Oral administration of prussian blue 250mg/kg daily divided into 3-4 doses. prussian blue should be combined with 5-10% mannitol for paralytic ileus. Charcoal hemoperfustion if still within 48 hours. Hemodialysis with potassium supplementation in later stages of intoxication.
Fungicides	Pentachlorophenol	Hepatotoxic, nephrotoxic and cardiotoxic	None	Exchange transfusion and diuresis with furosemide and mannitol have been shown to be effective
	Thiocarbamates	Neurotoxic, mitochondrial uncoupling	None	Supportive therapy
	Organomercury compounds	metallic taste, neurotoxic	Succimer (DMSA)	Irrigation of contaminated areas and supportive therapy and Succimer (DMSA) Note: Dimercaprol (BAL) exacerbates the neurologic manifestations and is consequently contraindicated.
	Organotin compounds	Neurotoxic	None	Decontamination of affected areas and supportive therapy.
Herbicides	2, 4-Dichlorophenoxy - acetic acid	Neurotoxic and Hepatotoxic	None	Alkaline diuresis
	Glyphosate/ POETA (Polyethoxylated tallow amine)	Cardiotoxicity, nephrotoxicity	None	Supportive therapy. Gastric lavage and administration of activated charcoal within the first hour of ingestion. Intravenous fat emulsion therapy for refractory hypotension
	Paraquats and diquats	Pulmonary fibrosis (paraquat)	None	Irrigation of exposed skin for a minimum of 15 minutes with soap and water and eyes with isotonic saline for 30 minutes. Analgesia for pain management. Gastric lavage within the first hour with activated charcoal (1-2 g/kg) or Fuller's Earth (1-2 g/kg in 15% aqueous solution)

Pesticide category	Pesticide class	Predominant manifestations	Specific antidote	Treatment
				Supplemental oxygen must be avoided to prevent the creation of further reactive oxygen species leading to more tissue damage (if the patient is severely hypoxic, only enough oxygen is to be given to maintain a PaO_2 of 60 mmHg).
Cross-classified pesticides	Chloropicrin	Mucosal irritant	N-acetyl-cysteine	Irrigation of affected areas. N-acetylcysteine treatment. Bronchodilators for bronchospasm.
	Arsenic	Varies by target organs	Chelating agents: Unithiol, dimer-caprol, succimer	Irrigation of contaminated areas. Unithiol slow IV infusion of 3-5 mg/kg for 20 minutes every 4 hours or Dimercaprol 3-5 mg/kg IM every 4-6 hours. Once stabilised, switch to an oral chelating agent; unithiol (4-8 mg/kg every 6 hours) or succimer (7.5 mg/kg every 6 hours or 10 mg/kg every 8 hours)
	Metal phosphides	Neurotocicity, hepatotoxicity, nephrotoxictity, cardiotoxicity	None	Gastric lavage, activated charcoal or potassium permanganate. Alternately, coconut oil and sodium bicarbonate may be used for gastric lavage. Liquid paraffin to accelerate excretion of phosphine. Treatment of hypomagnesemia with magnesium sulphate.

Index of common pesticide products

Pesticide Category	Pesticide class	Pesticide products
Insecticides	Organophosphates and Carbamates	Organophosphates: Acephate®, Orthene®, Azinphos®, Guthion®, Chlorpyrifos®, Govern®, Lorsban®, Nufos®, Warhawk®, Whirlwind®, MSR®, Diazinon®, Dimethoate®, Cygon®, Di-Syston®, Mocap®, Nemacur®, Fyfanon®, Dibrom®, Curacron®, Imidan®, Malathion®, Monitor®, Phorate®, Thimet®, Supracide® and Penncap-M® Carbamates: Temik®, Carbaryl®, Prokoz®, Sevin®, Furadan®, Award®, Logic®, Mesurol®, Lannate®, Vydate®, and Larvin® contain carbamate
	Organochlorides	Aldrin, chlordecone, chlordane, dieldrin, heptachlor, and mirex are no longer used many developed countries. Endosulfan and Dicofol marked under the trade names Kelthane® and Phaser®/ Thiodan®, respectively
	Pyrethoid compounds	Allethrin (RAID®, etc), Bifenthrin (Capture®, Talstar®), Cyfluthrin (Baythroid®, Tame®), Cyhalothrin (Karate®, Warrior®, Demand®, Scimitar®), Cypermethrin (Ammo®, Fury®, Mustang®), Deltamethrin (Decis®, DeltaGard®, Demand®), Esfenvalerate (Asana®), Fenpropathrin(Danitol®, Tame®), Fluvalinate (Mavrik®, Zoecon®), Permethrin (Ambush®, Pounce®), Resmethrin (RAID® Flying Insect Killer, Crossfire®, Scourage®, etc), Tefluthrin (Force®), Tetramethrin (Duracide®), and Tralomethrin (Scout®, etc)

Pesticide Category	Pesticide class	Pesticide products
Rodenticides and Avicides	Warfarin and derivatives, calciferol, sodium fluoroacetate	D-Con®, Havoc®, Jaguar®, Talon®, Contrac®, Hawk®, Maki®, Tomcat®, V Rat®, Bonide®, Kaput®, Rodex® Agrid3®, Quintox®, Rampage®, Terad3® Epibloc®, Talon G®, Gold Crest Tracking Powder®, Fluoroacetamide/1080®, Gophacide® and Gopher-Trol®
	Chloralose Thallium	PESTOFF® and AlphaRapid® N/A
Fungicides	Pentachlorophenol	Chlon®, Chlorophen®, Dowicide 7®, Penta®, Pentachlorol®, Pentacon®, Penwar®, Santophen® and Sinituho®
	Thiocarbamates	Ferbam®, Metam® and Vapam®, Aules®, Thiram®, Ziram® and Vancide®
	Organomercury compounds	MEMA®, Panogen®, Panogen M®, MEMC®, Emisan 6®, Ceresan®, Agrosan®, Shimmer-ex®, Tag HL 331®, Unisan®, Gallotox®, and PMAA®
	Organotin compounds	Triphenyl Tin®, Suzu-H®, Super Tin®, Tubotin®, Tinmate®, Batasan®, Brestan®, Phenostat_A®, Phentinoacetate®, and TPTA®
Herbicides	2,4-Dichloro phenoxy-acetic acid	Agsco 400®, Barrage®, Brush Rhap Low Volatile®, Cornbelt®, Evert 171®, Formula 40®, Hi-Dep®, Phenoxy®, Salvo®, Sutvu®, Weedar®, Weedone®, Weed Rhap®, Weed Pro®, etc.
	Glyphosate/POETA	Glyphomax®, Honcho®, Jury®, Mirage®, Pondmaster®, Protocol®, Ranger®, Rascal®, Rattler®, Rodeo®, ROUNDUP®, Ruler®, Silhouette® and Touchdown® among others.
	Paraquats and diquats	Paraquats: Bonedry®, Bonfire®, Cyclone®, Firestorm®, Gramoxone®, Helmquat®, Paraquat®, Para-shot®, Parazone®, and Quik-Quat® Diquats: Aquavet®, Diquash®, Diquat®, Edge®, Edger®, Eliminator®, Enforcer®, Harvester®, Knockout®, Liberator®, Liquid Trim®, Littora®, Razorooter®, Reglone®, Reward®, Rowrunner®, Sudden Death®, Tribune®, Tsunami®, Ultra Pondweed®, Weedplex®, Weedtrine® and Weedtrol®
Cross-classified pesticides	Chloropicrin Arsenic Metal Phosphides	Chlor-O-Pic®, Chloropicrin®, and Timber Fume® Scott's Post Emergent Crabgrass Control®, Gordon's Crabgrass and Nutgrass Killer®, and Ferti-Lome Crabgrass and Dallis Grass Killer® Postoxin®, Fumex®, Drex-PH3®, Fumitoxin®, GasToxin®, Phosfume®, Quickphlo-R®, Weevil-Cide®, Magtoxin®, Eco2Fume® and Vaporph3os®

Points to Remember

- ***The major categories of pesticides are insecticides, rodenticides and avicides, fungicides and herbicides and class classified pesticides.***
- ***Organophospates and carbamates are the widely used insecticides.***
- ***Gastric lavage or activated charcoal within two hours, atropine, oximes and benzodiazepines are used in the management of organophosphate poisoning.***
- ***The anticoagulant effect of warfarins used as rodenticides is treated with vitamin K and supportive care.***
- ***The toxic effects of thiocarbamates widely used in preservation of seeds, seedlings, fruits and vegetables managed with supportive care.***

- ***Unithiol or dimercaprol is used as a chelating agent for arsenic toxicity.***
- ***Majority of non-intentional poisonings result from occupational exposure to the pesticide due to ignorance and mishandling.***
- ***Management includes appropriate investigations , supportive care and use of recommended antidotes.***

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CLIPPINGS

COVID-19 Pandemic and Infant Neurodevelopmental Impairment-A Systematic Review and Meta-analysis

This meta-analysis of 8 studies using Ages and Stages Questionnaires, Third Edition (ASQ-3), were used for quantitative meta-analysis. It included 21,419 infants and found that 7% of infants who had neurodevelopmental screening during the COVID-19 pandemic were at risk of neurodevelopmental impairment, and 12% of those with gestational exposure to SARS-CoV-2 were at risk for neurodevelopmental impairment. Compared with the prepandemic cohort (2015-2019), the pandemic cohort was more likely to have communication impairment without significant differences in other ASQ-3 domains (eg, gross motor, fine motor, personal-social, and problem-solving). In contrast, maternal SARS-CoV-2 infection was not associated with significant differences in any neurodevelopment domain in offspring, except for increasing the odds of fine motor impairment. Thus communication impairment was the sole neurodevelopmental domain of significantly increased risk of occurrence during the COVID-19 pandemic.

These findings suggest that overall neurodevelopment was not changed by the COVID-19 pandemic, but birth or being raised during the SARS-CoV-2 pandemic, regardless of gestational exposure, was associated with a significant risk of communication impairment among the infants.

Hessami K, Norooznezhad AH, Monteiro S, et al. COVID-19 Pandemic and Infant Neurodevelopmental Impairment: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(10):e2238941. doi:10.1001/jamanetworkopen.2022.38941.

NEWS AND NOTES

RESPICON 2022

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TOXICOLOGY - I

HEAVY METAL POISONING

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Abstract: *Minerals are found everywhere and many of these are metals and are essential for the normal functioning of the body. Some are essential in very small quantities but dangerous when the body is exposed to high doses. Heavy metals like lead, arsenic, mercury and cadmium are listed as chemicals of concern. They affect many systems of the body and managed with investigations, supportive care and chelating agents in many situations. Dimercaprol is useful in acute arsenic and inorganic mercury toxicity. Calcium disodium edetate in lead toxicity, dimercapto-1-propane sulfonic acid in acute and chronic mercury toxicity. 2,3Dimercaptosuccinic acid in acute toxicity due to lead, cadmium and also in chronic arsenic toxicity, penicillamine in low grade mercury poisoning and lead toxicity.*

Keywords: *Heavy metal poisoning, Lead, Cadmium, Arsenic, Mercury.*

Minerals form a major component of the earth's core and are distributed widely in the environment. Many of these are metals and are essential for the normal functioning of the body. These metals, however, are dangerous when the human body is exposed to higher than tolerable quantities. The last two centuries of rapid industrialization and movement of human populations has led to a marked increase in the exposure of humans to dangerous levels of these metals. Lead, arsenic, mercury, and cadmium are the four heavy metals listed among the World Health Organization (WHO) list of 10 major chemicals of concern.[1]

Heavy metals are those with a specific gravity of more than 4 or those with atomic weight more than that of sodium. Many of these are found in small quantities in our body and have physiological roles like co-factor for enzymes, as a part of proteins (iron in hemoglobin, myoglobin) or as a part of enzymes (zinc, selenium, chromium). Some of these are also used solely or in combination in the treatment of some conditions (gold in rheumatoid arthritis, aluminum in antacids for gastritis, or iron, zinc, and selenium in food supplements).[2] As in any toxic exposure, management revolves around decreasing absorption, treatment of toxic manifestations, increasing excretion and monitoring for recovery of organ functions.[2] In this article, we shall discuss these 4 common heavy metal exposures (lead, mercury, arsenic and cadmium), with respect to their modes of exposure, mechanism of toxicity, clinical manifestations and management principles.

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Lead

Lead has been used by humans for its unique properties since antiquity such as low melting point; ease of casting; high density; ease of fabrication; acid resistance; chemical stability in air, water, and soils; and the ability to attenuate sound waves, atomic radiation, and mechanical vibration. The toxic effects of lead fumes were recognized by the Romans. Human exposure to lead has increased dramatically over the past two centuries with the industrial revolution, the burning of fossil fuels, the use of lead-based paints and mining industries.[3,4] Lead is a bluish-white lustrous metal. It exists in four isotopic forms in nature. Because of its non-corrosive and non-biodegradable nature, it accumulates in the environment with its continuous use.

Main sources of exposure

Sources of lead exposure can be classified as occupational, environmental and recreational (Table I). Children are vulnerable to lead poisoning because of their curiosity and age-appropriate non-nutritive hand-to-mouth behavior. It results in the swallowing and ingestion of lead-containing objects and soil or dust.

Pathophysiology

After absorption, lead is disseminated throughout the body. More than 90% of lead is stored in the bones, where it can reside for decades. In the body, it circulates bound to

Table I. Sources of lead

Environmental sources	Occupational sources	Recreational sources
1. Lead-based paints 2. House dust 3. Water due to leaking from leaded plumbing, cooking utensils 4. Contaminated air from leaded gasoline and industrial emissions 5. Food- lead solder in cans, liquors, contaminated flour, candy.	1. Automobile industry, glass industry, lead smelting and refineries 2. Metal welding and construction, painters, PVC plastic manufacturing industries 3. Ship building 4. Storage battery manufacturing 5. Rubber industry and pottery glazing	1. Ceramic crafts 2. Furniture restoration 3. Home remodeling 4. Painting 5. Automobile/boat repair 6. Target shooting and lead bullet recasting

red blood cells. A very small fraction is found in plasma. When red blood cells become saturated with lead, plasma levels begin to increase. The plasma lead gets distributed to various organs and tissues and is responsible for lead toxicity. This being a slow process, it takes months to years before clinical toxicity occurs.

Various pathophysiological mechanisms described are:

1. It has a high affinity for electron-donor ligands like sulfhydryl groups leading to its binding and affecting the function of various receptors, structural proteins and enzymes. Two major enzymes involved in heme synthesis are susceptible to lead's inhibitory effects.
2. Lead has a higher affinity for calcium-dependent processes, thereby inhibiting calcium uptake and disrupting intra and intercellular signaling and mitochondrial function.
3. It interferes with the neurotransmitter functions at the presynaptic level by inhibiting calcium-dependent protein-kinase C, which is required for brain function.
4. During infancy and childhood, it inhibits the formation of interneuron connections which results in an abnormal irreversibly damaged tertiary brain structure.
5. Lead has mutagenic effects on mammalian cells. It has definitively been shown to be carcinogenic in rats and mice.

Clinical features and complications

The appearance of clinical symptoms varies among individuals and as the lead exposure increases, the range and severity of symptoms also increase. Children are more vulnerable to lead poisoning because they absorb lead 4-5 times as much as adults.[3,4]

Neurologic: The nervous system is most vulnerable to lead toxicity in children. CNS effects are primarily because of the calcimimetic effects of lead leading to alterations in synaptic function. Neurological symptoms include headache, lethargy, seizures, papilledema, coma and death. Poor scholastic performance and behavioral changes like hyperactivity are reported in school-age children. Adolescents may present aggressive, violent behaviors.[2] The severity of symptoms shows some correlation with blood lead levels (BLL) though the susceptibility of each individual to the toxic effects varies. BLL less than 50 ug/dL usually remain asymptomatic or the child might show impaired cognition, hearing, behavior and balance. Levels between 50-70 ug/dL lead to excessive irritability and decreased interest in play. Levels between 70-100 ug/dL lead to features of seizures, ataxia, and cranial nerve palsies. BLL> 100 ug/dL lead to cerebral edema features of raised ICP and coma.[5] Peripheral neuropathy and foot drop have been seen in older patients. Prenatal lead exposure has also been implicated in cognitive and behavioral disorders.

Renal: Renal tubular dysfunction is seen at levels more than100 μg/dL. Plumbism leads to decreased energy dependent ion transport in proximal tubules leading to Fanconi's syndrome. These changes are reversible. Tubulointerstitial fibrosis, glomerulosclerosis and chronic renal failure may occur with chronic toxicity.[5]

Gastrointestinal: Gastrointestinal symptoms include anorexia, abdominal pain, vomiting and constipation. These symptoms are usually seen at BLL more than 20 μg/dL.

Hematologic: Anemia is seen as lead interferes with the activity of essential enzymes like delta-aminolevulinic acid dehydratase and ferrochelatase involved in heme biosynthesis. A decrease in the activity of ferrochelatase results in an increase of the substrate erythrocyte protoporphyrin in the red blood cells. Acute lead poisoning results in hemolytic anemia by disrupting the red cell membrane. Chronic lead poisoning induces anemia by diminishing red cell survival as well as heme biosynthesis.

Others: Chronic exposure results in accumulation in bones resulting in demineralization and rachitic deformities in children. Hearing defects, growth retardation and delay in puberty are proportionately worse with levels of lead exposure.

Diagnosis

There is no known safe blood lead concentration. Centers for Disease Control and Prevention have set the standard elevated blood lead levels (BLL) for children to be 5 mcg/dL and for adults 10 mcg/dL of the whole blood. Imaging - Bands of increased density at metaphyses of tubular bones (growing bone) Fig.1.

Management

Prevention of exposure remains the key in sustaining a low lead level. Treatment of iron deficiency and food fortification with iron has been found to decrease blood lead levels in children.

Chelation therapy: Chelation therapy is lifesaving in children with lead poisoning. Guidelines for chelation are based on blood lead levels (BLL). Children with BLL of 40-70 μg/dL can be treated with a single agent, whereas those with levels > 70 μg/dL require two agents. DMSA and calcium disodium edetate are the preferred agents (Table III). Other agents which can be used are BAL and D-Penicillamine. For children with encephalopathy, a combination of calcium disodium edetate and BAL is used. These chelating agents reduce the circulating lead levels and do not reverse neurological impairment. Eventually, the lead levels rise despite preventing further exposure, probably originating from the bone reservoir. Repeat chelation may be indicated if the BLL surge beyond 45 μg/dL after a treatment gap of 3 days.

Prevention

1. Identification and elimination of environmental sources of lead exposure.
2. Counsel the parents regarding regular hand washing and behavioral modification to reduce hand-to-mouth activity.
3. Ensure adequate dietary intake of essential minerals like iron and calcium as lead competes with these minerals for absorption.
4. Prevent malnutrition.

Mercury

Mercury exists in three forms in the environment: elemental, organic and inorganic form. Mercury toxicity

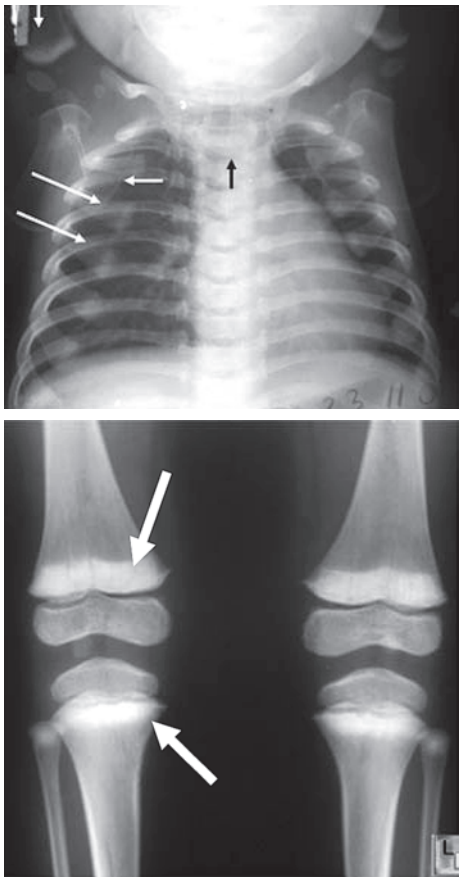

Fig.1. Radiodensity pointed by arrows in the humerus, anterior ends of the ribs, manubrium sternum, femur and fibula due to lead poisoning. Courtesy: Dr.S.Muralinath, Pediatric Radiologist, Chennai.

can occur from all three forms. At room temperature, it exists in elemental form as a silvery-white liquid metal. Inorganic forms are being used as a mixture in ayurvedic products, traditional skin-lightening creams, pesticides, fungicides, button batteries and as preservatives in medicines (thiomersal). Organic forms (methyl mercury) exist in the environment polluted with mercury and enter the human body by ingestion of contaminated food items, especially seafood. It accumulates through the food chain and is found in high quantities in predator fish like sharks, tuna, swordfish and other seafood like mussels and crayfish.[2,6]

Historically mercury poisoning with its clinical effects was described in the USA in the 1800s when it witnessed an epidemic of 'Danbury shakes' in hat industry workers. Another epidemic of note was in Japan (1959, called Minamata disease) due to the ingestion of fish contaminated with methylmercury.

Common modes of toxicity

Exposure may be to elemental mercury or mercury salt acute or chronic, small household spill or industrial from manufacturing facility.

Acute exposure

a) Biting and swallowing a mercury thermometer bulb: Fever thermometer contains only 0.5-0.7 g of mercury. Only 0.01% of the elemental mercury is absorbed and this will not cause systemic toxicity.

b) Spillage of mercury from thermometer: If properly removed, it will not cause toxicity. Removal by vacuum cleaner or broom can increase vapor production and can promote inhalation toxicity.

c) Mercury salts: They are more corrosive than elemental mercury, which enhance gastrointestinal permeability and absorption. This includes salts, such as mercurous chloride, mercuric chloride and mercuric oxide, found in adulterated skin and face creams used as cosmetic products

d) Skin contact with this metal can result in minimal absorption

e) Mercury exposure from compact fluorescent lamps (CFL): On average, mercury content in CFL is very small about 4 mg about 1/100th of mercury present in fever thermometer which is not is released when the bulbs are intact. But mercury vapor and very small beads of mercury can be released when a CFL is broken. The risks to human health from individual broken CFLs are minimal.[7]

Chronic exposure commonly occurs with the ingestion of contaminated seafood or the ingestion of traditional ayurvedic medicines and dental amalgams. Maximum permissible levels of mercury in drinking water is 2 parts per billion parts of water and for seafood 1 parts per million (ppm).

Table II. Pharmacokinetics of mercury

	Elemental	Inorganic	Organic
Route of exposure	Inhalation	GIT	GIT
Tissue of distribution	CNS, kidney	Kidney	CNS, kidney and liver
Mode of clearance	Renal, GIT	Renal, GIT	Methyl: GIT Aryl: Renal, GIT

Pharmacokinetics of various forms of mercury (Table II)

Elemental mercury is absorbed rapidly through the lungs and is distributed all over the body especially to the central nervous system due to its lipid solubility. However, enteral absorption is poor (<0.1%). In tissues, it is oxidized to form a cytotoxic divalent compound by the hydrogen peroxidase-catalase pathway. Once oxidized, its ability to cross the tissue barriers is restricted and hence elimination is impeded.

Inorganic forms are absorbed poorly (10%) through the gut and hence toxicity is less with this form. Whereas the organic form (methyl mercury) is rapidly absorbed through the gut and is distributed throughout the body and crosses the blood-brain barrier. It binds with cysteine to form a complex and is transported across the tissues through carrier proteins. Half-life in humans ranges from 44-80 days.

Mercury or its compounds in the environment are methylated by soil microbes to form methyl mercury. Enteral absorption of this form is high (90%). It has a high affinity for sulfhydryl groups and binds with reduced glutathione and avidly binds to metallothionein in kidneys and if accumulated in large quantities can cause acute renal failure.[5]

Pathophysiology: Elemental mercury is a cellular poison that disrupts multiple enzymes, proteins, and cellular membrane functions. The primary target organs are the central nervous system and kidneys. Skin or eye contact with elemental mercury can cause local irritation and contact dermatitis. Due to its avidity for covalent bonding with sulfur it displaces H ions in widely distributed sulfhydryl groups in the body. Mercury also interacts with carboxyl and phosphoryl groups that are present in various proteins and enzymes leading to dysfunction in various cellular functions. It also creates oxidative stress and disruption of DNA synthesis and membrane integrity inside the cell.[5]

Clinical features

Acute exposure

a) Most clinically significant exposures to small elemental mercury spills occurred via inhalation of mercury vapor usually from heated elemental mercury, which can result in acute lung injury with respiratory symptoms like cough, sore throat, chest pain, dyspnea, headache and visual disturbances. Other symptoms include fever, chills, gastrointestinal complaints,

metallic taste, headache and weakness. In severe cases, these symptoms may progress to respiratory failure due to necrotizing bronchiolitis and interstitial pneumonitis.

b) Neurological disturbances like tremors, movement disorders and excessive sensitivity may develop later.

c) Acute ingestion of inorganic compounds can present with gastrointestinal symptoms like nausea, severe abdominal pain, hematochezia and hematemesis.

d) In severe cases, it can progress to result in myocardial infarction, arrhythmias, renal failure, and ingestion of large quantities can result in death due to myocardial infarction.

Chronic exposure

Prolonged inhalation of small quantities of mercuric vapors (elemental form) and ingestion of inorganic compounds or contaminated seafood (organic) are the common modes of chronic toxicity.

a) Clinical manifestations include a triad of fine tremors, neuropsychiatric symptoms and gingivostomatitis. Symptoms begin with malaise, headaches, lack of concentration, hair loss, excessive salivation and gingivitis. If prolonged, neurological symptoms like tremors, movement disorders, ataxia, incoordination and behavioral disturbances like delirium, insomnia and memory loss can occur.

b) Renal manifestations like proteinuria, hematuria and nephrotic syndrome have been described.

c) Pink disease or acrodynia occurs as dermatological hypersensitivity to mercury in children. Clinical presentation includes reddish pink exanthems, pain, desquamation and oedema of hands and feet with neurological symptoms like paresthesia. Other features like anorexia, tremors, insomnia, excessive sweating, photophobia and proximal weakness can occur.

Investigations

- After acute inhalation of mercury vapor, chest X-ray can show infiltrates or pulmonary edema.
- Urinary mercury levels estimated in the 24-hour sample is the preferred method for all forms except organic compound exposure (methyl mercury). It is useful in measuring the total body burden of elemental and inorganic mercury, especially in occupational exposure. Peak levels are attained about 2-3 weeks of exposure. Treatment is warranted for urinary levels >100 μg/L.[8]
- For organic compound poisoning, blood and hair mercury levels can be estimated. Blood levels have a half-life of only 3 days and hence, have limited value if estimated beyond this time. Blood levels of >35 μg/L is an indication of chelation.[8]
- Renal injury can be detected by microalbuminuria.

Management

Patient should be referred to appropriate toxicology centre, with place and urgency guided by the severity of illness and circumstances of the exposure.

Chelation therapy: Dimercapto -1- propane sulfonic acid (DMPS) and DMSA are preferred chelating agents for both acute and chronic mercury toxicity (Table III). They both bind inorganic mercuric compounds and are effectively excreted. However, they do not chelate from the central nervous system and their effectiveness in reversing symptoms is not clear.

Prevention

a) Prevention of exposure from broken CFL or thermometer: If broken indoor, a small amount of mercury vapor is released immediately. Open windows, leave the room without stepping into the mercury spill, and close the door. Stay out of the room for at least 15 minutes. Turn off the heat or air conditioning so that any mercury vapor is not circulated. Do not use a vacuum or broom to clean up the pieces but remove the mercury stiff piece of paper or cardboard or using damp paper towels. Put all debris in a sealed glass jar or sealed plastic bag and keep it outside. Finally wash your hands. Check with your community about disposing of the material.[7]

b) Chronic dietary intake of mercurial compounds can be prevented by avoiding seafood grown from contaminated waters. The United States Environmental Protection Agency recommends avoiding fish with mercury more than 0.66 μg/g. Inhalation of mercury vapors can be prevented by avoiding exposure to broken fluorescent bulbs or elemental mercury from broken thermometers.

Arsenic

Arsenic is an abundantly available toxic metal in the natural earth's crust. The chemical forms available are elemental arsenic, arsine gas, inorganic arsenic salts and organic arsenic. Among these, arsine gas is the most toxic. Arsenic toxicity can be accidental, intentional, environmental or iatrogenic in nature.

Chemical characteristics

i) Elemental arsenic is insoluble in water, hence not absorbed and non-toxic.

ii) Arsine gas is a colorless, non-irritant gas emitted when arsenic compounds are treated with acid. Inhalation of even small quantities like 25-50 ppm can result in death in 30 minutes and quantities up to 150 ppm can cause immediate death.

iii) Inorganic form is found in \pesticides, dyes, homeopathic medicines and household medications. It is well absorbed through the skin and mucosal membranes and eliminated predominantly by the kidneys. The trivalent form (arsenic trioxide) is lipid soluble and hence more toxic. Exposure to about 2mg/kg in a child can be fatal.

iv) Organic compounds are poorly absorbed through the gut and are less soluble and less toxic.

Main sources of exposure

i) Natural resources: Rocks, soil, well water

Humans are exposed to an average of 20 μg/day from food and water.[8] According to WHO guidelines, drinking water should not contain more than 10 μg/L of arsenic.[9] Epidemiological studies in West Bengal, Uttar Pradesh, Bihar, Jharkhand and Assam have revealed higher levels in drinking water and a high prevalence of skin manifestation of arsenic poisoning.

ii) Parental smoking

iii) Industrial sources: The burning of fossil fuels, as a byproduct in the smelting of copper, lead, zinc, as a component in wood preservatives and pesticide manufacture

iv) Medicines: Cancer chemotherapy, alternative medicines, opium, homeopathic remedies, 'moonshine ethanol', kelp, melarsopol

Pathophysiology

After exposure to arsine gas, absorbed metal binds to hemoglobin and is oxidized to arsenic dihydride and elemental arsenic, which results in cell membrane instability and massive hemolysis. Arsenic trioxide (inorganic form) binds to sulfhydryl groups and causes uncoupling of oxidative phosphorylation by being substituted for phosphate in the glycolytic pathway and decreases adenosine triphosphate production by inhibiting enzymes like pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase complex. It also inhibits thiolase there by affecting fatty acid oxidation leading to further impairment of ATP production. It also induces reactive oxygen species and oxidative stress which in turn triggers apoptosis and cell death. Arsenic also alters cardiac repolarization and hence can lead to ventricular dysrhythmias. Arsenic is methylated and mainly excreted by kidneys with a half-life of 2.5 days. High concentrations are reached in bone and keratinized tissues like hair, nails and skin.[8]

Clinical features

Acute arsenic toxicity

Gastrointestinal manifestations are common and begin within 30 minutes after oral consumption of arsenic compounds; often presenting with dysphagia, garlic taste and severe thirst. Abdominal pain, vomiting, and bloody or rice water diarrhea are also common. Inhalation of arsine gas results in malaise, gastrointestinal side effects, massive hemolysis presenting as hemoglobinuria, jaundice, pallor, and renal failure. Cardiac arrhythmias like torsade de pointes and ventricular fibrillation are common. Severe muscle cramps, neurological manifestations like delirium, seizures, encephalopathy, coma and death can occur. Exposure to low doses presents with maculopapular eruptions in the intertriginous areas along with other manifestations. Patients who recover from the acute illness may develop peripheral neuropathy, hematuria and proteinuria after days to weeks of exposure.

Chronic toxicity

It usually occurs in areas with high concentrations of arsenic in drinking water. Clinical manifestations usually appear after 5 to 20 years of exposure. Common manifestations are

i) General: Garlic odor on breath, generalized fatigue, Excessive perspiration, hyperpigmentation (raindrop-shaped spots, diffuse dark brown spots, diffuse darkening of the skin), keratosis especially of palms and soles, Mees lines on the nails (transverse white striae)

ii) Neurological: Intellectual disabilities, muscle weakness, and tenderness on examination, Sensorimotor polyneuropathy - paresthesia of hands and foot

iii) Others: Gangrene of foot, features of bone marrow suppression, cancers of lung, bladder and skin in adults

Prenatal arsenic exposure can lead to spontaneous abortion, stillbirth, and an increased risk of pneumonia and diarrhea in infancy.

Management

In patients with acute toxicity, stabilize the airway, breathing and circulation. Gastric lavage should be performed if the patient presents within the initial few hours of exposure. Chelation therapy should be initiated for those with clinical signs of acute toxicity (Table III). Those exposed to arsine gas need close monitoring for evidence of hemolysis. Patients with circulatory failure may require fluids, blood transfusion, vasoactive medications and mechanical ventilation for stabilization.

Chelating agents are dimercaprol or dimercaptosuccinic acid (DMSA) or d-penicillamine. In acute toxicity, dimercaprol is most preferred while DMSA is preferred in the chronic toxicity.[9] Monitoring in the intensive care unit is indicated in patients with hemodynamic compromise, neurological symptoms, respiratory failure, severe hemolysis and those with multiple organ dysfunction syndrome.[10]

Invesigation

Arsenic concentration should be estimated with a 24-hour urine sample and any level more than 50 μg/L suggests toxicity and is an indication for chelation therapy.[2] Other organ function tests including liver function tests, renal function tests, total leucocyte counts, platelet counts, urine protein and urine hemoglobin tests can be done based on clinical presentation. Estimation of arsenic levels in hair, nails and skin can be done in patients with chronic toxicity.

Prevention

Drinking water should be periodically tested for concentration of arsenic. Children should be prevented from being exposed to smoke from burning treated wood, pesticides and smelting industrial smoke. Passive smoking should also be prevented.

Cadmium

Cadmium is a heavy metal widely used for a variety of industrial purposes. In combination with other metals cadmium forms alloys with low melting points leading to its extensive use in welding and soldering industries. It is also used in electroplating as well as in nickel-cadmium batteries.

Chemical forms: Cadmium toxicity continues to be a health hazard in developing economies. Cadmium exists in the form of salts (sulfide and oxide). Cadmium oxide fumes also can cause acute toxicity.

Table III. Chelating agents

Drug	Dose	Route	Indication	Side effects
Dimercaprol (BAL)	3 mg/kg (max 150mg) 4 hourly for 2 days followed by twice daily for 10 days (for inorganic mercury toxicity - 5 mg/kg on first day followed by 2.5nmg/kg every 12 hourly for 10 days)	Intramuscular	Acute arsenic toxicity Inorganic mercury toxicity	Pain at injection site, nausea, abdominal pain, feeling of constriction of chest, sweating, tachycardia, hypertension, hemolysis in G6PD deficient
Calcium disodium edetate	1000-1500 mg/m^2/day divided every 12 hourly for 5 days	Intravenous infusion or intramuscular	Lead toxicity	Proteinuria, pyuria, rising blood urea nitrogen. creatinine
Dimercapto-1-propane sulfonic acid (DMPS)	10 mg/kg/dose thrice daily for 3 days	Oral, intravenous	Acute and chronic mercury toxicity	Nausea, vomiting, fatigue, rash, pruritus
2,3 - Dimercapto-succinic acid (DMSA)	350 mg/m^2 or 10mg/kg every 8 hourly for 5 days. Then 12 hourly for 14 days	Oral	Acute lead toxicity, cadmium toxicity, chronic arsenic toxicity	Nausea, vomiting, diarrhea, anorexia, transaminitis, transient hemolysis, reversible neutropenia
Penicillamine	5-7.5 mg/kg every 8-12 hourly for 4 to 12 weeks	Oral	Low grade mercury poisoning, lead toxicity	Leucopenia, thrombocytopenia, proteinuria, fever, rash, transaminitis

Sources of exposure

1. Animal foods: Fish, oysters, mussels from polluted water bodies
2. Rice and wheat grown in contaminated soil
3. Tobacco smoke
4. Industrial dust - copper or zinc smelting factories, batteries, paints, plastics, coal mining

Pathophysiology

Cadmium is a highly toxic heavy metal. It is absorbed in the body after ingestion or inhalation of cadmium-containing compounds. Intestinal absorption is to the tune of 5-20% but increases in children during calcium, zinc and or iron deficiency states. After absorption, it binds with metallothionein and the circulating free metal determines the toxicity. Cadmium generates metabolic stress and affects mitochondrial respiration and oxidative phosphorylation and increases the production of reactive oxygen species. At higher concentrations, it affects cell proliferation, halts metabolism and induces apoptosis. Acute exposure can affect the kidneys with damage to proximal tubules resulting in acute tubular necrosis. With chronic exposure, cadmium gets deposited in bones, causing demineralization and skeletal deformities. It also gets concentrated in the kidneys and causes cortical damage and chronic kidney disease. Along with lead exposure, it can act synergistically resulting in neurodevelopmental disabilities and a high risk of proteinuria and renal failure in children

Clinical features

Acute toxicity usually involves the site of entry. Inhalation of toxic fumes often leads to severe pneumonitis and can be fatal. Cadmium pneumonitis mimics metal fume fever. Constitutional symptoms and respiratory symptoms usually begin within 6-12 hours of exposure. Those who survive acute pneumonitis may develop chronic respiratory complications like small airway disease and pulmonary fibrosis. Ingestion of cadmium can often lead to significant GI toxicity. A dose of about 70mg/kg may prove fatal.[11] Acute GI toxicity mimics that of caustic injury. Chronic cadmium exposure is much more common, and it affects the bones, kidneys and neurodevelopment. Bone involvement clinically manifests as osteomalacia in severe cases (also called as Itai-Itai disease in adults, first described in Japan). It can result in renal damage presenting early with features of proximal tubular dysfunction like polyuria along with aminoaciduria, sub-nephrotic proteinuria, glucosuria, phosphaturia and hypercalciuria. In long term, these patients may evolve into chronic kidney diseases. Neurodevelopmental disabilities like hyperactivity, cognitive dysfunction, and behavioral changes have been described with chronic toxicity and in those with in-utero cadmium exposure. Immune dysfunction especially of T cell lineage is increasingly described. Inhalation of cadmium vapor can manifest with signs of lung inflammation and may evolve into emphysema and some cases pulmonary fibrosis. Cadmium is carcinogenic and has been associated with liver, bladder, gastric and hematopoietic malignancies in adults.

Investigations

Cadmium can be detected in blood and urine. Elevated blood levels indicate acute exposure while elevated urinary levels indicate high cadmium load in the body suggesting chronic exposure. Urinary cadmium concentration of more than 0.5 μg/g of creatinine correlates with renal injury.[11] Blood cadmium levels can be detected if it is above 0.3 μg/L. It can also be estimated in nails, hair and saliva. Accurate testing of the total body load of cadmium requires urine provocation testing.

Management

Chelating agent: Dimercaptosuccinic acid (DMSA) and its mono esters are effective in cadmium toxicity. Commonly used DMSA monoesters are - monoisoamyl DMSA, monomethyl DMSA and monocyclohexyl DMSA. They bind both the circulating and the intracellular forms and are more effective in chelation. A combination of DMSA and its monoester can also be used. N-acetyl cysteine decreases heavy metal-induced hepatic and renal oxidant stress and has been recommended as adjuvant therapy. Zinc and magnesium are protective by decreasing reactive oxygen species and lipid peroxidation and can be used in reversing cadmium-induced renal toxicity. BAL binds with cadmium to form a complex (BAL-cadmium complex) which is more nephrotoxic, increases liver and kidney cadmium levels, and may result in poor outcomes. Hence, BAL is not used in cadmium intoxication.

In severe cases with renal failure, hemodialysis may be needed as a supportive measure. Plasma exchange in younger children or plasmapheresis has been used in patients with high levels of cadmium as a measure to remove the protein-bound heavy metals.[12]

Prevention

Cadmium emissions from the smelting factories should be strictly monitored and the surrounding areas are

screened for contamination. Epidemiological studies targeting human exposure, air, soil levels, and drinking water levels should be undertaken. Food grown in these contaminated areas should be screened for cadmium levels. Indoor passive smoking should be avoided.

Conclusions

Environmental heavy metal poisoning is a common and preventable cause of morbidities in children. Preventive measures include regular screening of drinking water, soil, and air to assess the exposure to these metals, legislative measures to ban the use of these chemicals in household products, relocating of factories in non-residential areas and creating public awareness about the problem. The acuity of exposure, duration, route, type of compound, clinical manifestations and organ systems involved should guide the diagnosis and treatment of heavy metal toxicity.

Points to Remember

- ***Lead, arsenic, mercury and cadmium are the four heavy metals listed among the WHO list of 10 major chemicals of concern.***
- ***Acute lead poisoning results in hemolytic anemia . Chronic lead exposure leads to multisystem involvement, of which the nervous system is the most vulnerable, gastrointestinal ,renal , hematological and bone can be affected and a BLL of >40 ìg/dL requires chelation.***
- ***Garlic odor on breath, muscle weakness, tenderness, generalized fatigue, excessive perspiration, sensorimotor polyneuropathy, hyperpigmentation, keratosis of palms and soles and Mees lines on the nails are classical manifestations of chronic arsenic toxicity.***
- ***A triad of fine tremors, neuropsychiatric symptoms and gingivostomatitis indicate chronic mercury toxicity.***
- ***Acute tubular injury and necrosis is the predominant manifestation of acute cadmium toxicity.***
- ***Management revolves around decreasing absorption, treatment of toxic manifestations, increasing excretion and monitoring for recovery of organ functions.***
- ***The use of unleaded petroleum products is recommended to reduce lead exposure .***

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TOXICOLOGY - I

POISON INFORMATION CENTRE

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Abstract: *Poison information centres are specialized units that advise on the diagnosis and management of poisonings with additional roles in public outreach, response to chemical incidents, training of health providers, public awareness and identification and evaluation of toxic risks in the community. In India, with a population of 1.3 billion with over 20,000 estimated deaths related to deliberate self-harm, poison information services are yet to become popular. Poison information centres have been noted to be cost-effective and efficient in disseminating emergency information related to poisoning and envenoming. They have a pivotal role in toxovigilance, chemical outbreak prevention and exposure management, capacity building and outreach of the centres in India which are subpar to the western counterparts. In this article, we focus on the various functions of poison information centres and the challenges faced in the Indian setting.*

Keywords: *Poison information centre, Unintentional poisoning, Pediatric poisoning.*

Poisons information centres (PICs) are defined by the World Health Organisation (WHO) as specialised units which provide advice on diagnosis and management of poisonings in patients of all ages.[1] All modes of exposure, routes and circumstances such as accidental, environmental, intentional and unintentional are handled by such centres.[1] Additionally, PICs may also assist in poisoning prevention strategies, public outreach, response to chemical disasters, training of health providers, public awareness and identification and evaluation of toxic risks in the community.[1]

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The structure and function of PICs tend to vary worldwide. However, at a minimum, they provide advice on the diagnosis, treatment, and prevention of poisonings in cases of human and in some instances, animal exposures.[1] This constitutes the basic function of a poisons information service. Some units are additionally attached to diagnostic laboratories and/or clinical treatment units.[1] This update focuses on the structure, function and challenges faced by poisons information centers in the Indian context.

The need of PICs

Since the establishment of the first poisons information centre in 1949 at Netherlands, developed countries have expanded the numbers and function of PICs manifold. The drive for this expansion was due to industrialization and the development of new drugs and chemicals. Healthcare professionals need to update their skills because of the changing spectrum of poisoning. Therefore, the need for a source of readily accessible information and expert advice on management was necessary.[2] However, there has been limited progress in the development of poison information centres in developing countries. As of January 2021, only 47% of WHO member states have a poison information centre.[3] These services are severely lacking in many developing countries where the need is the most.[4]

The WHO estimates that 2,50,000 deaths occur due to poisoning every year worldwide.[5] Of these, 1,50,000 deaths are due to pesticide poisoning, predominantly in low and middle-income countries.[6] Though a formal reporting system is lacking in India, reports from institution-based studies suggest accidental poisoning being responsible for 36.6% of all deaths due to poisoning. Mortality in the rural population due to poisoning has been reported to contribute to 83% of all poisoning related deaths.[7] Furthermore, a recent review supplemented by WHO mortality data estimated that the highest number of poisoning-related deaths in the South-East Asia region, amounting to approximately 65,000 each year, were being reported from India, this despite the gross under-reporting due to lack of ICD-10 code usage and failure to transfer data to the WHO Mortality Database.[6] Additionally, with nearly 60,000 annual deaths due to

snakebite envenoming each year, India has the highest snakebite-related mortality rate in the world.[8]

Despite these alarming statistics, in an observational study amongst emergency physicians in India, 44% of respondents reported the lack of poison information centres for availing expert opinion in times of emergency.[9] Till date, India has less than ten well-established WHO-listed poison information centres for a population of over 1.3 billion.[10] In yet another survey amongst medical officers in rural India, 70% were not confident in managing of poisoning cases and felt that training, workshops and access to information in times of emergency was necessary.[11]

Structure and function

The workforce involved in a poison information centre is multidisciplinary and usually includes specialists in poisons information and physicians with experience or specialised training in toxicology. Poisons information specialists belong to varied biomedical or health backgrounds and are generally trained specifically in receiving and responding to poisoning related queries in emergency settings. Additionally, several specialist advisors including experts in toxinology, epidemiology botany, entomology, herpetology, teratology and veterinary sciences can be affiliated with PICs to provide advice from time to time.[12] While these experts are not permanent members of staff, they are usually linked to information centers through formal agreements defining expectations of the centre and details on timings and modes of contacting them. The workflow through a poison information centre is illustrated in Fig.1.

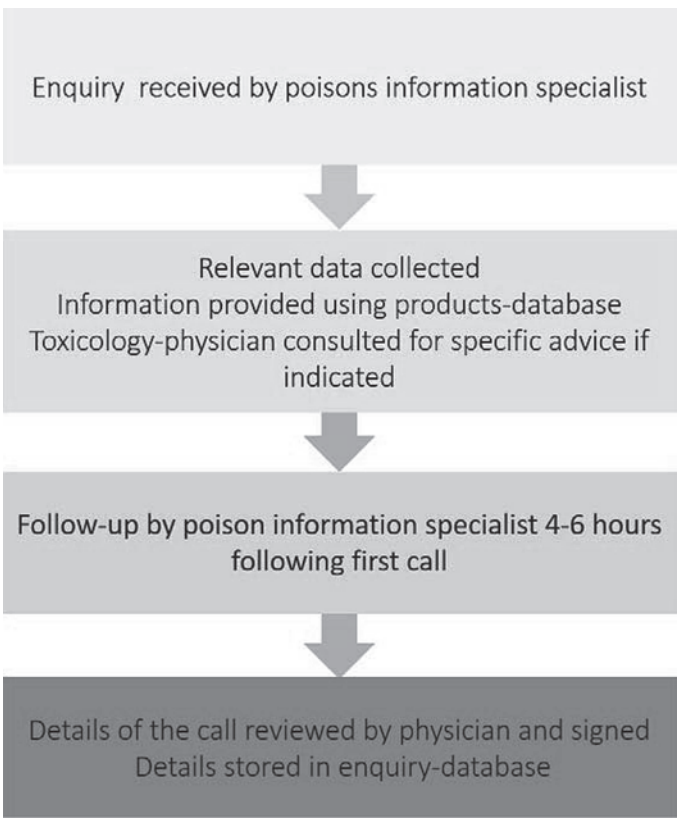

Fig.1. Workflow through a typical poisons information centre

Information regarding poisons is shared predominantly via the telephonic medium which is especially useful during emergencies. Many centres run the telephonic service 24-hours a day, 7 days a week to assist with emergency information though the timing of availability can often vary. Additional channels of communication include computer networks, written responses to enquiries and publications. With the advent of easier means of multimedia communication and their widespread use, many centres are now accessible via media like WhatsApp ©. In this role, PICs have been able to aid in the remote identification of indigenous plant poisons, pesticides and pharmaceuticals and guide management of associated poisonings in remote and rural settings through verbal descriptions of the toxidrome and shared pictures of the implicated agent via telephone camera or computer.[13]

Callers who seek advice from a poison information centre may be health professionals, other professionals (such as police, schools) or the general public. The information is tailored to the circumstances and is appropriate to the enquirer's level of knowledge and understanding.[14] Evidence-based advice on recognition of the toxidrome, relevant investigations and management is provided, thus preventing ineffective or unnecessary treatment.

Access to toxicology databases is critical in disseminating information to callers regarding the toxic dose, toxokinetics, clinical features and management of the exposure. Various restricted-use clinical toxicology databases such as AFRITOX, POISINDEX, TOXBASE and TOXINZ, are available on subscription for registered users. A potential limitation associated with such databases is that many are skewed towards poisons and chemicals prevalent in the country of origin. Consequently, they provide limited or no data on agents of concern to PICs in other parts of the world. This is especially important in the Indian setting where information on a variety of indigenous plant poisons and animal toxins is limited or absent from most international databases, necessitating the compilation of local repositories on regional poisons and venomous animals by centres. Additionally, product-related information is often missing or incomplete on container labels of chemicals commonly implicated in poisonings in

India. This complicates the task of accessing product information from available databases and highlights the need for clinicians in Indian centres to identify likely culprit agents through analysis of the presenting toxidrome, before databases can be accessed. Potential errors in the identification of the toxin, injudicious use of antidotes can thus be avoided in the presence of poison information centres.[15] Online repositories such as PubChem and other general toxicology databases are freely available over the world. Other important sources of information include bibliographic databases, journals and books.

The systematic collection and storage of toxicological data from all received enquires is a key function of PICs. This stored knowledge forms the "enquiry database" and is vital for providing accurate information on indigenous poisons, venoms and toxins. It also helps track poisoning-trends across a country or region, thereby aiding in the early identification of outbreaks or chemical disasters.

Newer roles

In addition to information provision, poisons information centres can play key roles in toxicovigilance and chemical disaster response. Toxicovigilance refers to the active identification and assessment of the risk of toxicity from exposure of a community or population to consumer products, pesticides, pharmaceuticals, environmental and industrial chemicals, controlled substances and natural toxins.[1] Poisons information centres can participate in toxicovigilance by identifying trends in poisoning via registry of cases on a daily basis and surveillance of the collected cases. The emergence of a new risk associated with an agent of concern can thus be rapidly identified and health authorities notified for planning containment exercises and countermeasures.[15]

The commonest mode of toxicovigilance practised worldwide is through mandatory reporting. For instance, in Brazil, notification of poisonings attributed to pesticides and highly toxic substances, has been mandatory since 2012. Likewise, there has been a recent move for improved notification of pesticides and street poisons in South Africa.[16]

In the Indian setting, mandatory reporting of poisonings with organochlorines such as endosulfan, (which are still being used in certain parts of the country despite a nationwide ban under the Insecticide Act in 1968), recreational agents like cannabis, opium and methanol,[17] can result in significant reduction in the rates of preventable deaths and poisoning-related morbidity burden in the country.[18,19]

In yet another aspect of toxovigilance, reporting of adverse drug reactions due to counterfeit medications, and medication errors[20] can help save many lives. An example of this was the notification of potentially counterfeit Percocet tablets in Georgia, USA. Percocet contains acetaminophen and prescription-strength oxycodone. This was bought over the counter without a prescription by affected individuals. Post-ingestion, six individuals developed central nervous system (CNS) and respiratory depression, later identified as an opioid toxidrome at the regional medical centre. All patients required high doses of naloxone to reverse symptoms and one patient eventually died. These events were rapidly notified by the emergency department of the treating centre to the Georgia Poison Center which played a pivotal role in coordinating multiagency joint-response measures that included messaging the public and regional hospitals on the risk of counterfeit medicines, developing a counterfeit Percocet cluster case definition and contacting the Georgia Bureau of Investigation for chemical analysis of obtained pills which led to the identification of cyclopropyl fentanyl and U-47700, two rare and potent illicit synthetic opioids capable of causing fatal respiratory depression even at relatively low doses as the culprit agents.[21]

In India and other snakebite endemic countries where reporting of snakebite envenoming is poor, making snakebite a notifiable condition could improve the collection of epidemiological data to support targeted mitigation initiatives, antivenom development and provision.[22]

Chemical safety, prevention and mitigation of an outbreak

A chemical incident can be defined as the uncontrolled release of a toxic substance resulting in potential or actual harm to public health and the environment.[1] This includes events such as an explosion at a factory or chemical spillage on roadways and other transport routes, natural events such as volcanic fires and exposure to natural toxins like aflatoxin or arsenic or fluorine contaminated ground water.[23,1] In 2007, the Global Plan of Action agreed by the International Conference on Chemicals Management (ICCM1) reinforced the importance of poison information centres in chemical safety and management of outbreak.[1]

Poison information centres are usually the first set of agencies notified of a chemical emergency, often by a call from a concerned member of the public or first-response health-facilities (Box 1). Therefore, poison information centres play the role of an alert system for preparedness against chemical terrorism attacks and accidental exposures.[19]

Box 1. Experience of the poisons information center at Christian Medical College (CMC-PCC) in chemical incident mitigation

The poison centre at the Christian Medical College (CMC), Vellore receives queries on aspects of poisonings, bites and stings from the general public and health-providers from across India. Listed below is a summary of emergency calls received at the centre following recent chemical incidents and disasters.

7 May 2020

Styrene leaked from a chemical factory at the outskirts of Visakhapatnam, Andhra Pradesh on May 7 2020. This leak resulted in a vapor cloud that spread over a radius of 3 Km and left 11 people dead. The CMC poison centre first started getting calls from local hospitals requesting help in managing patients who were presenting with a respiratory irritant effect and CNS depression. Through follow-up calls to these hospitals the centre tracked the incident in real time and supported health authorities and local hospitals with information on first aid and emergency management of styrene poisoning.

6 January 2022, 4:45 AM

A mixture of toxic gases was released when a tanker dumped its sulfuric acid rich contents into a public drain in Surat, Gujarat. The poison centre was called by the Surat Government Hospital within 40 minutes of the incident. A clinical diagnosis of hydrogen sulphide and sulphur dioxide inhalational poisoning was made. The centre supported health providers with information on managing gas poisoning for nearly 45 victims of the exposure.

14 April 2022, 1AM

Three workers at a lead-acid battery recycling plant located nearly Mangalore, Karnataka were exposed to a toxic gas while improperly handling lead dross. They rapidly developed kidney failure and were admitted to a local hospital. The poison centre was called for information on likely diagnosis and management. A clinical diagnosis of acute arsine poisoning was made and the patients transported by ambulance to the clinical toxicology unit at CMC. Diagnosis of arsine poisoning was confirmed and the patients treated with oral chelation and renal support.

Challenges and prospects of PICs in India

Western studies show that poison centres reduce the need for referral of low toxicity exposures. The American Association of Poison Control Centres (AAPC) report showed that there was 1:14 benefit for each US dollar spent amounting an annual benefit of US $ 1.8 billion, with similar reports worldwide.[24] In a systematic sampling of care-takers of under-six year old children, amongst those interviewed, 93% managed the children at home, mostly requiring no treatment. 43% would have sought medical attention for the child at a health care facility if the poison centre did not exist and of those 81% would have gone to an emergency centre or hospital for evaluation.[25] Similarly, a telephone survey of primary healthcare providers calling the National Poisons Information Service of the United Kingdom estimated that these services prevent approximately 41,000 emergency department referrals annually.[26] In the United States of America, in the year 2020, 55 U.S. poison control centres provided telephone guidance for over 2.1 million human poison exposures.[27]

Amongst emerging economies, Thailand is a leading example of how poison information centres can positively impact health outcomes of the country as a whole. The Ramathibodi Poison Centre at Bangkok was established in 1996 when access to poisons information and antidote availability were a challenge.[28] The centre met these needs through round the clock consultations and a national antidote and antivenoms program.[29] In 2020, the centre provided guidance to over 29,000 unique consultations.[30]

Despite the bleak statistics on poisoning and envenoming-related mortality and morbidity in India, the concept of poison information centres is yet to catch-on. The few well-established poisons information centres that India possesses continue to be grossly under-utilized. A retrospective analysis of poisoning calls received by the National Poisons Information Centre showed a total of only 2719 calls over a period of three years (April 1999-March 2002).[31] A South Indian observational study noted that only 40% health care workers were aware of the availability of poison information centre. 31% preferred

to use the internet or department reference libraries (25%), even though these may be unreliable or outdated.[32]

Amongst those Indian health-providers who do access poisons information centres, a majority appear to do so late in the natural history of toxicological illnesses, when patients clinically deteriorate. For instance, analysis of data on poisoning calls received between 2020 and 2021 at the CMC Poisons Centre revealed that 68% of all calls from health-providers were made after the clinical status of a patient worsened. Additionally, the injudicious use of snake antivenom (92%) in unknown bites and intravenous atropine in agrochemical poisonings with non-organophosphates (87%) were highly prevalent (unpublished data). The situation is worsened further in the current context as there are very few training options in medical toxicology in India. Further complicating issues are paucity of formal training courses in medical toxicology, challenges in financing of poison centres and the lack of legislation for mandatory reporting of poisoning incidents.

The development of poisons information centres in India urgently requires awareness campaigns amongst the general public and sensitization measures on their need and functions amongst Indian health-workers. This must be complemented with the establishment of adequate numbers of centres and access to reliable databases. In addition, good networking amongst existing poison centres and with policy makers and government authorities is vital for a sharing of data and resources, and exchanging information on incidents and co-ordination of countermeasures for effective toxicovigilance and chemical disaster response.[33]

Conclusion

The onus of improving care for patients with poisoning lies on the physicians, teachers of medical curriculum and government regulatory bodies alike. The need to encourage interest among medical students, postgraduates in the field of toxicology is required. There is also need for hospitals in different regions of the country to develop training and capacity to set up poisons information centres. Through poisons information centres, knowledge related to toxicology and appropriate evidence-based management of poisoning and envenoming can be ensured to health care professionals in primary, secondary and tertiary health care setting. Dissemination of awareness about poisons information centres and their availability for answering queries of the caller helps prompt guidance.

In the future, poisons information centres will continue to expand their roles involving training of health care professional and general public in appropriate first aid, referral of sick poisoned patients and appropriate antidote usage, education of at risk individuals regarding occupational and worker safety, prevention of occupational diseases and management of substance abuse. In collaboration with the government, data collected from poison registry can help in enforcing stricter regulations on manufacture of toxic agrochemicals and proper labelling of all chemicals can have far reaching benefits for overall improvement in poison care.

Points to Remember

- ***PICs are specialised multidisciplinary units which provide information on diagnosis and management of poisonings to the health care provider.***
- ***In addition to information provision for an individual patient, poisons information centres can play key roles in toxicovigilance, chemical disaster response, etc.***
- ***Many emergency referrals can be avoided because of the poison control centres, which provide advice for those who may not require any treatment.***
- ***Mandatory reporting of poisonings can result in significant reduction in the rates of poisoning related morbidity and mortality.***
- ***India urgently requires awareness campaigns amongst the general public regarding poisoning as well as establishment of adequate numbers of centres and access to reliable databases.***

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GENERAL ARTICLE

TELECOUNSELING IN CLINICAL PRACTICE

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Abstract: *Globally, telemedicine has been accepted as an important means to provide medical care, especially during the pandemic. Telecounseling is an adjunct to telemedicine which has evolved over the last two decades in India and has reached parents and children for treatment, effective follow up and health education. Telehealth is the digital summation of telemedicine. Pediatricians should follow Government of India's telemedicine guidelines 2020 during telecounselling sessions.*

Keywords: *Telecounseling, Telemedicine, Telehealth, Children.*

"Telemedicine is the natural evolution of health care in the digital world."[1] It delivers health care services effectively using information and communication technologies where distance to access medical help is a major limiting factor. In 1959, the first known video consultation was done by doctors at University of Nebraska, U.S.A for neurological examination.[2] Telemedicine in India got a vital start when Indian Space Research Organisation did a telemedicine pilot project in 2001 linking Apollo Hospital, Chennai with Apollo rural hospital at Aragonda village in Chittoor district, Andhra Pradesh.[3] Tele-psychiatry after care clinics at National Institute of Mental Health and Neurosciences were established way back in in 2017 during prepandemic years which have provided treatments and follow ups to various psychiatric disorders.[4] COVID-19 pandemic was a challenge to the medical fraternity to reach out to patients to provide timely medical care. On 13th April 2020, the Ministry of Health and Family Welfare, Government of India launched the 'e-Sanjeevani' telemedicine service. Of the 1 crore patients served by e-Sanjeevini, around 18 % of patients are 20 years or younger.[5] Triage of COVID patients along with treatment and follow up for those who were under home care was done through telemedicine.[6] There are many instances where telemedicine and tele counseling has been used in India in various pediatric subspecialties. Children with asthma, chronic kidney disease, diabetes and cancer were effectively followed up. A first visit by direct consultation followed by several tele counseling sessions were successfully provided for 250 adolescent children in Bengaluru for acne, obesity, eating disorders, anxiety, depression, stress management along with parent counseling sessions for good parenting skills.[7] A pilot study from Chandigarh demonstrated nurse led telecounseling intervention to potentially supplement the ongoing treatment for children with central visual impairment.[8] During the pandemic, Teleyoga sessions for adults, children and adolescents were initiated by National Institute of Mental Health and Neurosciences. Children showed promising reduction in hyperactivity and peer conflicts. Adolescents reported significant reduction in hyperactivity, emotional problems and conduct issues.[9] Telehealth is the new revolution in telemedicine. It provides patient care, health education and self-care via telecommunication and digital communication platforms. Distance ECG monitoring, tele radiology and tele opthalmology and diabetes patient care are a few examples for promising tele health services. The focus of this write up is on clinical implication of tele counseling.

Indications

Telemedicine and telecounseling are indicated in the following situations

1. Remote location: Medical facilities in rural India have improved enormously but the actual fact is that, only 31% of India's population is in the cities where 75% of the doctors practice.[12] Tele consultation along with tele counseling is a boon to enrich rural health care facilities.

2. Pandemic and natural disasters: COVID -19 pandemic had stagnated the normal flow of health care facility world-wide and telemedicine proved to be the best remedy.

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Definitions

Telemedicine: Delivery of health care services, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities, where distance is a critical factor.[10]

Telehealth: Delivery and facilitation of health and health related services including medical care, provider and patient education, health information services and self-care via telecommunications and digital communication technologies.[10] Telehealth offers nonclinical services like administrative meetings, public health, research, training of health care professional and continuing medical education for doctors.

Counseling: Professional relationship that empowers diverse individuals, families and groups to accomplish mental health, wellness, education and career goals.[11]

Telecounseling: Distant professional help offered by trained professionals (doctors/nurses/psychologists/counsellors) to clients by phone calls or video consultations which helps the clients to identify problems (personal/health/psychological/social) brain storming solutions, make decisions and implement them confidently according to their psychosocial, spiritual and financial needs.

Telemedicine is promising during calamities like floods, cyclones, earth quakes, etc.

3. Expertise availability: In India, current doctor patient ratio is 0.62:1000, much below the WHO expected standard of 1:1000.[12] Telemedicine will enable doctors and health services to reach many needy patients and thus ensure equity and universal healthcare.

Scope of telecounseling

Telecounseling can be offered by trained professionals to clients in different clinical contexts as outlined below with examples.

Individual: A 20 year old medical student with migraine who drinks 6 cups of coffee per day is counseled about life style modifications over medication for migraine.

Couple: A couple who have not been able to conceive despite fertility treatment need to decide whether they need to try some more cycles of in vitro fertilization or think about adopting a child.

Family: Family members of a 10 year old obese child are counseled regarding diet, exercise and hobbies.

Group: Adolescent counseling to school students can be given regarding life skills, peer pressure, quitting addiction, mental health issues, etc.

Critical situations: 'Crisis hotline' is a helpline number which provides immediate help like suicide prevention, rape, bullying, runaway children and human trafficking. **Quit line** is a telephone help line offering treatment for addiction and behavioural problems like cessation of smoking and alcohol. Child help line (a telephone number which ensures child protection, safety and rescue in crisis of child abuse, child abduction and bullying) (Table I).

Table I. Help line numbers

National help lines	Phone number
NIMHANS mental health help line	080-46110007
KIRAN Suicide prevention help line	18005990019
National tobacco quit line	1800112356
Child line India	1098

Process of telecounseling[10] Practice of telemedicine for individual telecounseling, is based on 2020 Telemedicine guide lines laid down by Government of India. (Boxes 1-4) A revision of the guidelines is in the pipeline in 2022.

Limitations of telecounseling

- Lack of direct physical examination is a major setback which makes it suitable only for follow ups after an in-person physician consultation
- It is not suitable for treatment of any medical emergencies
- Rapport building and privacy may be difficult
- Client should be able to use the telephone or computer efficiently
- Poor telephone and internet connections may interrupt the sessions

Box 1. Practice tips: Before the telecounseling session

Be familiar with the gadget to be used (mobile phone/ laptop/tablet)

Check the internet connection/ telephone network and anticipate trouble shooting with solutions

Choose the mode of telecounseling (telephone call/ video call/ text)

State the fees and mode of payment

Obtain photo or scanned copy of patient id before the session

Check patients name, sex, age and address in the id proof

Patient's consent needs to be recorded before the session verbally or in writing through email

Adolescents above 18 years can give consent for drug treatment and investigations[13]

Dress up appropriately as for in person consultation

Keep mobile phone in silent or vibration mode

Make sure that the consultation room is noise free

Day light or white LED light is preferred

White background is preferred

Box 3. Practice tips after the telecounseling session

Thank the patient and accompanying person

Send the prescription along with signature and medical council number (Box 4)

Acknowledge the payment received

Give a follow up date

Share useful and relevant information leaflets/ websites/ patient group details

Save the details of the session securely

Do not share patient information on social media

- Client may be subjected to situational pressures
- Privacy and confidentiality may be a challenge for the client
- Medical data may be prone for hacking

Box 2. Practice tips during the telecounseling session

Login at the appointment time

Greet and introduce yourself formally with name, degree and designation

Sit in a straight posture and maintain eye contact

Speak in a loud audible range

Find out which language is preferable for the session

Identify the patient

Accompanying person needs to be identified and the relationship with the patient to be stated

Adolescent can be seen with the parents initially and later on privately during the session

Rule out a medical emergency

Clearly state the purpose of the session

Do not use medical terms, abbreviations, jargons

Actively listen to the chief complaints and concerns of the patient. Elicit a routine pediatric history. Follow HEEADSSS (home, education, eating, activities, drugs, suicide/ depression, sexual history, safety) assessment for adolescents[14]

Review investigations, if available

Explain the different treatment modalities/ interventions and order investigations, if required

Check for understanding

Only prescribe drugs as per telemedicine guidelines (Table II)

Summarise the conversation

Allow the patient and family to decide on the treatment, after analysing the pros and cons and respect their decisions

Judicious use of telemedicine and telecounseling provides timely, cost effective and quality medical care. It is mandatory to rule out a medical emergency. In the event of an emergency which is encountered during teleconsultation/telecounseling, the patient needs to be advised first aid measures and simultaneously directed to appropriate health care facility. Following current telemedicine guidelines, makes medical practice legally safe. More research is needed to prove the effectiveness of telecounseling in pediatric clinical practice.

Box 4. Sample prescription[10]

Registered medical practitioners name	
Qualification Address	Medical council number Contact details (e mail & phone number)
Date of consultation: Age: Sex: Name of patient: Height: Weight: Address:	
Chief complaints: Relevant points from history: Examination/ Lab findings: Suggested investigations: Special instructions:	Diagnosis & provisional diagnosis Treatment: (Names of all the medicines in capital letters only with generic name, drug formulation, frequency & duration) 1. 2. 3.
(NOTE-This prescription is generated on tele -consultation)	RMP'S signature & stamp

Table II. Drug dispensing for teleconsultation[10]

List Group	Mode of Consultation (video/audio/text)	Nature of consultation (first consultation /follow up)	List of Medicines
O	Any	Any	List O*
A	Video	First consultation Follow up for continuation of medicines	List A$
B	Any	Follow -up	List B#
Prohibited	Not to be prescribed	Not to be prescribed	Schedule X of Drug and Cosmetic Act and Rules or any Narcotic and Psychotic substance listed in the Narcotic drugs and Psychotropic Substances, Act 1985@

* This list includes commonly used 'over the counter 'medications such as paracetamol, oral rehydration solution, antacids, etc.

This list also includes medicines that may be deemed necessary during emergencies and would be notified from time to time.

$ This list includes usually prescribed medications for which diagnosis is possible only by video consultation such as antifungal medications for Tenia cruris, ciprofloxacin eye drops for conjunctivitis and refill medications for chronic diseases like diabetes, hypertension, asthma, etc.

\# This list includes add on medications used to optimize an existing condition

@ Narcotics like morphine, codeine and anticancer drugs

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NEWS AND NOTES

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DRUG PROFILE

SUBLINGUAL MEDICATIONS IN CHILDREN

Jeeson C Unni

Abstract: *Delivering drugs sublingually is effective for medications that need to have a rapid onset of action and short duration at a low dose. This is possible because of the good permeability of the sublingual area and because the drug by-passes the hepatic first pass metabolism. This article reviews the process of sublingual absorption of drugs and discusses sublingual medications available for use in children.*

Keywords: *Sublingual, Therapy, Children.*

Dysphagia is not an uncommon problem in children with cerebral palsy, acquired/traumatic brain injury, other neuromuscular disorders, craniofacial malformations, airway malformations, congenital cardiac disease, gastrointestinal disease and corrosive injuries, as well as children born preterm[1]. For these children, sublingual administration results in delivering the drug directly into the systemic circulation via the sublingual varices under the tongue to the facial veins, internal jugular vein and finally the brachiocephalic vein. Passive diffusion via the lipoidal membrane accounts for most of the drug absorption through the buccal mucosa. The thickness of the sublingual epithelium is 100-200 μm; much less than the buccal thickness. Sublingual absorption is therefore far superior to that by the oral route; and only less than by parenteral route.[2] The formulations available as powder, capsules, spray or films need very small amount of saliva for disintegration in the oral cavity. The absorption potential of oral mucosa is influenced by its dual property of lipid solubility and solubility on aqueous salivary solutions. Compounds with favourable oil to water partition coefficient in the range of 40-2000 is considered optimal for the drugs to be absorbed sublingually. Drugs with the same pH of 6 as in saliva favours better absorption.

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Advantages[2]

a) A relatively rapid onset of action can be achieved compared to the oral route and therefore useful in emergencies,

b) The formulation can be removed if therapy is required to be discontinued.

c) Liver is bypassed and also drug is protected from degradation due to gastric pH and digestive enzymes of the gastro-intestinal tract.

d) Better patient compliance due to the elimination of associated pain with injections.

e) Administration of drugs is possible in unconscious or incapacitated patients

f) Convenience of administration as compared to injections or oral medications - as there is no need for or chewing

g) Low dosage with high efficacy and less toxicity as hepatic first pass metabolism is avoided.

Disadvantages[2]

a) Since sublingual administration interferes with eating, drinking and talking it is considered unsuitable for prolonged use

b) Not well suited to administer sustained delivery systems.

c) Sublingual medications cannot be used in uncooperative or unconscious children

d) Smoking causes vasoconstriction and thus reduces absorption of sublingual medications

e) Oral ulcers become painful due to the irritant medication

f) If swallowed, bioavailability of these preparations is poor due to hepatic first pass metabolism

Drugs studied for sublingual administration

Sublingual buprenorphine

May be used for relief of moderate to severe pain in children.[3] Absorption is rapid, with variable bioavailability

of 30%-60% due to protein binding and individual variability. Cmax is reached at 2 hours. Plasma concentrations fall rapidly in the first 6 hours, then a gradual decrease is observed for 24 hours. Sublingual tablets not licensed for use in children under 6 years.

Dosage[4] : Child weighing 16-25 kg : 100 mcg every 6-8 hrly; 25-37.5 kg: 100-200 mcg 6-8 hrly; 37.5-50 kg: 200-300 mcg 6-8 hrly; 50 kg and above: 200-400 mcg 6-8 hrly. It has a much longer duration of action than morphine and sublingually is an effective analgesic for 6 to 8 hours. Unlike most opioid analgesics, the effects of buprenorphine are only partially reversed by naloxone hydrochloride. It is rarely used in children,

Sublingual desmopressin

Used for the treatment of primary nocturnal enuresis, nocturnal polyuria in both children with uropathy or nephropathy[5,6] and diabetes insipidus[7]. Desmopressin lyophilizate sublingual tablets are a valuable option for treating central diabetes insipidus (CDI) in infants and young children, with evidence of more stable absorption than intranasal formulations and oral tablets.[8] However, it can be difficult to split these sublingual tablets into small doses for infants.

Dosage:[9] Diabetes insipidus - 2-17 years: Initially 60 mcg 3 times a day sublingually, adjusted according to response; usual dose 40-240 mcg 3 times a day; Primary nocturnal enuresis - 5-17 years: 120 mcg once daily, increased if necessary to 240 mcg once daily, dose to be taken at bedtime, limit fluid intake from 1 hour before to 8 hours after administration, dose to be increased only if lower dose is not effective. Reassess after 3 months by withdrawing treatment for at least 1 week. Repeated courses of desmopressin can be used in responsive children who experience recurrences of bedwetting, but should be withdrawn gradually at regular intervals (for 1 week every 3 months) for full reassessment.

Sublingual nicotine

Show promise as a nicotine substitution strategy for tobacco harm reduction and smoking cessation treatment[10] especially useful in individuals who smoke fewer than 20 cigarettes each day. Adolescent children should be prescribed enough treatment to last 2 weeks after their agreed quit date and be re-assessed shortly before the prescription ends. Children who are unwilling or not ready to stop smoking may also benefit from the use of nicotine replacement therapy (NRT) as part of a 'harm reduction approach', because the amount of nicotine in NRT is much lower and less addictive than in smoking tobacco.

Dosage:[11] 12-17 years: One tablet every 1 hour, increased to 2 tablets every 1 hour if required, if attempting smoking cessation, treatment should continue for up to 3 months before reducing the dose.

Sublingual atropine sulphate

Safe and effective in the short-term treatment of sialorrhea; however, randomized placebo controlled and long-term follow-up studies are necessary[12].

Dosage: 20 μg/kg/dose. Minimum dose was 0.25mg, while maximum dose was 0.03mg/kg.

Sublingual lorazepam[13]

Lorazepam plasma level necessary for seizure control (60-80 ng/ml) may not be achieved consistently with sublingual administration-reported to peak at 14-16 ng/ml.[13]

Sublingual nifedipine

It was used at a dose of 2.5 mg for children weighing less than 10 kg and 5 mg for children weighing between 10 and 20 kg to treat hypertensive crises of infants and children.[14] Several cases of profound and unpredictable changes in BP were later noted. A few patients had clinically significant adverse events. These included change in neurologic status, profound hypotension and oxygen desaturations. Though many of these children had comorbid conditions, presently it is advisable to use nifedipine for hypertensive emergencies in children with caution.[15]

Sublingual immunotherapy (SLIT)

SLIT induces allergen-specific immune tolerance by sublingual administration of a gradually increasing dose of an allergen. Immunotherapy means treating the cause of allergies by giving small doses of substance for which a person is allergic, which increases tolerance to the allergen and reduces the allergic symptoms. In SLIT the allergen is given as drops under the tongue. It has been increasingly used instead of subcutaneous immunotherapy for treatment of mite allergies,[16,17] ragweed allergen induced allergic rhinoconjunctivitis,[18] egg, peanut and other allergies.[19]

Conclusion

Sublingual drug delivery has been used for formulation of many drugs; especially for the drugs that require the rapid onset of action. These preparations overcome the difficulty in swallowing. Although significant advances in drug formulation for sublingual administration have been reported, very few of them have been developed for clinical use.

Points to Remember

- ***Sublingual administration results in delivering the drug directly into the systemic circulation via the sublingual varices in children with dysphagia due to any cause***
- ***Sublingual buprenorphine may be used for relief of moderate to severe pain in children***
- ***Sublingual desmopressin is used in diabetes insipidus and also in primary nocturnal enuresis, nocturnal polyuria in children with uropathy or nephropathy***
- ***For nicotine replacement therapy nicotine tablets are found to be useful***
- ***Sublingual immunotherapy is now used for treatment of allergy due to mite, ragwood, peanut, egg and other allergens***

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RADIOLOGY

CONGENITAL LUNG MALFORMATIONS - II

*Venkateswaran S

Vascular abnormalities

Pulmonary arteriovenous malformations (PAVMs) are rare vascular anomalies of the lung, in which abnormally dilated vessels provide a right-to-left shunt between pulmonary artery and vein. They are generally considered as direct high flow, low-resistance fistulous connections between the pulmonary arteries and veins.

They can be classified as simple, complex or diffuse.

- **Simple type:** commonest; has a single segmental artery feeding the malformation; the feeding segmental artery may have multiple subsegmental branches that feed the malformation but must have only one single segmental level.
- **Complex type**: Have multiple segmental feeding arteries (~20%).
- **Diffuse type**: Rare (~5% of lesions) characterised by hundreds of malformations, some can have a combination of simple and complex AVMs within a diffuse lesion.

Radiological features

A number of modalities are available for the diagnosis of PAVMs, including contrast echocardiography, radionuclide perfusion lung scanning, computed tomography (CT), magnetic resonance imaging (MRI) and the gold standard, pulmonary angiography.

Chest X-ray: Pulmonary varix (dilated vessel) may be apparent as a non-specific soft tissue mass, often with a relatively unusual orientation compared to adjacent vessels. More than one suggests the possibility of hereditary hemorrhagic telangiectasia (Fig 17a).

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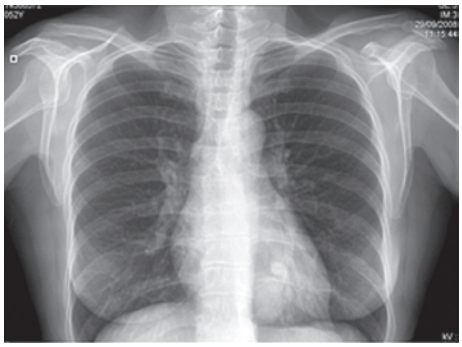


Fig.17a. Nodular opacity, paravertebral in left lower lung.

CT chest -This is often the diagnostic imaging modality of choice. The characteristic presentation of a PAVM on non-contrast CT is a homogeneous, well-circumscribed, non-calcified nodule, upto several centimetres in diameter or the presence of a serpiginous mass connected with blood vessels. Occasionally associated phleboliths may be seen as calcifications. Contrast demonstrates enhancement

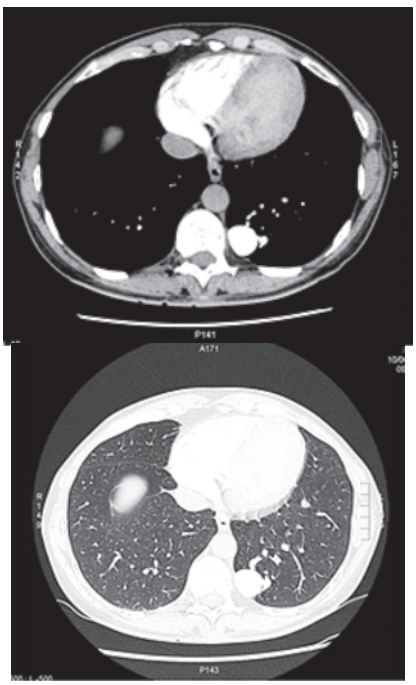


Fig.17b, c. Contrast enhanced CT chest well-defined nodule, posteriorly in left lower lobe with a hypertrophied feeding artery and a draining vein

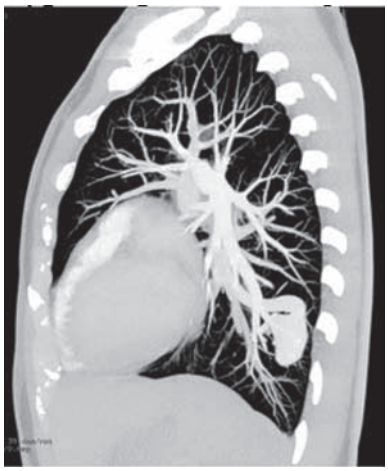


Fig.17d. Contrast CT - Maximum intensity projection: well-defined nodule posteriorly in the left lower lobe with feeding artery and draining vein.

of the feeding artery, the aneurysmal part and the draining vein on early-phase sequences (Fig.17 b, c, d).

MRI-Three-dimensional Contrast-enhanced MR Angiography is considered as the MR technique of choice for imaging vascular structures in the thorax. Most lesions within the lung have relatively long relaxation time and produce medium to high-intensity signals. Lesions with rapid blood flow result in a signal void and produce low-intensity signals.

Table II. Types of partial anomalous pulmonary venous connection

Types	Characteristics
Supra-cardiac	Persistent left superior vena cava Right superior vena cava (most common) Brachiocephalic veins (innominate veins)
Cardiac	Right atrium Coronary sinus
Infra-cardiac	Portal vein Hepatic veins Inferior vena cava (Scimitar syndrome)
Mixed	A combination of two or more of the above anomalies

Partial anomalous pulmonary venous return

Partial anomalous pulmonary venous return (PAPVR), also known as partial anomalous pulmonary venous connection (PAPVC), is a rare congenital cardiovascular condition in which some of the pulmonary veins, but not all, drain into the systemic circulation rather than into the left atrium. Four types of PAPVR have been described Table II.

Left-sided PAPVR has been reported to be found more often in adults, whereas right-sided PAPVR is reported more commonly in children. It is unclear, if this is because of a higher proportion of symptomatic manifestation of

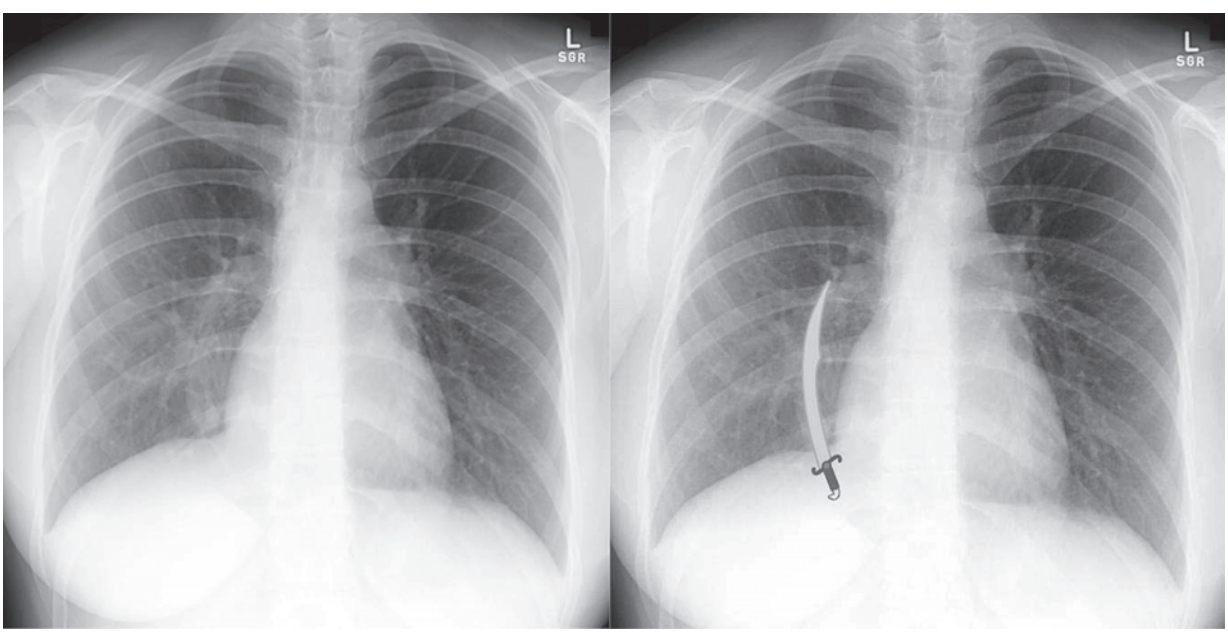


Fig.18a & b.X-ray Chest.Curvilinear tubular opacity in medial right lower zone paralleling right heart border representing a scimitar (Turkish sword). The right lung is slightly more dense and smaller than left lung.

the latter. The left upper lobe vein anomaly is thought to be the most common.

Radiological features

Chest X-ray: Chest radiographic features are specific to each subtype of PAPVR. The abnormal vein is rarely identified, except in cases of Scimitar syndrome. Pulmonary venous congestion can be seen if the venous drainage is obstructed.Cardiomegaly can also be seen if significant abnormal intracardiac venous drainage occurs (Fig.18a and b).

CT : Utilisation of contrast-enhanced studies with MDCT (multi-detector computed tomography) technology enables both detection and characterisation of the anomalies. It is considered as the imaging modality of choice (Fig.19a,b,c,d).

Total anomalous pulmonary venous return (TAPVR): A congenital cyanotic heart anomaly with abnormal drainage anatomy of the entire pulmonary venous system. This contrasts with partial anomalous pulmonary venous return (PAPVR) where only part of the pulmonary venous anatomy is abnormal.

In TAPVR, all systemic and pulmonary venous blood enters the right atrium and nothing drains into the left atrium. A right-to-left shunt is required for survival and is usually via a large patent foramen ovale (PFO) or less commonly, atrial septal defect (ASD).

Classification

TAPVR can be classified into four types (in decreasing order of frequency) depending on the site of anomalous venous union (Table III).

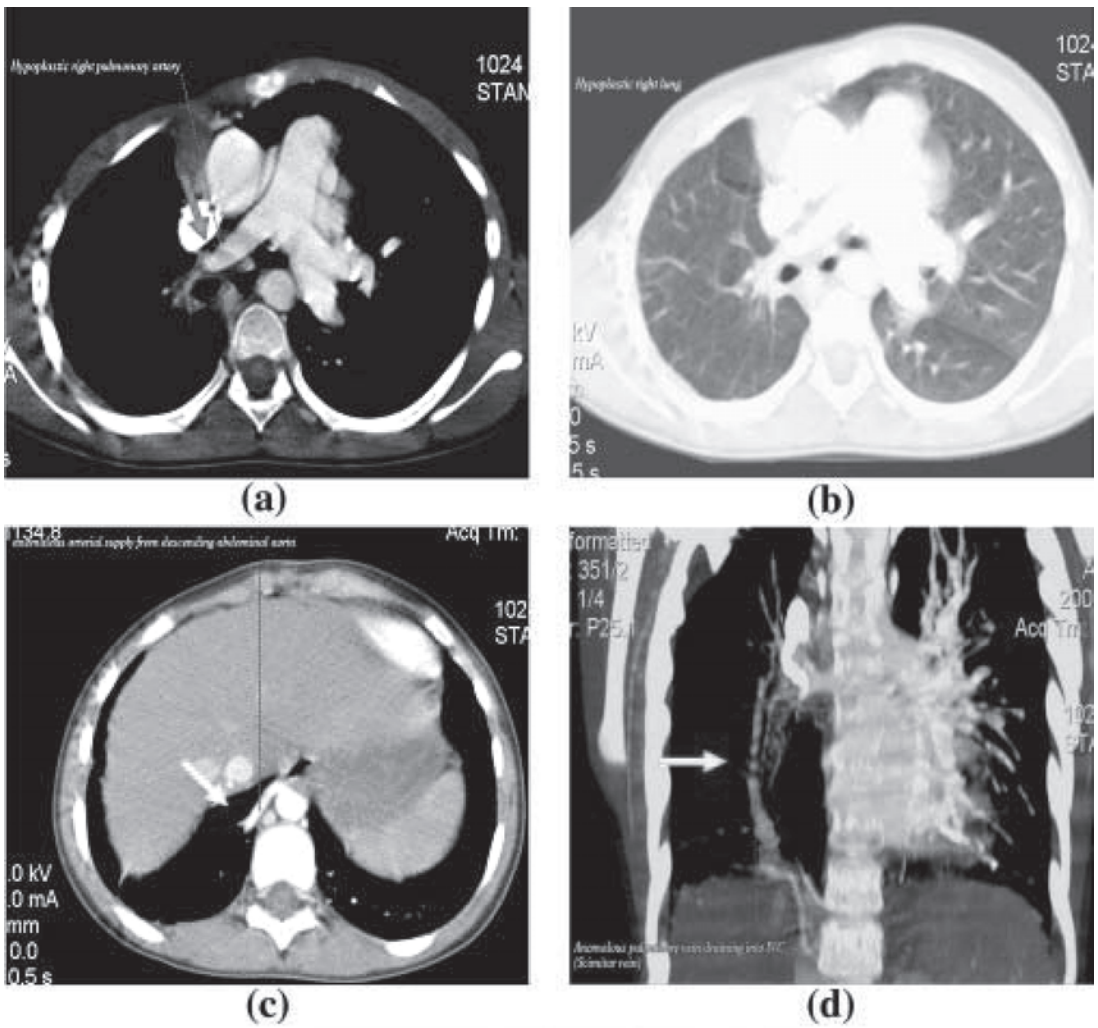


Fig.19. Scimitar congenital venolobar syndrome (a) Axial CT image showing hypoplastic right pulmonary artery (red arrow). (b) Axial CT image with lung window/level showing hypoplastic right lung. (c) Axial CT image showing anomalous arterial blood supply from abdominal aorta to right lower lobe (blue arrow). (d) Coronal reformatted CT image: anomalous venous drainage into infradiaphragmatic inferior vena cava (green arrow)

Table III.Types of total anomalous pulmonary venous return

Types	Characteristics
Type I: Supracardiac	Most common type (over 50% of cases) Anomalous pulmonary veins terminate at the supracardiac level.Pulmonary veins converge to form a left vertical vein which then drains to either brachiocephalic vein, SVC, or azygous vein
Type II: Cardiac	Second most common (~30% of cases). Pulmonary venous connection at the cardiac level. Drainage is into the coronary sinus and then the right atrium
Type III: Infracardiac	Connection at the infracardiac level The pulmonary veins join behind the left atrium to form a common vertical descending vein The common descending vein courses anterior to the oesophagus passes through the diaphragm at the oesophageal hiatus and then usually join the portal system Drainage is usually into the ductus venosus, hepatic veins, portal vein, or IVC
Type IV: Mixed pattern	Least common type. Anomalous venous connections at two or more levels

Radiological features

Chest X-ray: The right heart is prominent in TAPVR because of the increased flow volume, but the left atrium remains normal in size. Types I and II result in cardiomegaly.The supra cardiac variant (type I) can classically depict a snowman appearance on a AP/PA view, also known as "figure of 8 heart or cottage loaf heart" (Fig.20). The dilated vertical vein on the left, brachiocephalic vein on top, and the superior vena cava on the right form the head of the snowman; the body of the snowman is formed by the enlarged right atrium. CT angiography findings are shown in Fig.21.

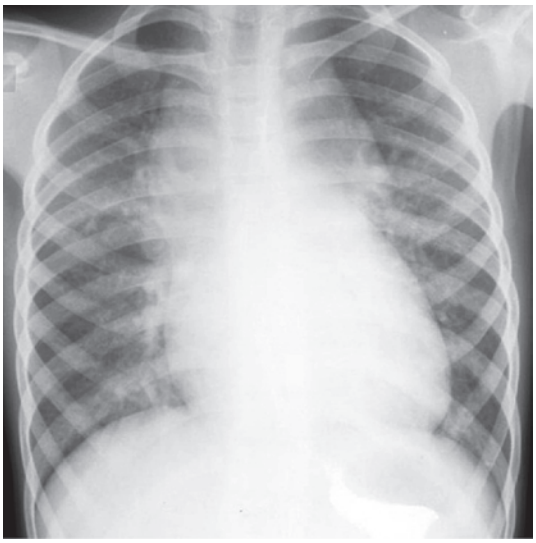


Fig.20. TAPVR cardiomegaly with increased pulmonary arterial markings.

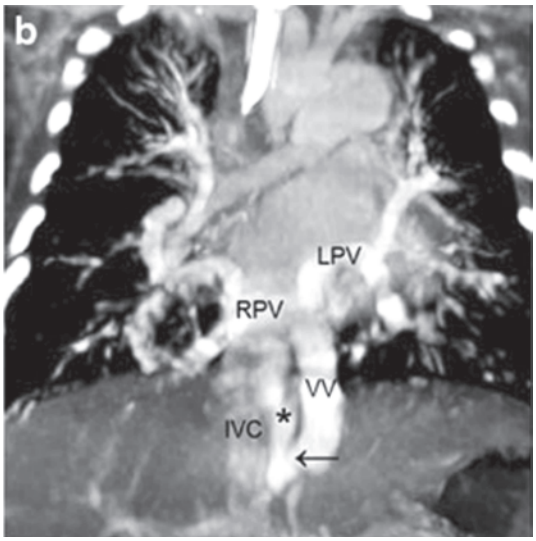


Fig.21. CT angiography in a 1-day-old girl with infracardiac total anomalous pulmonary venous connection (TAPVC). Maximum-intensity projection CT angiography demonstrates individual pulmonary veins (LPV left pulmonary vein, RPV right pulmonary vein) forming a venous confluence and draining to a vertical vein (VV) that passes downward through the diaphragm. The vertical vein enters the ductus venosus (*), which drains into the inferior vena cava (IVC). Note the stenosis (arrow) at the connection between the vertical vein and the ductus venosus.

Aberrant left pulmonary artery

Aberrant left pulmonary artery, also known as '**pulmonary sling'**, represents an anatomical variant

characterised by the left pulmonary artery arising from the right pulmonary artery and passing above the right main bronchus and in between the trachea and oesophagus to reach the left lung. It may lead to compression and focal stenosis of the trachea.

Radiological features

Chest X-ray: Conventional radiographs obtained in neonates at birth may show fetal fluid retention or air, with a mediastinal shift usually to the left side. In adults, a left-sided deviation of the trachea and an anterior bowing of the right main stem bronchus in lateral film may be seen (Fig.22a, b). In cases of ring sling complex, radiographs often show an absence of unilateral pulmonary aeration. The esophagogram demonstrates extrinsic compression of the esophagus consistent with a vascular ring (Fig.23a,b,c).

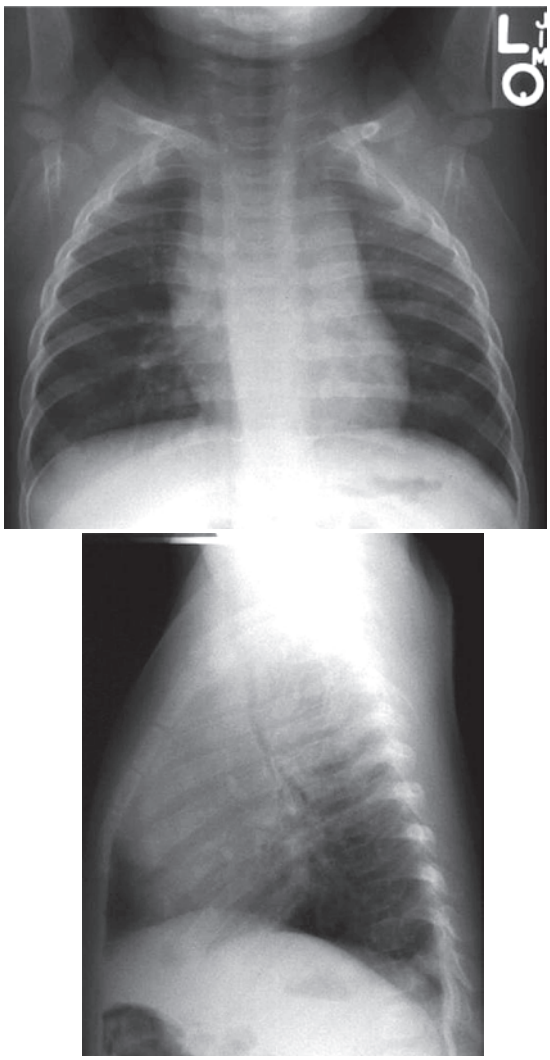
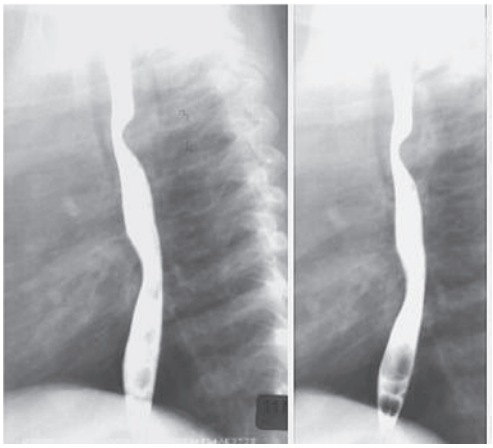


Fig.22a Chest PA view unremarkable Fig.22 b) Lateral view narrow tracheal air column which is also bent suggesting extrinsic compression of trachea.



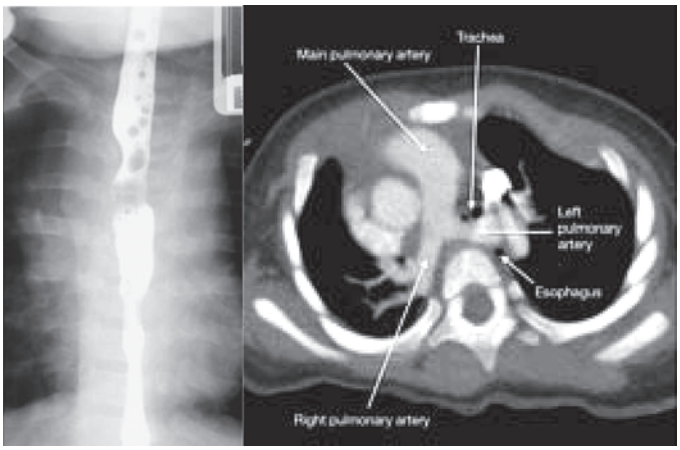


Fig.23a,b,c. Barium esophagogram demonstrates extrinsic compression of esophagus. Fig.23.d.CT shows left pulmonary artery arising from the right pulmonary artery and passing in between trachea and esophagus to reach left lung.

CT/MRI -The main bronchi have horizontal courses (i.e. low T-shaped carina) and vascular anatomy is normally well delineated on CT or MR angiography. Atelectasis may be seen in the upper lobes (Fig.23d).

Pulmonary venous varix

Pulmonary vein varix (PVV), also sometimes termed a pulmonary venous aneurysm, refers to a localised aneurysmal dilatation of a pulmonary vein. As it involves a venous structure, the former term is usually considered more appropriate. They are rare and may be congenital or acquired.

Radiological features

Chest X-ray:Non-specific and can present as a mass (Fig.24a).

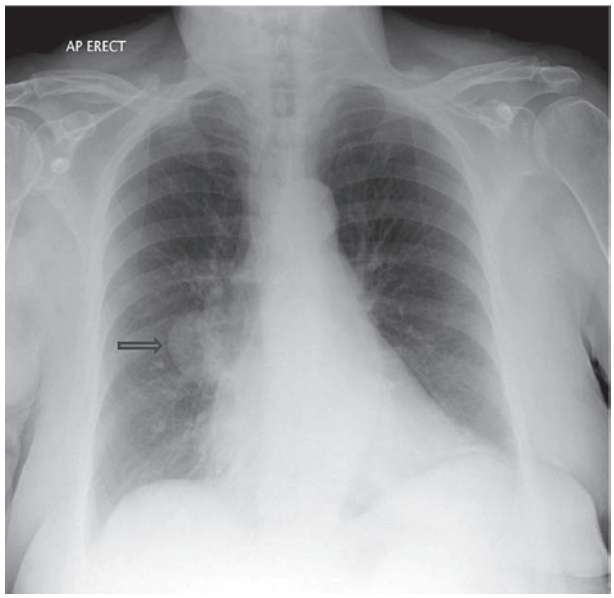


Fig.24a. X-ray Chest:Well defined ovoid mass projected over the right hilum. Note the 'hilum overlay' sign - the pulmonary artery being identified separately from this 'mass'.

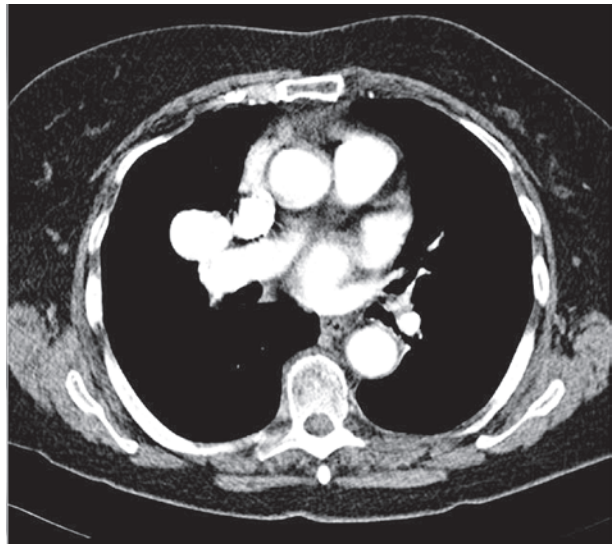


Fig.24b. CT Chest: Contrast filled pulmonary vein aneurysm anterior to the right main pulmonary artery and lateral to the SVC.

Contrast CT pulmonary angiography: Pulmonary angiography has been the mainstay of diagnosis which allows accurate delineation of arterial and venous anatomy (Fig. 24b).

Pulmonary lymphangiectasia

Pulmonary lymphangiectasia (PL) refers to a rare, fatal congenital abnormality of the lungs characterised by grossly dilated lymphatic channels in the sub pleural, interlobar, perivascular and peribronchial areas. It is divided into two main types-cardiac-associated lymphangiectasia (secondary type) and non-cardiac associated lymphangiectasia (primary type),which may be early onset or late onset.

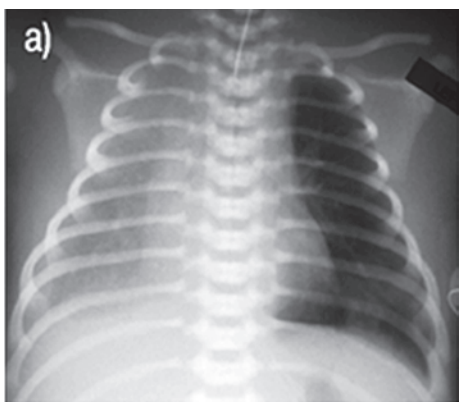


Fig.25a. Bilateral pleural effusion (right >left)

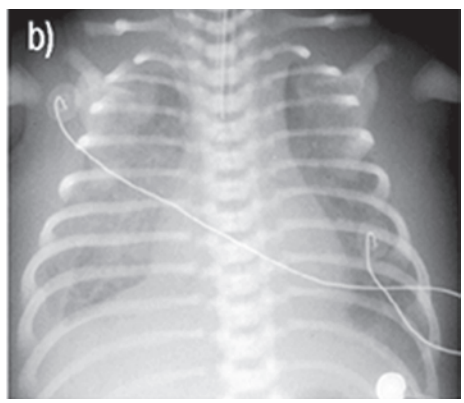


Fig.25b. Increasing bilateral pleural effusion (right >left)

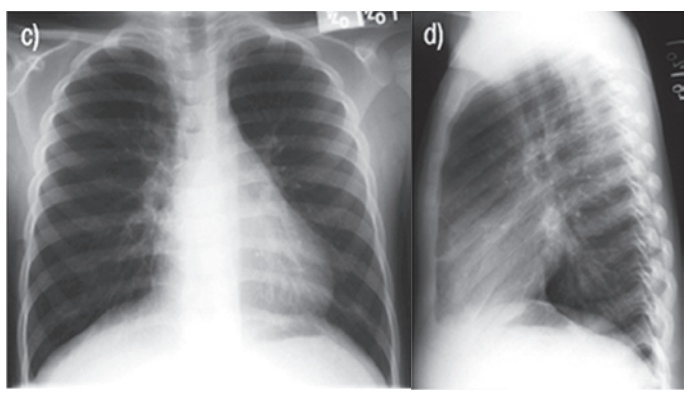


Fig.25c,d. PA and lateral: (at five years) shows minimal interstitial prominence and hyper-inflation

Radiological features

Antenatal ultrasound: Hydrops fetalis (associated feature)

Chest X-ray may show perihilar infiltrates, pleural effusion and varying degrees of hyperinflation (Fig.25a,b). Fig.25c,d shows the chest X-ray findings of the same child during 5 years of follow up.

HRCT-Perihilar infiltrates with air bronchograms, interstitial and interlobular septal thickening and pleural effusion (chylothorax) may be seen (Fig.26a,b,c,d).

MRI: **T1** films (especially coronal) can reveal interstitial thickening, pleural effusion and atelectasis. **T2** films (especially axial) usually show high-signal material within the pulmonary interstitium.

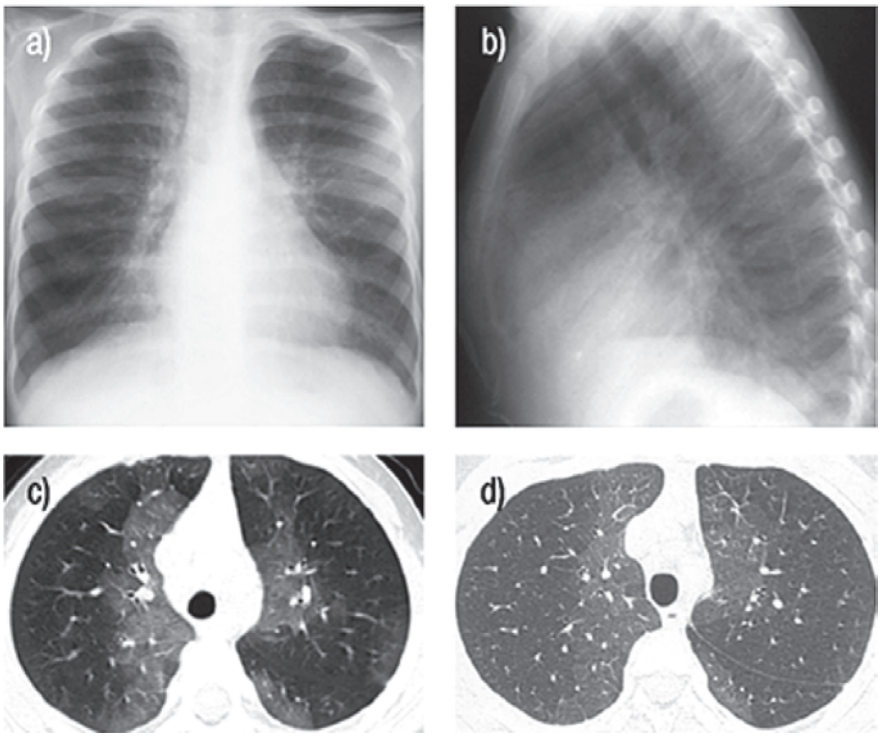


Fig.26. a to d: a) PA chest radiograph at aged 4yrs reveals perihilar and peripheral patchy opacity and hyperinflation. b) Lateral chest radiograph from the same time as a) demonstrates a mild pectus excavatum configuration to the anterior chest wall. c) High resolution computed tomography (CT) scan from the same period demonstrates perihilar and peripheral ground-glass opacities. d) Repeated high resolution CT scan 5yrs later at 9yrs demonstrates similar findings at the same level with a slight decrease in the ground-glass component.

Lymphoscintigraphy will show radiotracer accumulation in the lungs and asymmetric visualisation of lymphatic channels.

Summary

In terms of diagnosis, although prenatal US and postnatal CT scan are currently considered the gold standard tests for diagnosis of congenital lung malformations, MRI is increasingly used for their diagnosis both antenatally and postnatally. Postnatal MRI has also been used as a radiation-free technique to study any vascularization or re-vascularization after embolization of a systemic arterial supply.

Advances in antenatal and postnatal imaging which has increased detection of both clinically symptomatic and occult congenital lung malformations has facilitated better antenatal counselling, planning management strategy and surgical intervention, wherever appropriate.

CASE REPORT

SPONTANEOUS EXPULSION OF PULMONARY HYDATID LUNG CYST

*Vijayasekaran D
**Kalpana S

Abstract: *Pulmonary echinococcosis often requires prolonged and complicated therapy, sometimes requiring extensive surgery. Spontaneous expulsion of pulmonary hydatid cyst is an uncommon complication reported anecdotally. We report one such case presenting with spontaneous expulsion of hydatid cyst through intrabronchial rupture resulting in complete resolution of the cyst.*

Keywords: *Pulmonary hydatid, Spontaneous expulsion.*

Echinococcosis, also known as hydatidosis is a zoonotic disease occurring in humans due to accidental ingestion of larvae of the dog tapeworm. Though both liver and lungs are the most frequently involved organs, pulmonary disease appears to be more common in younger individuals.[1] We report a boy expectorating the contents of a huge pulmonary hydatid cyst spontaneously, followed by reduction of symptoms and size of the cyst.

Case Report

A 5 year old boy presented with intermittent fever, cough and loss of weight and appetite for 8 months. He was hospitalized several times and given multiple courses of intravenous antibiotics. Evaluation for tuberculosis was negative. Chest radiograph showed opacity on left lower zone with mild left sided pleural effusion. Since his symptoms persisted he was referred to us for further management.

On admission, the child was undernourished, with stable vitals and was comfortable at rest. His respiratory system examination was unremarkable except for dull note on percussion and decreased air entry on the left infra scapular region. Chest X-ray showed diffuse homogenous opacity in the left hemithorax (Fig.1a).

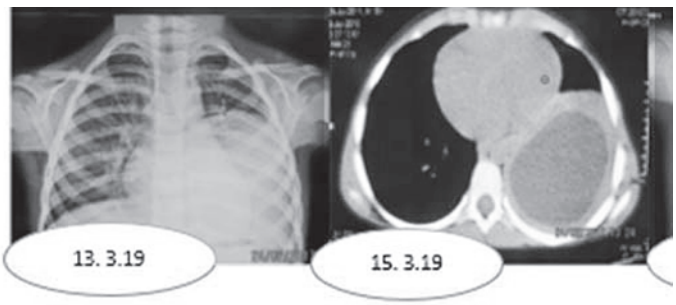


Fig.1a **Fig.1b**

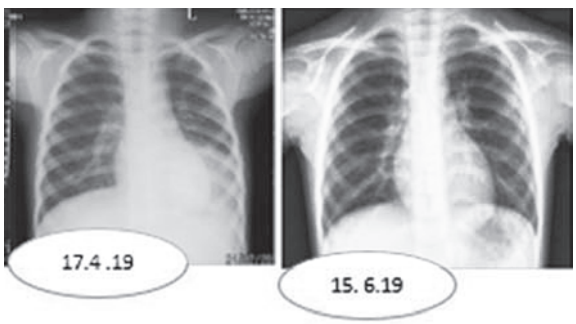


Fig.1c **Fig.1d**

Fig.1(a) Chest radiograph and 1(b) CT Chest showing large well-defined thick-walled cyst in the left lower zone 1(c) Repeat chest radiograph showing marked reduction of the opacity. 1(d) Complete resolution of the cyst on completion of albendazole therapy

Ultrasonography chest revealed a large an-echoic lesion on the left lung with mild pleural effusion. Contrast enhanced computed tomography showed large cyst in the lower part of the left lung (maximum diameter of 5.1cm) with homogenous content and smooth, hyper dense walls suggestive of hydatid lung cyst (Fig.1b). Echinococcosis serum IgG was positive. Since the parents were not willing for invasive management, he was treated with albendazole (15 mg/kg/day in 2 divided doses orally) for 2 months (with 14 days interval between the two months).

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One month into his albendazole regimen, parents gave history that the child had started coughing out small bits of fleshy material with unpleasant odour for 2 weeks and his symptoms improved.

On examination, the child was afebrile but pale. His pulse rate was 120/min, BP - 120/70 mm Hg, respiratory rate - 28/min, SpO_2 - 96% on room air, hemoglobin - 9.4 gm and ESR 140mm in 1 hour. His repeat chest radiograph showed reduction in size of the lung cyst compared to the imaging done one month before (Fig.1c). However, the fleshy material was not available for histopathological examination as the child had stopped bringing out the material after the second visit to us.

Discussion

Lung is considered a favourable site for echinococcosis in the pediatric age group because it allows a rapid growth in size of cyst due to its compressible nature, vascularization and negative pressure.[2] 72% of hydatid cysts typically involve one lobe, usually at the lung base as in the index case where the left lower lobe was involved.[3] The common symptoms of pulmonary hydatidosis are cough, chest pain, dyspnea and occasionally hemoptysis.[4]

Serology and imaging are considered the primary modes of diagnosis of pulmonary hydatid cysts. Spontaneous cyst rupture is the most feared complication; it leads to a sudden onset of chest pain, hemoptysis, cough and fever. This may be associated with allergic manifestations, including urticaria, pruritus and anaphylactic shock, but the index case presented with insidious symptoms of expectorating small bits of whitish fleshy material following the rupture of the cyst.[5] Similar reports of insidious expulsion of hydatid cyst by expectorating foul smelling cyst contents have been reported in adults.[6]

Fetid expectoration of material is one of the most common complaints in ruptured hydatid lung cyst. Dramatic decrease in size of the cyst could not be explained by albendazole only which usually takes 5 to 9 months to disappear with medical management.[7]

Though CT chest play a major role in the diagnosis, lung ultrasound and chest radiograph should be advised in the follow-up to identify unnoticed seeding of the bronchial or alimentary tree or simultaneous hepatic lesions.[8] Since the size of the cyst had considerably reduced in the second visit, the child was advised to continue albendazole (15 mg/kg in 2 divided doses orally) for 2 more months with drug free intervals in between. At the end of therapy, the X-ray and ultrasound were normal with no evidence of residual cyst. Complete resolution of bilateral large echinococcal cysts with albendazole treatment alone in an adult patient have been reported.[9] The dose of albendazole recommended is 15 mg/kg/day in two divided doses, orally, taken with meals, (Max 800 mg/day) for 28 days then 14 drug free days, for 3 cycles.

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CASE REPORT

SEVERE DENGUE PRESENTING AS ENCEPHALITIS

***Vijayalaxmi Budihal**
****Aundhakar CD**
*****Kshirsagar VY**

Abstract: *A 9 months old boy, resident of a dengue endemic area Shirol, who presented with history of high grade fever for three days and one episode of generalized tonic-clonic (GTC) seizure. IgM antibodies for dengue was positive. We report this case of severe dengue with encephalitis, with peculiar MRI findings.*

Dengue fever and dengue hemorrhagic fever is caused by the dengue virus, a single-stranded RNA virus belonging to the Flaviviridae family.[1] Dengue fever encephalopathy is a common neurological complication. Dengue encephalopathy is frequently caused by a combination of various factors such as shock, hepatitis, coagulopathy and co-infection. Dengue encephalitis is a distinct condition caused by the direct invasion of brain.

Case Report

We report the case of a previously well 9 months old boy, resident of Shirol, a dengue endemic area, presented with history of high grade fever for three days and an episode of generalized tonic-clonic (GTC) seizure. The seizures commenced on the morning of the fourth day of the illness which lasted for 5 minutes. There was no recent history of vaccination or skin rashes. Past medical history was unremarkable with no history of seizure or hospitalization.

On admission he was febrile, with a temperature of 102°F, blood pressure of 90/40 mmHg (MAP-60 mmHg), tachycardia and cold extremities. Oxygen saturation was 85% in room air. He was pale with nasogastric bleeding. There was no skin rash, edema or icterus. His Glasgow Coma Scale (GCS) was 6/15 (E-1, V-1, M-4) with sluggishly reactive, mid dilated pupils. Anterior fontanel was bulging and pulsatile, deep tendon reflexes were exaggerated with extensor plantar. There was no neck stiffness. In view of respiratory compromise and low GCS child was electively intubated and ventilated. There was no hepatosplenomegaly. He was resuscitated with fluids, FFP and PRBC. First dose of vancomycin and meropenem was given empirically in view of the possibility of bacterial infection. Fundus examination revealed papilloedema. Hence, CSF study was not done. Infant was managed with anticonvulsants and antiedema measures. Blood pressure and urine output improved after initial resuscitation with crystalloids. Hemogram is summarized in Table I.

Serum IgM antibodies for dengue were positive. Covid-19 RT PCR, antibodies and peripheral smear for malarial parasite were negative.

Electroencephalography (EEG) performed on the day of admission showed diffuse slowing of background activity suggestive of generalized cerebral dysfunction (Fig.1).

A magnetic resonance imaging (MRI) of his brain showed bilateral symmetrical multifocal (confluent and discrete) areas of altered signal intensities appearing iso to hypointense on T1, hyperintense on T2/FLAIR, predominantly showing hyperintense signal on DW1 and hypointense signal on ADC suggestive of diffusion restriction, involving all lobes of cerebral hemisphere, bilateral caudate nuclei, basal ganglia, thalamus, cerebellar hemispheres, corpus callosum and brainstem. Diffuse abnormal leptomeningeal enhancement including basal cisterns noted and these imaging features are suggestive of meningoencephalitis (Fig.2).

Child was continued on supportive management without any clinical improvement. On the day 10, child developed pulmonary hemorrhage and succumbed eventually.

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Table I. Serial hemogram

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
HB	8.7	8.8	9.5	6.9	7.6
PCV	29.9	27.5	27.7	22.7	28
TLC	3100	4400	8000	10100	10100
N/L/E/M	54/42/04/0	60/37/3/0	81/14/1/4	72/24/2/2	18/80/2/1
PLT	90000	90000	54000	45000	65000

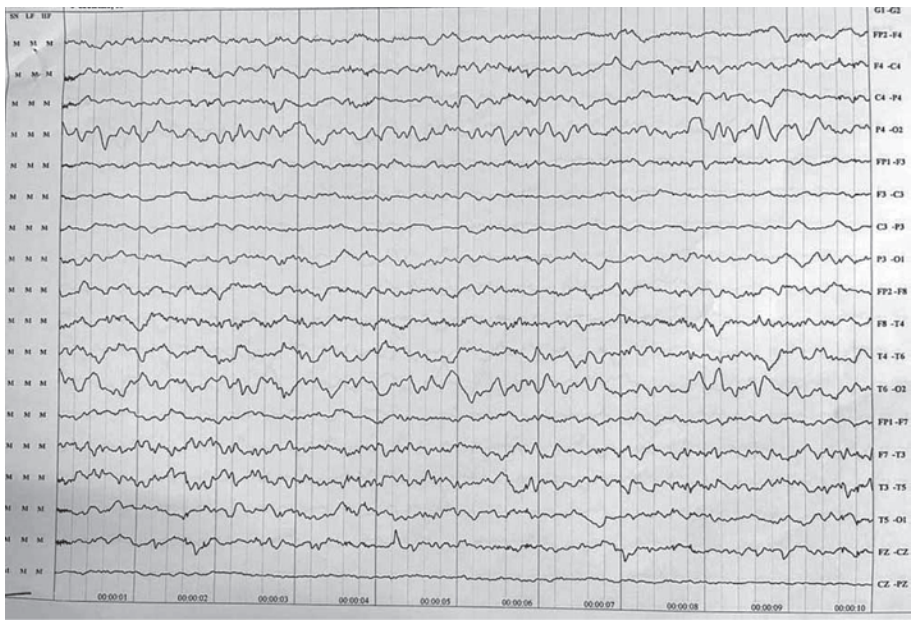

Fig.1. Electro encephalographic tracing

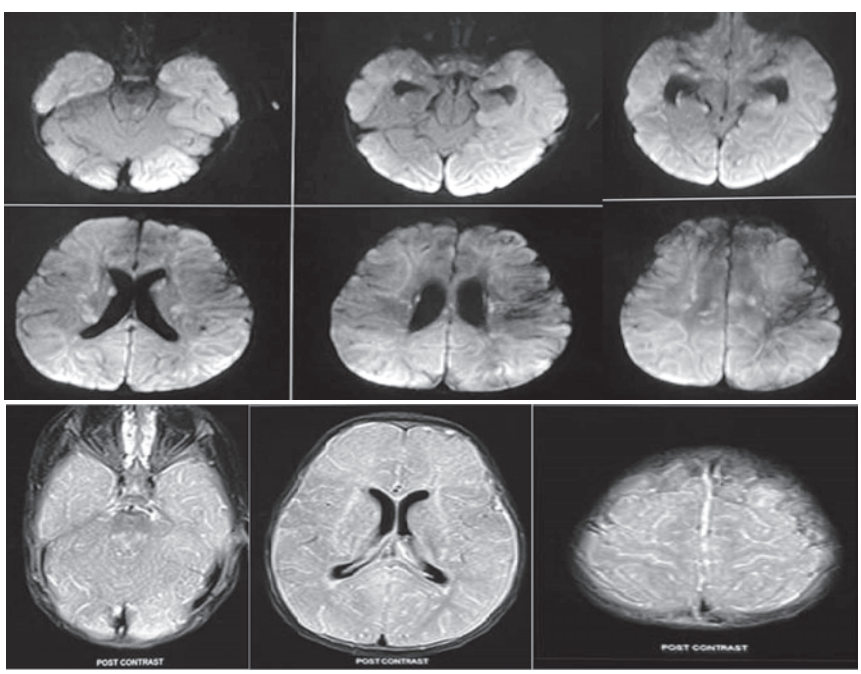

Fig.2. T2 FLAIR and T2-weighted images showing involvement of thalamus, pons and cerebellum, with presence of hemorrhage on T2 and restricted diffusion on DW

Discussion

Dengue encephalopathy is a well-known complication with prevalence of 0.5 to 6.2%.[2] Hepatic encephalopathy, shock, cerebral edema, electrolyte disturbances and intracranial hemorrhage are the possible explanations. There are subsets of patients in whom the cause for neurological injury remains unclear even after excluding the above-mentioned factors. These raise the possibility of direct neuronal injury due to the dengue virus. Dengue is thought to be a non-neurotropic virus.[3] However, there are reports of the demonstration of dengue virus antigen and IgM antibody in the cerebrospinal fluid (CSF) of patients with encephalopathy. There are case reports from India, and from Vietnam.[2,4] In the Indian study 11 patients were seen with confirmed dengue infection, without CSF analysis. Vietnamese study reported dengue encephalitis in nine patients, but either virus or antibody were found in the CSF only in two cases. Few other studies showed the association of dengue with encephalitis.[5-8]

Dengue is classically thought to be a non-neurotropic virus but DEN-2 and DEN-3 are the most frequently involved serotypes in neurotropism.[9] Although it is a rare occurrence, autopsy studies have proved the presence of virus antigen in brain parenchymal cells using immunoperoxidase stain.

On admission, our patient had a history suggestive of encephalopathy with shock, coagulopathy, metabolic acidosis and normal liver functions. This encephalopathy is usually explained by the abnormalities mentioned earlier in the text.[10] However, MRI showed evidence of encephalitis in the form of bilateral thalamic involvement with foci of hemorrhage, with involvement of temporal lobe and brain stem, which has been reported earlier. This case is presented to highlight the possible extensive involvement of the brain by dengue virus.[10]

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NEWS AND NOTES

CASE VIGNETTE

PILOMATRICOMA - A LESS KNOWN CUTANEOUS TUMOUR

***Kinattinkara Ramachandran Subbaraman**
****Vidhu Ashok**

Abstract: *An eight-year-old girl with normal growth and development was brought with an asymptomatic skin lesion on left forearm of 7 months duration. Examination revealed small tumour like lesion 1.5 x 2cm (Fig.1); skin over swelling was greyish white. Consistency was firm to hard and it was mobile. Ultrasonogram of left arm showed well defined hypoechoic lesion in subcutaneous plane along lateral aspect of arm measuring 15x11x16mm with no significant vascularity and with multiple small calcifications.Complete excision biopsy including clear margins suggest two firm to hard tissue measuring 1.5cm. and 0.5 cm. respectively. Cut section was yellowish and showed calcification. Histopathology (Fig.1) showed well demarcated lesion with thin connective tissue capsule. Lesion composed of basaloid cells with abrupt keratinization and nest of shadow cells and cells had central clear area. Periphery showed scattered lymphocytes and occasional giant cells with diagnosis of pilomatricoma, which is a benign skin tumor associated with hair follicles.*

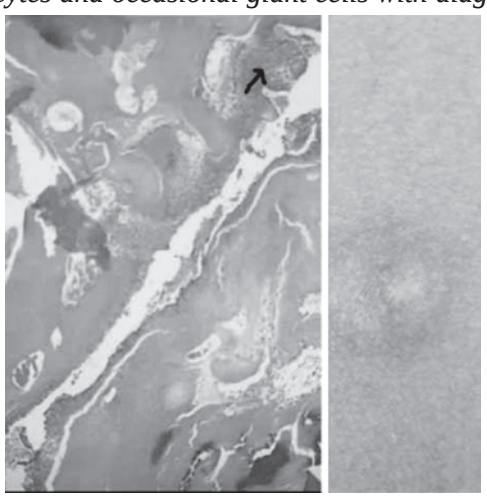

Fig. 1. Marked arrow shows nest of shadow cells

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Pilomatricoma or pilomatrixoma or calcifying epithelioma of Malherbe was first described in 1880 by Malherbe and Chenanatis[1] as a benign subcutaneous tumour arising from sebaceous glands. In 1961 Forbis and Helwig[2] proposed the term Pilomatrixoma to denote its origin from hair matrix cells. In 1977, the term was changed as Pilomatricoma to be more correct etymologically. Pilomatricoma is a rare non-cancerous tumour that grows slowly in matrix cells of hair follicles with a regular or irregular shape, firm to hard consistency and with blue red discolouration of overlying skin, most common on head and neck but can appear anywhere on the body.[3] In very rare cases, it turns into a cancerous growth called pilomatrix carcinoma or trichomatrical carcinoma. Clinically, it has a characteristic angulated shape when skin is stretched ('tent sign').[4] Pressing on one edge of the lump causes the opposite end to stick out, 'teeter-totter' sign. Acquired mutation of CTNNB1 gene is often noted. Association with conditions like myotonic dystrophy (Steinert disease), Gardner syndrome, Turner syndrome, Rubinstein Taybi syndrome are noted in some. Doughnut within the dermis with a calcified tail is described in ultrasound. Reliable diagnostic method is pathological evaluation. Histology shows sharply demarcated tumour surrounded by fibrous capsule or poorly demarcated tumour without capsule. There are darkly stained 'basophilic cells' and 'eosinophilic shadow cells' with missing nuclei. Treatment is complete excision including clear margins. Following excision, recurrences are relatively rare.Surgical excision is curative and prevents malignant transformation though it is rare in children.

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LEARNING TOGETHER

OSCE - Toxicology

1) 14yr-old female child,16 kg with history of consumption of 15 iron tabs (200 mg strength with 60 mg elemental iron each, total dose ingested 60 mg/kg) presented at 3.5 hrs with complaints of recurrent vomiting and increasing irritability.

On examination

Irritable severe dehydration - Irritable and severe dehydration was present

HR- 140/min RR- 44/min, No increased work of breathing, CFT- 2-3secs BP - 68/40mmHg

Investigation

Arterial Blood Gas

pH - 7.21

PCO2 - 19.4 mm Hg

PaO2 - 128 mm Hg

HCO3 - 12.5 mmol/l

Base deficit - 12.1

Electrolytes, Renal function tests - Normal

CXR Normal

Serum Iron 360 mcg/dl

a)What are the various stages of Iron toxicity?

b) When will you consider as toxic dose ingestion?

c) What is the management?

2) A mother and two children admitted with suspicion of poisoning.

Children had excessive salivation, anxiety, constricted pupil, bradycardia, muscle twitching and altered consciousness.

a) What is the likely poison?

b) What are the side effects, categorize them?

c) How to assess the severity?

d) Name some household items of same class?

e) What are the 6 steps in management?

f) What drugs are contraindicated in this poisoning?

g) What is the delayed complication

3) A 14 yrs old girl returned from school at 4 PM. When mother (single parent) returned from work saw her unconscious and convulsing at 9.00 PM. Presented to the ER with status epilepticus. ABC stabilized, intubated and ventilated. Poisoning suspected as the cause.

CLINICAL: Pupils Normal. No significant tachycardia

LAB: Glucose 200 mg

ABG: Metabolic acidosis HAGMA (high anion metabolic acidosis)

SGOT, PT: elevated

ECG: Normal

a) What are the poisons (both non medicines and medicines) that can cause seizures?

b) Any simple approach?

c) The triad of convulsion, hyperglycemia and HAGMA was seen. What is the poison?

d) Antidote, dose, route?

e) Ideal anticonvulsant?

4) Two year old boy received in ER at 11.00 pm. Child was apparently normal till 9:15 pm. Developed posturing/tonic seizures at 10:15 pm, was brought to ED for further management.

On arrival to ED - child was lethargic, intermittently awake, posturing - arching of back. Saturation was 96% in room air

Later because of poor respiratory effort intubated, Seizures /dystonia got controlled.

On whether questioning mother said she is taking carbamazepine for the last 5 years. She is not sure about possible poisoning.

a) What are the features of carbamazepine poisoning?

b) Decontamination procedures anything special?

c) Any antidote available?

d) Any other supportive management?

5) A previously healthy 4 years old boy came to ER with nausea, vomiting and sudden onset of unconsciousness. No history of trauma, when he was last seen an hour before, he was eating apricot. Within 20 minutes he started vomiting and he became unconscious.

ER- GCS of 7/15, RR- 28, temp-36.8°C and SpO2 on room air - 99%.

POC (Point of care) Lab results : High AG gap metabolic acidosis High venous PaO2 - 222 mm Lactate high, Capillary blood glucose, CBC, Electrolytes, renal and liver function tests, chest X-ray, ECG, troponin I, ECHO all are normal

5a) After stabilizing the ABC, what are the DDs (differential diagnosis) you will consider?

b) What salient features you identify in this case scenario?

c) What are the most reassuring features here?

d) State the single most likely Dx (diagnosis) and mention 4 clinical situations to strongly suspect this Dx?

e) How fruits lead to poisoning?

f) Pathophysiology of this type of poisoning?

g) Specific antidote apart from supportive management?

6) 45 days old baby was found crying. Because of crying spells, sleeping grandmother got up and administered some liquids (thinking as gripe water) in the night

Developed respiratory distress within ½ hour and brought to ER

a) After initial stabilization. What is the toxidromic dx?

b) Name two categories of this class and four examples of each?

c) Name the clinical features and group them into categories?

d) What is the management?

e) What are the methods of prevention ?

7) 10 months old child weighing 8 kg brought with history of Fever x 5 days, continuous, high-grade for 24hrs.

With poor feeding and vomiting and was treated with oral medications elsewhere. Inadvertently administered 250 mg syrup 10 ml 4 times in 6 hours

a) What are the various stages of toxicity?

b) What is the toxic dose?

c) What is the antidote, dosage, route, indications?

d) When is the serum level assessed?

e) What is the nomogram used? Comment on usefulness? Where it is not useful?

Answers

1. a) Stages of Iron Intoxication

Stage	Time after ingestion	Characteristics
1	30 min to 6 hrs	Vomiting, diarrhea, hematemesis/ hematochezia Profound fluid loss, hypovolemic shock
2	6 - 24 hrs	Resolution of GI (gastro intestinal) symptoms - quiescent phase Subtle signs of hypo perfusion
3	12 - 36 hrs	Multiple organ failure, metabolic acidosis
4	2 - 5 days	Fulminant liver failure and coagulopathy
5	4 - 6 weeks	Strictures and signs of GI obstruction

b) Serum iron levels should be determined at 4 hours of ingestion

- Serious iron toxicity is considered when ingestion > 60 mg/kg
- Serum iron concentration is >500 mcg/dL
- WBC Count >15,000/mm3
- Hyperglycemia
- Metabolic acidosis

c) Gastric lavage or whole bowel irrigation. Charcoal is ineffective

Deferoxamine chelation (dose 15mg/kg/hr iv infusion) is indicated when S. iron levels >500 mcg/dL. Hemodynamic collapse/acidosis regardless of S. iron level

Chelation therapy is continued till Sr. iron level returns to normal metabolic acidosis resolves, patient clinically improves and urine color returns to normal

2. a) OPC, carbamate poisoning

b) Muscarinic effects: (mnemonics)

SLUDGE: salivation, lacrimation, urination, diarrhea, GI upset, emesis) or DUMBELS: diaphoresis, diarrhea, urination, miosis, bradycardia, bronchospasm, emesis, excess lacrimation and salivation

Nicotinic effects: fasciculation and paralysis, bradycardia, tachycardia, arrhythmia

Autonomic nicotinic effects - hypertension, tachycardia, mydriasis, and pallor

CNS: Headache, dizziness, confusion, drowsiness, respiratory depression, Hyperglycemia and glycosuria also can occur.

Diagnosis - Clinical and serum cholinesterase estimation

c) Severity assessment

d) OPC preperation available in daily practice (other than pesticides): Surface and room sprays, baits for cockroaches, head lice shampoos, pet washes

To identify carbamates by brand names Carb - Bufencarb, Aldicarb, Carbaryl, Methiocarb, Pinmicarb, Bendiocarb, Carbofuran

e) i. Decontamination: Skin, Eye decontamination, GE. No charcoal

ii. General supportive: O2, Vitals monitoring and monitoring the need for ventilatory support

iii. Antidote: IV atropine 0.05 mg/kg every 10 mins till atropinization. Then less frequently or glycopyrrolate - 1mg iv every 10-15 min. Targeting on drying up the secretions and to stop when toxic features disappear

Assessment	**Severe**	**Moderate**	**Mild**
Level of consciousness	Unconscious no pupillary reflex, convulsions present	Conscious, anxious, restless but cannot walk miosis	Comes walking, headache, abdominal pain, vomiting
Respiration	Flaccid paralysis present, respiratory failure	Soft voice	
Serum AChE Acetylcholine esterase level	0.8U/L	0.8 - 2.0 U/L	1.6 - 4.0 U/L

iv. P2AM (pralidoxime) 30-40 mg / kg in NS over 30 mins. Can be repeated IV after 8 hrs as needed or Infusion 8 mg/kg/hr. Not indicated in carbamate poisoning

v. Monitor respiratory rate and provide respiratory support when needed

vi. Watch for intermediate syndrome

f) Drugs contraindicated are : Aminophylline (antagonizes PAM), aminoglycoside (worsens muscle weakness), scoline, morphine (is metabolized by cholinesterase, hence effects are prolonged)

g) Intermediate syndrome: Usually develops after 1-4 days, due to prolonged inhibition of cholinesterase and muscle necrosis. Weakness of respiratory muscles, head lag, proximal muscles of limbs, some cranial nerve palsy which may need respiratory support.

3. a) Seizures - Household substances - Camphor, neem oil, OPC, gammexane, insecticide, mosquito repellant

b) Convulsions. Further analysis can be done in the presence of associated features

Plus hypoglycemia - OHA (oral hypoglycemic agents),

Plus hypoglycemia, bradycardia - BB(Beta blockers)

Plus VT (ventricular tachycardia), dilated pupil - TCA (tricyclic antidepressant)

Plus hyperglycemia, metabolic acidosis, high transaminases - INH

Differential diagnosis can be acheived by checking blood glucose

Hypoglycemia - OHA/BB

High glucose - INH, theophylline

Normal glucose - TCA

INH -Toxic dose > 70 mg/kg potentially fatal

c) Triad of convulsions, HAGMA, Hyperglycemia- INH

d) Treatment: Supportive treatment

IV pyridoxine is given as a dose weight by weight of INH consumed or 70 mg/kg if the quantity is unknown.

If IV unavailable, tablets can be crushed and administered through (naso gastric tube) NGT

e) Benzodiazepines is ideal but phenytoin is contraindicated.

4. a) CNS: Cerebellar signs (ataxia, nystagmus) mydriasis, opthalmoplegia, posturing, dystonia, coma, seizures, myoclonus, hyperthermia

Cardiac: Sinus tachycardia, dysrhythmias, hypotension, AV block

Respiratory depression, arrest

Metabolic: Hyponatremia, hypokalemia,

Others: rarely transient pancytopenia

Usually half life is 4 to 8 hrs. But can be prolonged in sustained release preparations or due to pharmacobezoar where it is 24 to 48 hrs

b) Aggressive decontamination as there is delayed emptying, (pharmacobezoar, SR)

Multiple doses of AC

Whole bowel irrigation with PEG, if > 10 tab or SR preparation

Charcoal hemoperfusion, hemodialysis

c) No specific antidote

d) Supportive management - Fluid therapy and activated charcoal treatment started emergently and hemodialysis performed even in the absence of carbon hemoperfusion

5. a) DD for HAGMA in poisoning- Salicylate, methanol, ethanol, INH, iron, TCA, cyanide

b) Severe symptoms onset within 30 minutes. HAGMA, normal SpO2

c) Abnormal: Lactate high, VBG (venous blood gas) - high anion gap metabolic acidosis. High venous PaO2 - 222 mms

Normal: Capillary blood glucose, CBC, Electrolytes, renal and liver function tests, chest X-ray, ECG, troponin I, ECHO all are normal

d) Clinical scenarios where cyanide poisoning is suspected

- Death or rapid deterioration within 30 minutes of ingestion.
- Sudden collapse of lab or industrial workers - Jewellery shop, plastic industry (using nitriles as solvents)
- Fire victim or attempted suicide patient with unexplained coma or acidemia

- Ingestion of acetonitrile, solvent remover of acrylic sculptured nails.

e) Ingestion of seeds fruits or plants containing cyanogenic glycosides (apricot seed, apple seed, tapioca). The pits and seeds of many fruits contain amygdalin - a plant compound that our body converts to cyanide after eating. They are released only when the seeds are crushed or bitten

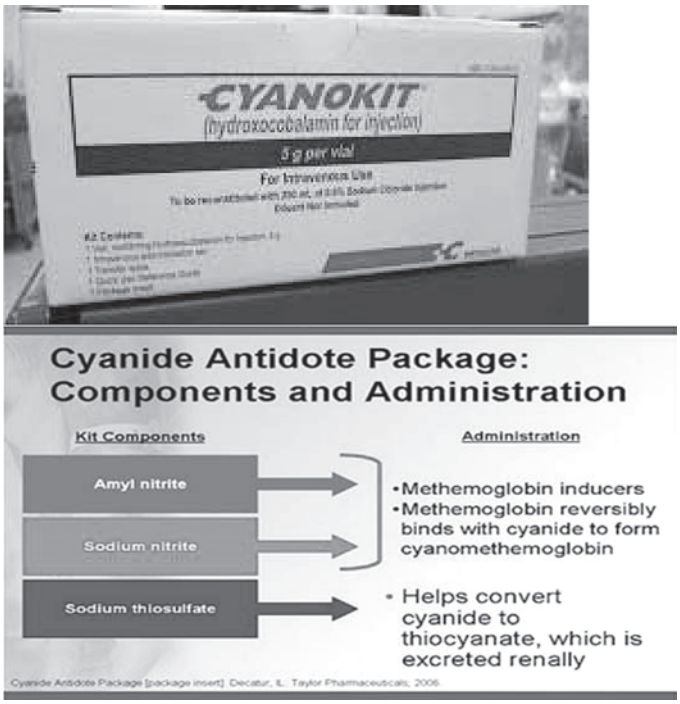
Lab Clue: High anion gap metabolic acidosis, high lactate, high venous PaO2 resulting in a decreased arteriovenous oxygen difference (< 10%)

f) Pathophysiology - Inside cells, principal toxicity results from inactivation of cytochrome oxidase, thus uncoupling mitochondrial oxidative phosphorylation and inhibiting cellular respiration, even in the presence of adequate oxygen stores.

Cellular metabolism shifts from aerobic to anaerobic, with the consequent production of lactic acid. Consequently, the tissues with the highest oxygen requirements (brain and heart) are most profoundly affected by acute cyanide poisoning.

g) Management: Correction of shock, acidosis.

Hydroxocobalamin (Cyanokit) is the first-line therapy. It functions by binding cyanide to its cobalt ion to form cyanocobalamin, which is essentially nontoxic and is cleared by the kidneys. Most preferred antidote, because of its better risk/benefit ratio.



6. a) Corrosive poisoning

b) Acid: Car battery liquid, rust cleaner, metal cleaner, disinfectants - phenol

Alkali: Household cleaners, ammonia-based disinfectants, bleach, drain cleaners, disc battery

c) Local: Painful swelling, mucous membrane burns, bloody emesis, abdominal pain,

Respiratory: Respiratory distress, laryngeal edema, voice change

Systemic: Thirst, shock, renal failure, convulsion, coma are terminal events

Late: Esophageal pyloric, gastric strictures

d) Intubation with caution, indication: Presence of soft stridor, voice change, drooling, shock, respiratory distress, abdominal symptoms

Avoid emetics, lavage. Steroids are not useful

Water or milk < 15 ml/kg can be given to dilute the toxin if the child comes within one hour. Avoid large volume to prevent vomiting. Opioids are given for pain relief

Early endoscopy may be useful if done within 24 hrs, provided a gentle and experienced pediatric endoscopist is available

e) Prevention strategies

- Don't give medicine in darkness
- Avoid keeping corrosive substances in bottles or containers used for drinking
- Never miss corrosive ingestion on examination

7. a) Stages of toxicity

Phase 1 (<24 h post ingestion) Day 1

Anorexia, nausea, vomiting, malaise and diaphoresis. Lab - normal

Phase 2 (24-72 h) Day 2, 3

Phase 1 symptoms less, tenderness in the right upper quadrant, hepatomegaly elevated ALT, AST, PT, bilirubin, BUN, creatinine.

Phase 3 (72-120 h) Day 4, 5

Hepatic failure with jaundice, hypoglycemia, bleeding, or encephalopathy, renal failure and cardiomyopathy

Lactic acidosis, PT, ALT and AST (>10,000 IU/L), bilirubin and hyperammonemia

Hepatic centrilobular necrosis. Acute tubular necrosis cerebral edema, sepsis, or may end fatally

Phase 4 (5-14 Days post ingestion)

Complete recovery or they die. No chronic dysfunction

b) Toxic dose -Single ingestion >200mg/kg - in children <12yrs of age.

Single ingestion >7.5gm in adolescents and adults.

c) NAC (N Acetyl cysteine)

Dosage / dilution PO: Loading: 140 mg/kg PO once

Maint: (4 h after loading): 70 mg/kg PO q4hr for 17 doses; total 18 doses - 1330 mg/kg over 72 hrs diluted to 5% solution (50 mg/mL) with fruit juice or carbonated beverage. with antiemetic

IV: Loading : 150 mg/kg IV 1 h; dilute 5ml/kg D5W

I maint : 50 mg/kg IV over 4 h; dilute in 10ml/kg

II maint : 100 mg/kg IV over 16 h; dilute in 20mL/kgD5W

Each infusion immediately follows the previous; total treatment time 21 hrs

Indications for IV NAC

- Frequent vomiting
- GI bleed
- Alterd mental status
- Pregnant mother with potential fetal toxicity

d) Serum level of paracetomol done at 4 hrs after ingestion

Before 4 hrs may not represent peak levels

e) Rumak Mathew Nomogram

Useful only for single acute ingestion

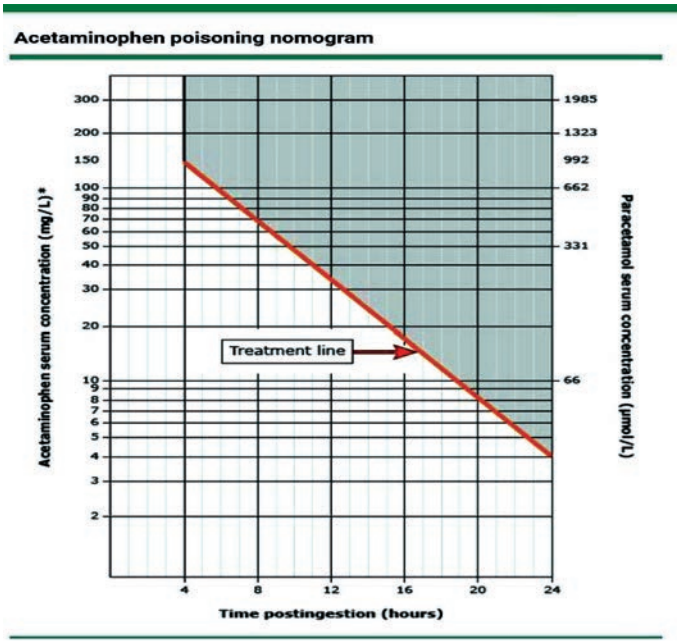
Time refers to time after ingestion, measured at 4 hours

If sustained release preparation is consumed repeated serum level done at 8 hrs.

Nomogram cannot be used if paracetomol levels measured after 24 hrs, for repeated ingestions, and when time of ingestion is not known

When paractomol is ingested along with drugs which slows gastric emptying

Rumak Mathew Nomogram



NEWS AND NOTES

GUJPEDICON 2022

48th Annual State Conference of Academy of Pediatric Gujarat

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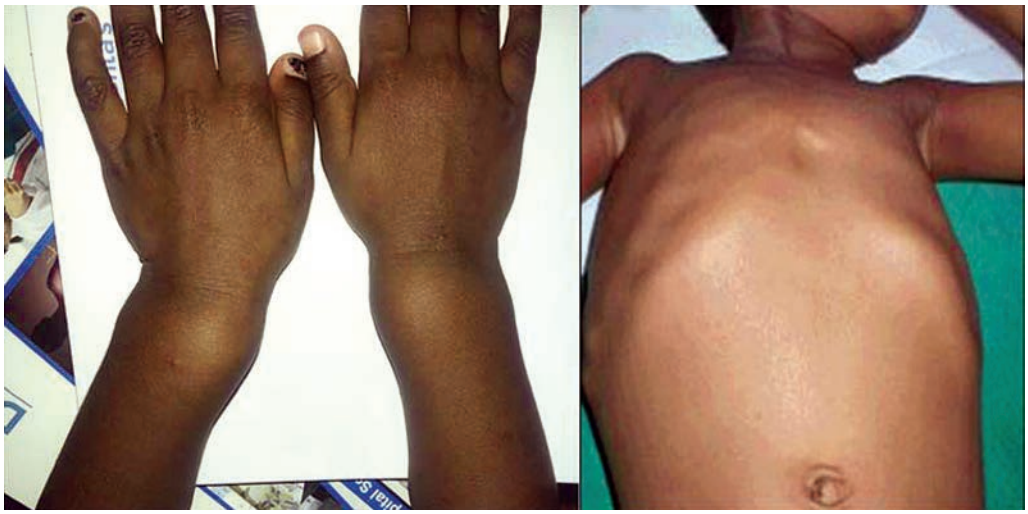
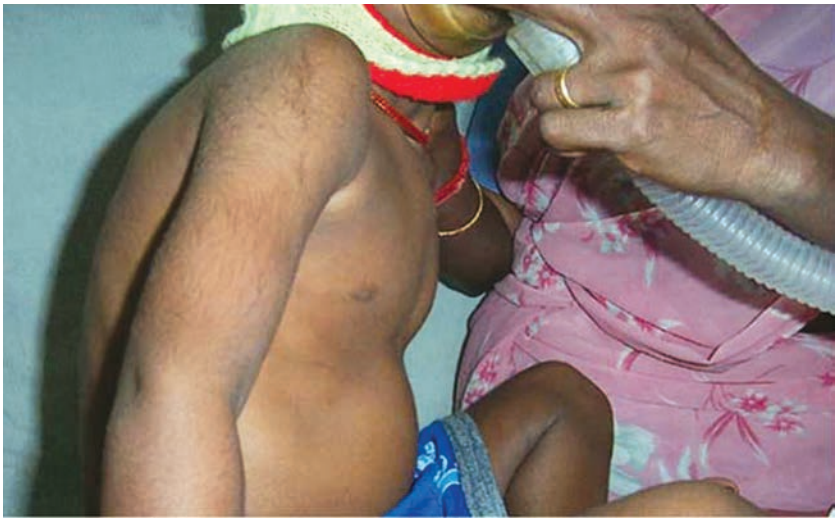
PICTURE QUIZ





Q 1) identify and name the clinical signs?

Q. 2) Mention two mimics for this condition?

Q. 3) If all the biochemical investigations are normal what is the possibility?

Q. 4) If there is albuminuria and glycosuria, What is the diagnosis?

Q. 5) What is the cardiac and neurological complication of this condition?

ANSWERS

1) Widened lower ends of ulna and radius, ricketty rosary, Harrison's sulcus

2) Metaphyseal dysplasia, Morquio's disease, hypophosphatasia

3) Metaphyseal dysplasia, Morquio's disease. In hypophosphatasia alkaline phosphatase levels are low

4) Fanconi syndrome

5) Cardiac: Vitamin D deficiency dilated cardiomyopathy. Neurological: Tetany, seizures, delayed motor mile stones

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