Pharmacology summarization

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CHAPTER 48
CHAPTER 48: CLINICAL TOXICOLOGY

Toxicology mean the study of poison.

*Routes of exposure for toxins:
1) Inhalation or insufflation (snorted)
2) Ingestion by oral
3) Injection
4) Dermal absorption

*common targets of toxicity:
The central nervous system (CNS), the lungs, the kidney, the heart, the liver, the blood, and even the intricate acid/base and electrolyte balance of the body.

*Emergency treatment of poisoned patient:
That mean what should we do with the poisoned patient
1) Follow the rule ABCD {A:airway, B:breathing, C:circulation, D:Dextrose}
2) Make diagnosis, history, exam, investigations Because it is possible the existence of any other immediately life-threatening toxic effect (for example, profound increases or decreases in blood pressure, heart rate, breathing, or body temperature, or any dangerous dysrhythmias). Acid/base and electrolyte disturbances, along with an acetaminophen and salicylate blood level, can be further assessed as laboratory results are obtained.
3) After administering oxygen, obtaining intravenous access, and placing the patient on a cardiac monitor, the poisoned patient with altered mental status should be considered for administration of the “coma cocktail” as possibly diagnostic and therapeutic. The “coma cocktail” consists of intravenous dextrose to treat hypoglycemia, a possible toxicological cause of altered mental status, along with naloxone to treat possible opioid or clonidine toxicity, and thiamine for ethanol-induced Wernicke encephalopathy.

[Note: Hypoglycemia may be caused by oral hypoglycemics, insulin, ackee plant, and ethanol.]

4) Now working on Decontamination to prevent absorption of the poisons. This may include flushing of the eyes with saline or tepid water to a neutral pH for ocular exposures, rinsing of the skin for dermal exposures, as well as administration of gastrointestinal (GI) decontamination with gastric lavage, activated charcoal, or whole bowel irrigation (utilizing a polyethylene glycol electrolyte balanced solution) for selected ingestions.
5) Elimination enhancement by:

*Hemodialysis: use it if certain properties are met: low protein binding, small volume of distribution, small molecular weight, and water solubility of the toxin. Some examples of medications or substances that can be removed with hemodialysis include methanol, ethylene glycol, salicylates, theophylline, phenobarbital, and lithium.

*Urinary alkalinization: Alkalization of the urine enhances the elimination of salicylates or phenobarbital. Increasing the urine pH with intravenous sodium bicarbonate transforms the drug into an ionized form that prevents reabsorption, thereby trapping it in the urine to be eliminated by the kidney. The goal urine pH is within the range of 7.5 to 8, while ensuring that the serum pH does not exceed 7.55.

*Multiple-dose activated charcoal: enhances the elimination of certain drugs (for example, theophylline, phenobarbital, digoxin, carbamazepine, valproic acid) by creating a gradient across the lumen of the gut. In addition, activated charcoal blocks the reabsorption of medications that undergo enterohepatic recirculation (such as phenytoin), by adsorbing the substance to the activated charcoal.

6) Use specific antidote

Antidote: a drug taken or given to counteract a particular poison.
**SELECT PHARMACEUTICAL AND OCCUPATIONAL TOXICITIES:**

**A. Acetaminophen**
Acetaminophen produces toxicity when its usual metabolic pathways become saturated. Usually, acetaminophen undergoes metabolism by sulfation, glucuronidation, and N-hydroxylation by the cytochrome P450 system. When a toxic amount of acetaminophen is ingested, the first two processes are overwhelmed and more acetaminophen is metabolized by the cytochrome P450 system to a hepatotoxic metabolite (N-acetyl-p-benzoquinoneimine, NAPQI). In therapeutic acetaminophen ingestions, the liver generates glutathione, which detoxifies NAPQI. However, in overdose, the glutathione is depleted, leaving the metabolite to produce toxicity. There are four phases typically describing acetaminophen toxicity:

- **Phase 1 (0 to 24 hours):** loss of appetite, nausea, vomiting, general malaise
- **Phase 2 (24 to 72 hours):** abdominal pain, increased liver enzymes
- **Phase 3 (72 to 96 hours):** liver necrosis, jaundice, encephalopathy, renal failure, death
- **Phase 4 (>4 days to 2 weeks):** complete resolution of symptoms and organ failure

The antidote for acetaminophen toxicity, N-acetylcysteine (NAC), initially works as a glutathione precursor and glutathione substitute and assists with sulfation. Later on, NAC may function as an antioxidant to aid in recovery.

![Chemical structure of acetaminophen and its metabolites with phase descriptions](image)
B. Alcohols

1. Methanol (wood alcohol) and ethylene glycol:
These primary alcohols are themselves relatively nontoxic and cause mainly CNS sedation. However, methanol and ethylene glycol are oxidized to toxic products: formic acid in the case of methanol and glycolic, glyoxylic, and oxalic acids in the case of ethylene glycol. Fomepizole inhibits this oxidative pathway by blocking alcohol dehydrogenase. It prevents the formation of toxic metabolites and allows the parent alcohols to be excreted by the kidney. In addition, cofactors are administered to encourage metabolism to nontoxic metabolites (folate for methanol, thiamine and pyridoxine for ethylene glycol). If untreated, methanol ingestion may produce blindness, metabolic acidosis, seizures, and coma. Ethylene glycol ingestion may lead to renal failure, hypocalcemia, metabolic acidosis, and heart failure.

[Diagram]

2. Isopropanol (rubbing alcohol, isopropyl alcohol):
This secondary alcohol is metabolized to acetone via alcohol dehydrogenase. Acetone cannot be further oxidized to carboxylic acids, and therefore, acidemia does not occur. Isopropanol is a known CNS depressant (approximately twice as intoxicating as ethanol) and GI irritant.
No antidote is necessary to treat an isopropyl alcohol ingestion.

C. Carbon monoxide
Carbon monoxide is a colorless, odorless, and tasteless gas, which is impossible for individuals to detect without a carbon monoxide detector. Following inhalation, carbon monoxide rapidly binds to hemoglobin to produce carboxyhemoglobin. The binding affinity of carbon monoxide to hemoglobin is 230 to 270 times greater than that of oxygen. Consequently, even low concentrations of carbon monoxide in the air can produce significant levels of carboxyhemoglobin. In addition, bound carbon monoxide increases hemoglobin affinity for oxygen at the other oxygen-binding sites. This high-affinity binding of oxygen prevents the unloading of oxygen at the tissues, further reducing oxygen delivery. The presence of this highly oxygenated blood may produce “cherry red” skin. The symptoms of carbon monoxide intoxication are consistent with hypoxia, with the brain and heart showing the
greatest sensitivity. Symptoms include headache, dyspnea, lethargy, confusion, and drowsiness, whereas higher exposure levels can lead to seizures, coma, and death.

D. Cyanide
Cyanide is just one of the toxic products of combustion produced during house fires. Once absorbed into the body, cyanide quickly binds to many metalloenzymes, thereby rendering them inactive. Its principal toxicity occurs as a result of the inactivation of the enzyme cytochrome oxidase (cytochrome a3), leading to the inhibition of cellular respiration. Therefore, even in the presence of oxygen, tissues such as the brain and heart, which require a high oxygen demand, are adversely affected. Death can occur quickly due to respiratory arrest of oxidative phosphorylation and production of adenosine triphosphate. The most recently developed antidote, hydroxocobalamin (vitamin B12a), is administered intravenously to bind the cyanide and produce cyanocobalamin (vitamin B12) without the worry of hypotension or methemoglobin production.

In patients with smoke inhalation and cyanide toxicity, the induction of methemoglobin with sodium nitrite should be avoided unless the carboxyhemoglobin concentration is less than 10%. Otherwise, the oxygen-carrying capacity of blood becomes too low.

E. Iron
Toxic effects can be expected with as little as 20 mg/kg of elemental iron ingested, and doses of 60 mg/kg may be lethal. Based on the quantity ingested, the patient’s weight, and the elemental iron concentration, an assessment of potential toxicity can be made. A serum iron level should be obtained, since levels between 500 and 1000 μg/dL have been associated with shock and levels higher than 1000 μg/dL with morbidity and mortality. If a significant amount of iron has been ingested, the patient usually presents with nausea, vomiting, and abdominal pain. Depending on the amount of elemental iron ingested, the patient may experience a latent period or may progress quickly to hypovolemia, metabolic acidosis, hypotension, and coagulopathy. Ultimately, hepatic failure and multisystem failure, coma, and death may occur. Deferoxamine, an iron-specific chelator, binds free iron, creating ferrioxamine to be excreted in the urine. The intravenous route for deferoxamine is preferred, but hypotension may occur if rapid boluses are administered instead of a continuous infusion.

F. Lead
Adults absorb about 10% of an ingested dose, whereas children absorb about 40%. Inorganic forms of lead are initially distributed to the soft tissues and more slowly
redistribute to bone, teeth, and hair. When lead makes its way to the bone, it impairs new bone formation and causes increased Calcium deposition in long bones visible on x-ray. Ingested lead is radiopaque and may appear on an abdominal radiograph if present in the GI tract. Lead has an apparent blood half-life of about 1 to 2 months, whereas its half-life in the bone is 20 to 30 years. Chronic exposure to lead can have serious effects on several tissues.

*effects of lead on:

1. **Central nervous system:**
The CNS effects of lead have often been termed lead encephalopathy. Symptoms include headaches, confusion, clumsiness, insomnia, fatigue, and impaired concentration. As the disease progresses, clonic convulsions and coma can occur. Death is rare, given the ability to treat lead intoxication with chelation therapy. Children are more susceptible than adults to the CNS effects of lead. Furthermore, blood levels of 5 to 20 μg/dL in children have been shown to lower IQ in the absence of other symptoms.

2. **Gastrointestinal system:**
Early symptoms can include discomfort and constipation (and, occasionally, diarrhea), whereas higher exposures can produce painful intestinal spasms.

3. **Blood:**
Lead has complex effects on the constituents of blood, leading to hypochromic, microcytic anemia as a result of a shortened erythrocyte life span and disruption of heme synthesis. Elevated blood lead levels can be used diagnostically for determining lead intoxication, provided that blood lead levels are greater than about 25 μg/dL.

Multiple chelators can be utilized in the treatment of lead toxicity. When levels are greater than 45 μg/dL, but less than 70 μg/dL in children, succimer (dimercaptosuccinic acid, DMSA), an oral chelator, is the treatment of choice. With lead levels greater than 70 μg/dL or if encephalopathy is present, dual parenteral
therapy is required with dimercaprol given intramuscularly and calcium disodium edetate given intravenously. Dimercaprol is suspended in peanut oil and should not be given to those with a peanut allergy.

**G. Organophosphate and carbamate insecticides**

These insecticides exert their toxicity through inhibition of acetylcholinesterase, with subsequent accumulation of excess acetylcholine producing nicotinic (mydriasis, fasciculations, muscle weakness, hypertension) and muscarinic (diarrhea, urination, miosis, bradycardia, bronchorrhea, emesis, lacrimation, salivation) effects. Carbamates reversibly bind to acetylcholinesterase, whereas organophosphates undergo an aging process to ultimately irreversibly inactivate the enzyme. Organophosphate nerve agents, such as sarin, soman, and tabun, have the same mechanism of action, but the aging process is much more rapid compared to insecticides. Atropine, a muscarinic receptor antagonist, and pralidoxime, an oxime to reactivate cholinesterase, should be administered intravenously or intramuscularly to treat the muscarinic and nicotinic effects, respectively.

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Important note: The following points are not present in slide:

D. Cyanide
E. Iron
F. Lead
G. Organophosphate and carbamate insecticides

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Good luck