Clinical toxicology Introduction

ا.م.د.اسامة ايوب

- studies the toxic effects of therapeutic agent used to treat, ameliorate, modify or prevent disease states.

- Non therapeutic agent
- chemicals whose exposure has an environmental component (metals)
- drug use as a result of societal behavior (alcohol and drugs of abuse)
- chemical by-products of industrial development (gases, hydrocarbons, radiation)
- Urban and agricultural technologies(pesticides, insecticides, herbicides)

The following general steps represent important elements of the initial clinical encounter for a poisoned patient:

1. Stabilization of the patient
2. Clinical evaluation
3. Prevention of further toxin absorption
4. Enhancement of toxin elimination
5. Administration of antidote
6. Supportive care and clinical follow-up

Clinical Stabilization

- It is the first priority this is the so-called ABCs (Airway, Breathing, Circulation) .
- Is the patient breathing? Oxygen support or mechanical ventilation.
- Is the patient blood pressure stabilized? Shock is best stabilized with fluid replacement. If necessary vasopressor agent.
- CNS involvement control convulsion
- Is the patients comatose? And other problems should be stabilized.
- Other points like cardiac rhythm, seizure or tremor,

Clinical evaluation

- A victim of poisoning must be carefully evaluated for extent of poisoning before management plan can be initiated

- After stabilization the next step is to obtain a history of the poisoning.(to determine substance ingested, as well as the extent and time of exposure)-------self-poisoning

- Information sources commonly employed in this setting include

✓ family members

✓ emergency medical technicians

✓ a pharmacist who sometimes can provide a list of prescriptions recently filled

✓ Employer in work environment

Clinical assessment

- Some poisons produce clinical characteristic that strongly suggest the involvement of a particular drug or chemical
- cholinesterase inhibition (organophosphorous insecticides) cholinergic effect like miosis, excessive salivation and diarrhea
- tricyclic antidepressant associated with anticholinergic activity like mydriasis, absent bowel sound and cardiac arrhythmia.
- Respiratory depression of barbiturate or opioid poisoning and the tachycardia and hypertension of poisoning with sympathomimetic agents.
- using blood, urine, and vomitus for toxicologic analysis where qualitative and quantitative assays can quickly identify a toxic substance.

Clinical evaluation

- A quick physical examination often leads to important clues about the nature of the toxin.
- These clues can be specific symptom complexes associated with certain toxins and can be referred to as ‘‘toxidromes

Cholinergic	Characterized by salivation, lacrimation, urination, defecation, gastrointestinal cramps, and emesis (“sludge”). Bradycardia and bronchoconstriction may also be seen	Carbamate Organophosphates Pilocarpine
Narcotic	Altered mental status, unresponsiveness, shallow respirations, slow respiratory rate or periodic breathing, miosis, bradycardia, hypothermia	Opiates Dextromethorphan Pentazocine Propoxyphene

Breath odor

- Aceton-------nail polish remover, salicylates, ketoacidosis
- Bitter almond------ Cyanide
- Ammoniacal--------uremia
- Coal gas--------Co
- Eggs--------hydrogen sulfide, disulfiram
- Fish--------hepatic failure, zinc phosphide
- Fruitlike-------amyl nitrite, ethanol, isopropyl alcohol
- Garlic---------arsenic, organophosphate, DMSO
- Mothballs------camphor containing substances
- Pearlike------ chloral hydrate
- Tobacco-------nicotine
- Wintergreen-----methylsalicylate

- Ataxia-----alcohol, barbiturates, phenytoin, organic solvent , hallucinogen

- Convulsion------alcohol, amphetamine, barbiturate withdrawal, antihistamine, cyanide, antidepressent

- GIT
- Emesis-----caffieine, corrosive, boric acid, theophylline
- Abdominal colic-----arsenic, organoph, mushrooms
- Diarrhea------boric acid,arsenic, organoph, mushrooms
- Constipation------ Lead, opoids

- Heart
- Heart rate
- Bradycardia-----digitalis, opoids, sedative
- Tachycardia------amphetamine, atropine, cocaine

Mouth

- Dry-------Amphetamine, atropine, antihistamine, opioids
- Salivation-------Mushrooms, organoph, strychnine
- Gum discoloration-----Lead and other heavy metals

Paralysis-----Botulism and heavy metals

Pupils

- Miosis------Muscarinic type mushroom, opioids, organoph,
- Mydriasis----Amphetamine, atropine, antihistamine, TCA
- Nystagmus-----Barbiturate, phenytoin, sedatives
- Vision disturbance-----Botulism, ethanol organoph

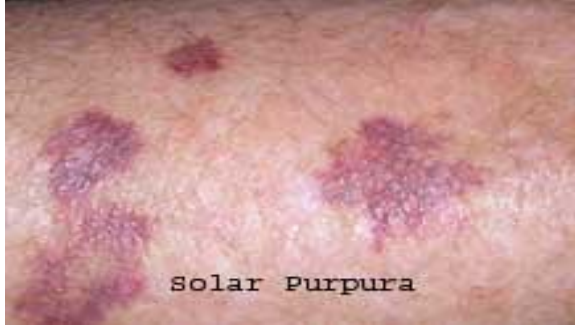
Respiration

Rapid rate---amphetamine, barbiturate, methanol, petrolium

Slow rate-----alcohol, opioids

Paralysis-----Botulism

Skin



Cyanosis------Nitrite, strychnine

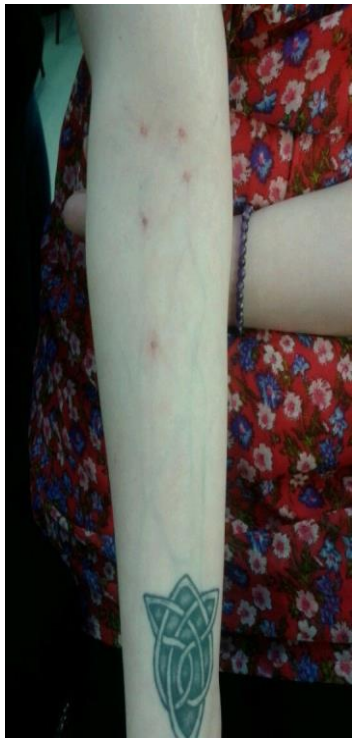
Red, flushed------alcohol, atropine, Co

Purpura--------salicylates, snake and spider bites

Jaundice-------Acetaminophen, CCL4,arsenic

Needle mark------Amphetamine, opioids, Phencyclidine

- Many toxic agents are not detected on routine screening, other tests required include:
- serum concentrations of specific drugs
- serum electrolytes
- anion gap
- Glucose
- Blood gas
- serum creatinine, and
- liver function tests



Prevention of Further Poison Absorption

- Toxic substances can enter the body through the dermal, ocular, pulmonary, parenteral, and gastrointestinal routes.
- a significant opportunity exists to prevent further absorption of the poison by minimizing the total amount that reaches the systemic circulation.
- For toxins in inhalation route, removing the patient from the environment and providing adequate ventilation and oxygenation for the patient.
- For topical exposures, clothing containing the toxin must be removed and the skin must be washed with water and tincture of mild soap
- chemical injuries to the eye → thorough irrigation of the eye with water for 15 minutes should be performed immediately.

GIT decontamination

- Severity of intoxication is proportional to the length of time an unabsorbed toxic agents remains in the body.

1-Dilution:

- Initial procedure often recommended

A-it helps reduce the gastric irritation induce by many ingested poisons

B-it adds bulk to the stomach that may be needed later for emesis induction

- 1-2 cupfuls for child and 2-3 cupfuls for adult.
- should not be forced and not administered to an unconscious patient or if the gag reflex is absent.
- Excessive water may distend the stomach wall causing premature evacuation of its content in to duodenum and making it more difficult to remove the poison

Emesis

- A mainstay for treating the ingestion of toxic agent

- In cases of hydrocarbon, corrosive and sharp object emesis should be avoided.

➢ **Syrup of ipecac** was first mentioned in Brazil in 1648

- Contain active alkaloids emetine and cephaeline.
- Ipecac cause vomiting through early and late phases of vomiting

✓ Early vomiting occur in 30 minutes due to direct stimulation effect on GIT

✓ Late phase occurs after 30 minutes result from direct stimulation effect on CTZ.

➢ The dose 30ml in adult, 15ml in (1-12 years) and 5-10ml in (1year).

➢ adverse effect include protracted vomiting, diarrhea, lethargy, diaphoresis and fever, emetin is cardiotoxic.

➢ *Other drugs induce vomiting*

➢ ***Apomorphin***

✓ produce rapid emesis with in 3-5min

✓ direct stimulation of CTZ, it is no longer recommended.

➢ ***Soap solution***

✓ used when rapid emesis is indicated and ipecac is not available

✓ 2-3 tablespoonfuls should be mixed with 6-8 ounces of water.

✓ Detergent produce vomiting by direct stimulation of GI mucosa.

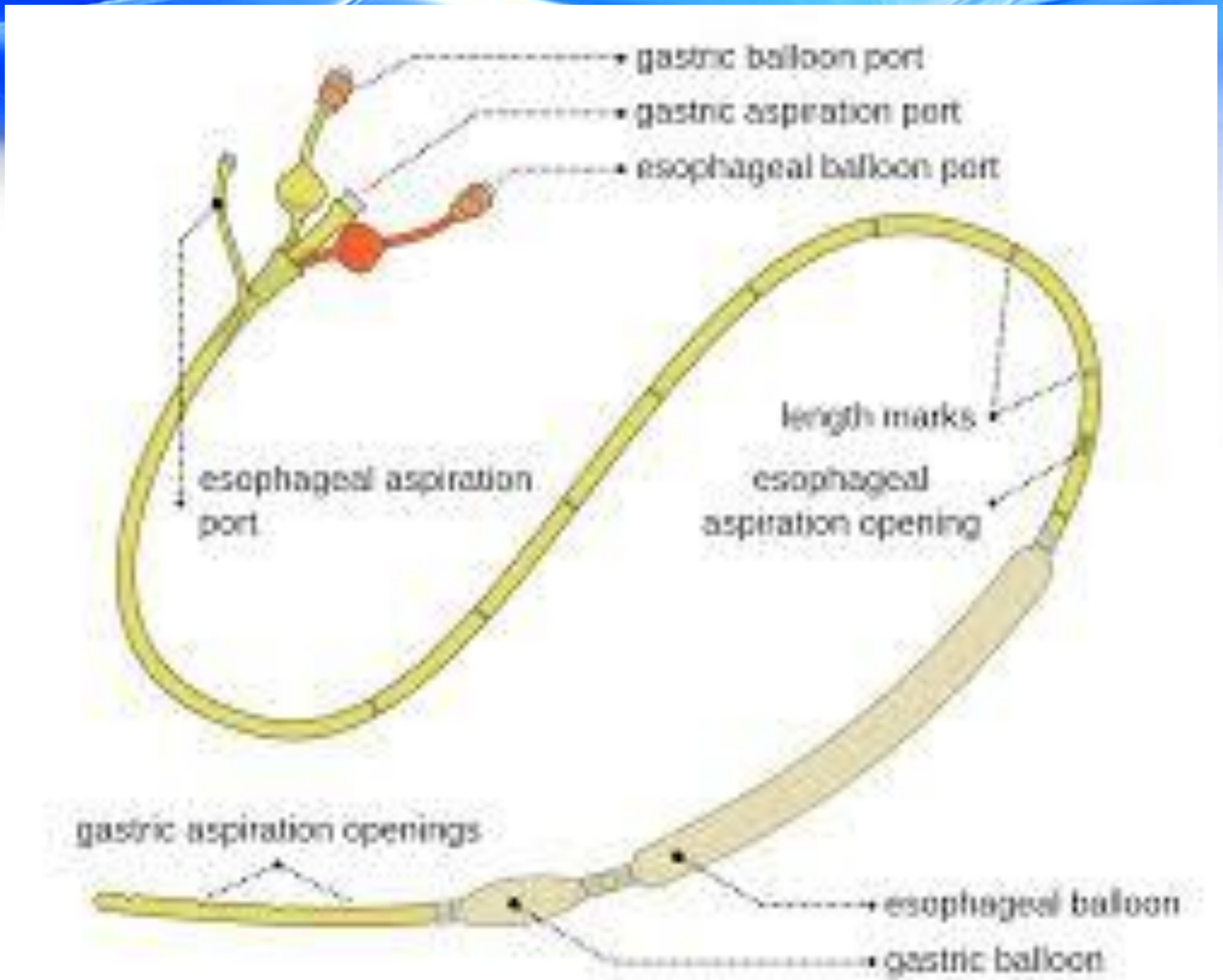
➢ ***Mechanical stimulation***

✓ Of the back of the tongue or pharynx by a blunt object has been recommended as a means to evoke emesis.

✓ Advantage is availability, disadvantage is lack of effectiveness.

Lavage

- Is a process of washing out the stomach with solutions, including water, saline, sodium bicarbonate, calcium salts, Pot. Permanganate.
- airway should be protected by intubation especially in un conscious or convulsent patients
- Aliquots of 50-100ml in children and 200-300ml in adult should be instilled allowed to mix and then drained into a collection bag positioned below the patient
- A minimum of 2L are required to washout most of the stomach content until returned fluid is clear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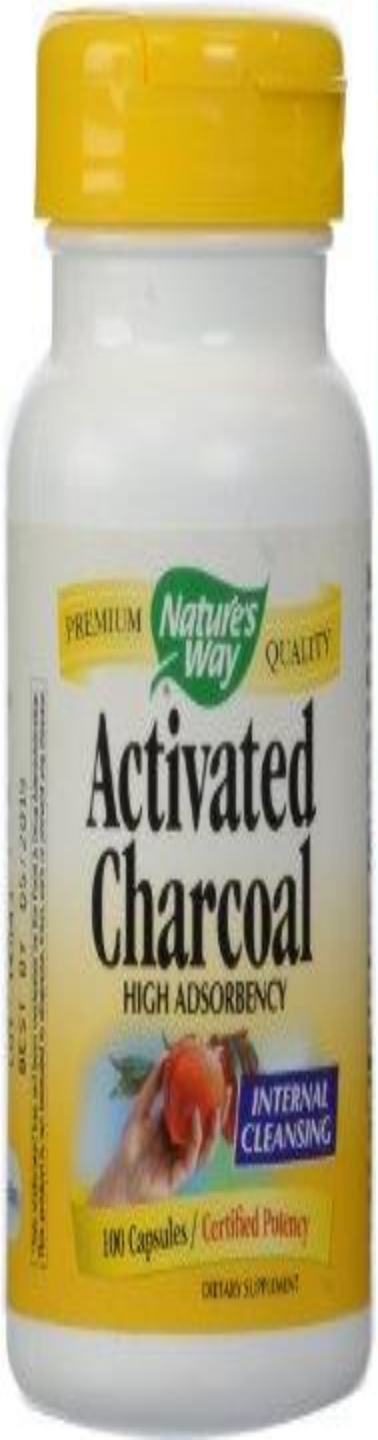

Adsorbent

- Several adsorptive substances like
  - ✓ Kaolin
  - ✓ Cholestyramine
  - ✓ Pectin
  - ✓ Activated charcoal is used routinely

- Frensh pharmacist Tourey---10 time lethal dose of strychnine +Activated charcoal 1831

- The activation process occurs when charcoal fragments exposed to oxidizing gas composed of steam or oxygen at temp 600-900-----the result increase SA 1000M2/g

- 50-100 g in adult
- 25-50 g in child
- 1g/kg in infant

- Activated charcoal is pharmacologically inert and not absorbed

- Large dose cause constipation and shouldn't be used in intestinal obstruction

- It enhance elimination of aspirin, carbamazepine, phenytoin , phenobarbiton, Digoxin, theophylline, nadolol and TCA

- Proposed Mechanisms

1. Interruption of enterohepatic circulation
2. Adsorption of depot forms of orally administered drug within GIT

- Not used within 30 minute of syrup of Ipecac Why?

- It is not effective for a number of poisonings including strong acids or alkali, cyanide, iron, lithium, arsenic, methanol, ethanol or ethylene glycol

- Factors affecting efficacy

1-time since ingestion

2-charcoal:drug ratio

3-drug dose

4-stomach content(PH, composition)

Cathartics

- Saline cathartics are preferred
- Reduce time of contact between poison and absorption site

- Shouldn't be used in

1. Corrosive
2. Electrolyte disturbance
3. Absent bowel sound
4. Stimulant and lubricant laxatives shouldn't be used except caster oil in phenol intoxication

- Magnesium sulfate(250 mg/kg in child and 5-10g in adult)and citrate(4ml/kg in child and 250-300ml in adult) always used
- Shouldn't be used in patient with renal failure ------cns depression by accumulation of Mg
- Sodium sulphate
- Na containing cathartics avoided in CHF----Na retention

Whole bowel irrigation

- Anew promising therapy
- Sodium sulfate and PEG electrolyte soln. most commonly used
- The procedure also used to clean bowel before surgery
- Movicol
  - ✓ PEG
  - ✓ NaCl
  - ✓ $NaHCO_3$
  - ✓ KCl
- Colo.Clean

Methods to increase elimination

- Several methods of enhancing the elimination of atoxic agent include

1. Forced diuresis and PH
2. Dialysis and hemoperfusion
   - Peritoneal dialysis
   - Hemodialysis
3. Hemoperfusion
4. Specific antidote

1-Forced diuresis and PH

- It is useful when compound or active metabolites eliminated from the kidney to enhance it is excretion
- Furosamide and mannitol was generally used, overdose of such drugs associated with complications like pulmonary and cerebral edema.
- Manipulation of urinary PH to enhance excretion of compounds is a corner stone in weak acid and weak base excretion
- Non ionized compounds move easily across cell membrane while polar compound less diffusible, the goal is to increase proportion of ionized form of drug in urine to be excreted

- Alkaline diuresis is achieved by administration of $NaHCO_3$ 1-2Meq/kg every 3-4 hr. the objective is to increase urinary PH to 7-8

- This use to increase excretion of weak acid like salicylates, and phenobarbital

- Acid diuresis is possible by using ammonium chloride, 75mg/kg/24hr. The end point for acidification is a urinary PH 5.5-6

- This use to increase excretion of weak base such as amphetamines, phencyclidine, and quinidine

- Because of complication of weak acid it is no longer recommended

Toxins Eliminated by Urine Alkalinization

2,4-D-chlorophenoxyacetic acid (Mecoprop)*
(urine pH >8 and urine flow of 600 mL/h)
Barbital (?)
Chlorpropamide*
Diflunisal* (2-fold increase)
Fluoride
Iopanoic Acid (?)
Isoniazid (?)
Mephobarbital
Methotrexate*
2-Methyl-4-chlorophenoxyacetic acid (MCPA)
Orellanine (?)
Phenobarbital*
Primidone
Quinolones antibiotic
Salicylates*
Sulfisoxazole
Uranium

Peritoneal dialysis

- It is the most easily performed method
- Associated with lower risk of complication like abdominal pain, IP bleeding, peritonitis, organ perfusion, protein loss and electrolyte imbalance

- The procedure undertaken by inserting a tube through small incision made in the mid abdominal area into peritonium
- Dialyzing membrane is (peritoneal membrane)

- Area of high concentration to low conc.(Osmosis Law)
- Blood------Peritoneal membrane-------dialyzing fluid

- Dialysis soln. consist of a balanced electrolyte and the osmotic pressure of fluid maintain above that of extracellular fluid with dextrose

Dialysis fluid modified by

- For chemicals high protein -bound addition of albumin to dialyzing fluid may be helpful to increase recovery
- Adjusting the PH like using alkaline soln. to increase recovery of phenobarbital
- Use lipid such as peanut oil to attract highly lipid soluble chemicals like glutethimide

Procedure

- A warmed sterile dialyzing soln. 2L. In adult and 1L. In child introduced to peritoneal cavity over aperiod15-20 min.
- The fluid is left in place for 45-60 min.
- Then a fresh soln. is reintroduced and the process repeated up to 30 L.

Hemodialysis

- The same principle of peritoneal dialysis but here a cellophane bag (artificial kidney) form the semipermeable membrane
- Two catheters are inserted into patient femoral vein. Blood is pumped from one catheter through dialysis unit and back through the other catheter the procedure continued 6-8hr.
- Low molecular wt. and small size diffuse passively across membrane
- Chemical with M.Wt. greater than 500 dalton not cross so it is less effective for drug highly protein bound
- Complications include clotting and seepage of blood from around connection, hypotension, convulsion, arrhythmias, infection and hematologic defect

Hemoperfusion

- It is more effective particularly for highly lipid soluble and highly protein bound

- Blood is withdrawn via an arteriovenous or venovenous shunt and passed directly over the adsorbing materials(char coal or anion exchange resin) contained in sterile columns.

- Efficacy depends on

1. Adsorbent capacity to eliminate chemicals
2. Vd of chemical should be low and half life is long

- Complications: trapping of WBC and platlate

Specific antidotes

- Classified in to four categories

1. Chemical antidotes:

- react with poisoned chemical to produce compounds of lesser degree of toxicity than parent compound
- such as
- dimercaprol and deferoxamine form chemical chalets with heavy metals water soluble and readily excreted by the kidney.
- In oxalic acid poisoning, calcium salts as antidote react with OA to yield poorly soluble comp.
- sodium nitrite, is given to patients poisoned with cyanide to cause the formation of methemoglobin, which serves as an alternative binding site for the cyanide ion, thus making it less toxic to the body(treated with methylen blue).

2-Receptor antidotes

- Compete with poison for receptor site
- Naloxone reverse morphine induce respiratory depression
- Atropine reverse cholinergic activity of physostigmine

3- Dispositional antagonism

Involve alteration of absorption, metabolism, distribution or excretion of toxic agents to reduce amount available to tissues

Such as NAC in paracetamol toxicity

4-Physiologic antagonist

- Act on one biochemical system to produce effects that are opposite from those produced on an other system

- During an anaphylactic reaction after administration of a drug the individual complain sever breathing difficulties, epinephrine reverse this effect and breathing normalized by other mechanism

Antidotes

Acetaminophen	N-acetylcysteine
Anticholinergics	Physostigmine
Benzodiazepines	Flumazenil
Beta blockers	Glucagon
Carbamates	Atopine
Calcium channel blockers	Calcium, glucagon, insulin/glucose
Carbon Monoxide	Oxygen
Cyanide	Amyl Nitrite, sodium nitrite, sodium thiosulfate
Digoxin	Fab fragments
Ethylene glycol/methanol	Ethanol, fomepizole

Antidotes

Iron	Deferoxamine
Isoniazid	Pyridoxine
Metals	BAL, EDTA, DMSA (Succimer),d-penicillamine
Nitrates/nitrites	Methylene Blue
Opiates	Naloxone, nalmefene
Organophosphates	Atropine, Pralidoxime
Snakes	Antivenin, CroFab

Special consideration in children

70% of poisonings occur in children under 5years

15% in children older than 5.

The reasons for such high percent are:

1-chidren believe toxic substances like candy to be ingested

2- children are curious and investigative (a closed cabinet door and high shelf quickly becomes a major challenge to see what is behind)

3-Many household products are marketed in attractive packages (flowers and bright red berries)

4-the natural tendency of children to place anything and everything in to their mouths regardless taste (taste discrimination is a trait that is learned later.

Special consideration in pregnant women

1. Drug absorption: high progesterone level in pregnancy prolong GIT transit time by 50%
2. Drug distribution: Total body water increase 8L, plasma albumin concentration fall by 5-10g/L where most acidic drug bind(like phenytoin and salicylate)
3. Drug metabolism: progesterone induce drug metabolism
4. Drug elimination: Renal plasma flow double in pregnancy increase, GFR increase by 70% and creatinine clearance by 50%

****Other physiologic changes in pregnancy decrease hematocrit , increase body fat , increase protein loss in urine and increase folic acid requirement

Example (Anticonvulsant)

- Effect of pregnancy on drug : drug concentration level fall because of increase extracellular fluid & VD , decrease plasma protein binding with more free drug for biotransformation, folate supplementation increase liver metabolism of phenytoin& increase GFR result in faster clearance of drugs

- Effect of pregnancy on disease condition Seizure frequency increased in 45%

- Effects of drugs on fetus:

phenytoin cause characteristic facial alteration , microcephaly, mental retardation, neuroblastoma & cardiac defect