# Urine analysis of toxins and chemicals

Sampling is utmost قصارى importance for a successful systematic toxicological analysis (STA). The reliability and accuracy of any toxicological result is usually determined by the nature and integrity of the specimen(s) provided for analysis. Furthermore, proper specimen selection and collection is of paramount importance for the analytical results to be accurately interpreted with scientific validity.

There are thousands of potentially toxic or lethal drugs and chemicals available for abuse or poisoning. Therefore, it is important that relevant case histories and the best available specimens be provided to the toxicologist in cases involving both living subjects and decedents when a case requires analysis.

**Urine**

The best specimen for comprehensive drug and poison screening is urine. The accumulation of drugs, poisons, and metabolites in urine will often result in high concentration that facilitate their detection. And urine toxicology tests are often inexpensive and quick. A minimum of a 30 ml sample of urine is required for thorough screening of this specimen. The advantages of urine in postmortem cases is similar to its advantage in specimens collected from living patients, many drugs and metabolites are present in higher concentrations in urine than in blood and they remain in urine for days or longer.

A disadvantage of urine occurs in instances in which death occurs very rapidly after exposure to a drug or poison. In these cases, the urine specimen may be negative for the causative agent, so caution must be used in evaluating results from this specimen. In most cases, all available urine should be collected in postmortem case.

Alcohol toxicology test are routinely performed on blood and breathe as well as urine.

**1. Screening tests**

Overall, drug screening tests are rapid, technically sample and economical. Generally, these tests are sensitive, meaning they can detect evidence of small amounts of drugs and metabolites. However, they are less specific and less reliable than confirmatory tests. In other words, drug screening tests are known to produce false-positive and false-negative test results.

Screening tests are typically batched, meaning that multiple urine samples are screened together. When a batch of multiple urine samples is found to be positive, the individual urine samples may be retested to identify the positive specimen. Once the urine sample has been identified as testing positive by a screening test, the specimen

is retested with a more specific (and more expensive) confirmatory test. Two of the more common screening tests are thin-layer chromatography (TLC) and immunoassays.

- **TLC**

Is a practical, economical and sensitive method of detecting drugs in urine specimens. TLC is particularly useful because multiple specimens can be tested and more than one drug can be determined for each application.

The test involves applying urine specimens onto a glass plate, which is sprayed with various reagents. The appearance and position of spots on the plate are used to identify the drug or drugs being sought. The certainty of the identification depends on:

1. The efficiency of the procedure.
2. The ability of the technicians performing the assays.
3. The ability of those making the identification.

  Specimen is extracted into organic solvent and spotted on plate coated with silica. Plate is placed into tank that contains a mobile phase which migrate to plate and separates whatever chemicals are present.

  There are TLC screening tests for most drugs of abuse, including the opioids, amphetamines, barbiturates, cocaine, marijuana, glutathimide and phenothiazines.

- **Immunoassay techniques**

Which use antibodies and allow reagents to react only with a substance that recognizes that antibody. Absorbance spectrophotometry, and fluorescence are used for the measurement such as the enzyme multiplied immunoassay technique (EMIT). They are commonly used for drug screening techniques in part because they are sensitive, quick and require a small sample. These tests utilize complex immunochemistry and the production of drug antibodies in an interaction with enzymatic detectors to reflect the presence of various drugs subject to misuse.

In addition to EMIT, other examples of immunoassay techniques include radio-immunoassays and fluorescence polarization immunoassays. Most drugs of abuse are detectable by immunoassays, including: opioids, amphetamines, barbiturates, cannabinods, cocaine and PCP.

**2. Confirmatory tests**
The basic principle of confirming a positive drug test is retesting the same urine sample with a different type of test. It is standard to first test body fluid with sensitive but less specific test and to confirm positive test results by retesting with sensitive and highly specific tests. Confirmatory tests generally have few false positive results.

- **Gas chromatography**
  Relies upon separation and emergence of substance from other components and measurement of retention time from the column.

- **Gas chromatography-mass spectrometry**
  Allows for separation and measurement of retention time of elements in a gas chromatographic column and mass spectrum analysis of substance.

- **Liquid chromatography-mass spectrometry**
  - Technology in which a liquid chromatography replaces the gas chromatography.
  - Mixture is swept into liquid instead of a gas.
  - Since no heat is needed for conversion to gaseous state, it is compatible with every organic chemical.

- **Forensic drug testing**

Since the word forensic indicates a relation to law or legal issue, forensic drug testing describes drug testing processes that meet legal standards and which may be scrutinized يتم تدقيقه in court. Forensic drug testing involves accepted standards for urine collection and storage, chain of custody العهدة and laboratory standards.

**Factors contributing to false-positive, false-negative and inconclusive results**
The appropriate collection, handling and testing of urine specimens is critical to avoid false-positive, false-negative and inconclusive test results.
a) Specimen collection:
The acceptable standard for collecting urine specimens is observed urine collection to avoid deceptive خادع switching or purposeful contamination. Contamination of specimen container, preparing the surfaces through which test materials are to be collected and cleaning the skin with isopropyl alcohol may cause false-positive results.

b) Specimen handling:
Several errors may cause inconclusive or misinterpreted test results. Such errors include mislabeling, specimen confusion and misidentification of the subject. Contamination of equipment, failure to clean glassware and operator error may result in test result error.

c) Other factors:
Errors may occur during any type of scientific measurement process, including drug testing. Human mistakes such as test equipment operator error may cause test error. Since many drug tests rely upon technician interpretation, human error can occur during this last stage.

Diluted urine can result in false-negative or inconclusive test results. Also, various drug tests will identify the presence of over-the-counter (OTC) drugs, prescribed medications and some foods that are chemically related to drugs of abuse. Historic examples include the amphetamine-related OTC drugs phenylpropanolamine and ephedrine registering an amphetamine test as positive, as well as foods that contain poppy seeds registering an opioid test as positive. Many drug tests are routinely modified to reduce cross-reactivity and to increase drug specificity.

**Drug detection times in urine**
The duration of detection times for all drugs depend to a great extent on the volume, dose and duration of drug use. For example, marijuana is commonly detected three days following inhalation of a single joint but, can be detected as much as thirty days following cessation of chronic, High-dose use. Elimination times may differ between neonates and adults. While the elimination rates of drugs are variable, the following table displays an approximate guideline of duration for detecting various drugs of abuse in urine.

The elimination of some drugs can be influenced by changes in urine pH, which can be altered by the ingestion of some acidic or basic substances. For example, PCP (phencyclidine) excretion can be somewhat accelerated by the ingestion of cranberry juice التوت البري

**Drug durations**

| Drug | Duration |
|------|----------|
| Amphetamines | 48 h |
| Alcohol | 12 h |
| Barbiturates | 10-30 days |
| Valium | 4-5 days |
| Cocaine | 24-72 h |
| Heroin | 24 h |
| Marijuana | 3-30 days |
| Methaqualone | 4-24 days |
| Phencyclidine | 3-10 days |
| Methadone | 3 days |

# Principles in the management of the poisoned patient

**Clinical assessment** التقييم السريري

Some poisons produce clinical characteristics that strongly suggest the involvement of a particular drug or chemical.

Clinical assessment generally begins with recording of vital signs, such as blood pressure, heart rate, respirations, and body temperature. Assessment of neurological function and level of consciousness is the next priority.

Another point to stress is the value in using blood, urine, and vomitus for toxicological analysis. Qualitative and quantitative assays can quickly identify a toxic substance. The results of these tests can be used to aid diagnosis of the poisoned patient, and evaluate the progress of treatment.

## Methods to reduce or prevent absorption: gastrointestinal decontamination

Once the patient is stabilized, attention should be directed to removing any unabsorbed poison from the GI tract and other sites such as the skin. Severity of intoxication in many instances will be proportional to the length of time an unabsorbed toxic agent remain in the body.

Gastric decontamination methods (emesis, gastric lavage, catharsis, and adsorption with activated charcoal) are undergoing critical scrutiny تدقيق.

### Dilution

The initial procedure often recommended whenever ingestion of a poison is suspected is dilution with water. The amount recommended is generally 1 to 2 cupfuls for a child and 2 to 3 cupfuls for an adult. Excessive liquid may distend the stomach wall, causing premature evacuation of its contents into the duodenum and making it more difficult to remove the poison.

Dilution with water accomplished at least two functions. First, it helps reduce the gastric irritation induced by many ingested poison. Second and more importantly, it adds bulk to the stomach that may be needed later for emesis.

# Emesis

Chemically induced emesis is generally accepted to be a first-line procedure in the management of poisoning because it can be easily done at home.

Conditions in which emesis should not be attempted

1- Do not induce vomiting if the ingested substances is a convulsant, hydrocarbon, corrosive, sharp object, or nontoxic substances.
2- Do not induce vomiting if the patient is unconscious, has sever cardiovascular disease, or emphysema, has recently undergone surgery, has hemorrhagic diathesis يعاني like cirrhosis, has vomited before this moment, and is under 6 months of age.

## Syrup of ipecac

Ipecac is derives from the root of Cephaelis ipecacuanha or C acuminatea. The principal active alkaloids are emetine and cephaeline. Ipecac causes emesis through both early and late phases of vomiting. Early vomiting usually occur within 30 min and is due to direct stimulant action on the GI tract. A second phase occurs after 30 min, resulting from direct stimulant action on the chemoreceptor trigger zone that activates the vomiting center located in the reticular formation. Therefore, if vomiting does not occur within the first 15 to 20 min, the drug should not be discontinued as ineffective.

## Toxicity of Ipecac

Syrup of ipecac is generally safe and well tolerated and toxicity is rarely seen in doses recommended. Some of its adverse effects may include protracted ممتد vomiting, diarrhea, lethargy, diaphoresis تعرق and fever.

## Apomorphine

Apomorphine is a morphine derivative that produces rapid emesis, usually within 3 to 5 min, through direct stimulation of the chemoreceptor trigger zone. Onset of emesis is more rapid, but recovery of gastric contents is essentially the same as with ipecac.

## Soap of solution

When rapid emesis is indicated and syrup of ipecac is not available, one alternative is to administer a dish-washing liquid detergent. Two to three tablespoonful should be mixed with 6 to 8 ounces of water. Detergents are

believed to produce emesis by direct stimulation of the gastrointestinal mucosa.

Liquid detergents should not be confused with laundry detergents or electric dishwasher granular products. The latter products are corrosive and may cause injury.

## Mechanical stimulation

Stimulation of the back of the tongue or pharynx has been recommended as a means to evoke emesis. This involves placing the victim in a spanking مؤخرة position and gently stroking the area with a blunt object such as a spoon or tongue depressor.

The advantage of this procedure is its availability. Its major disadvantage is lack of effectiveness, gagging is not the same as vomiting.

## Lavage غسيل

Lavage is a process of washing out the stomach with solutions, including water, saline, sodium bicarbonate, calcium salts, tannic acid, and potassium permanganate. Lavage is sometimes indicated when poisons must be quickly removed from the stomach or when emesis is contraindicated.

The patient's airway should be protected by intubation, using a cuffed endotracheal or nasotracheal tube. The patient is placed in the left lateral decubitus استلقاء position to permit pooling of gastric contents and to reduce the risk of aspiration of gastric contents into the lung.

Lavage is usually initiated using aliquots of tap water or normal saline. Saline is recommended in children to prevent electrolyte imbalance. The consensus اتفاق الرأي is to lavage the stomach until returned fluid is clear.

## Adsorbents امدصاص

Another means to reduce absorption of an ingested poison is by use of an adsorbent. Although several adsorptive substances, including kaolin, Fuller's earth, cholystramine, and pectin are occasionally recommended. Activated charcoal is used for routine adsorption of gastrointestinal poisons.

## Activated charcoal

Activated charcoal is a finely divided black powder that is sparingly soluble in water. It is prepared by pyrolysis الانحلال الحراري of organic materials, such as wool pulp.

Activated charcoal reduces absorption of a wide variety of poisons but has little or no effect on others. In the stomach and intestine, poisons

diffuse through the numerous pores on its surface to form tight chemical bonds. This charcoal-chemical complex then passes through the intestinal tract to reduce the chance of the chemical being absorbed. Effectiveness of adsorption is dependent on the quality of activated charcoal used and the time between ingestion and charcoal administration.

## Administration

Activated charcoal is unsightly بشع and readily adsorbs materials from the air and water when mixed and allowed to stand. Therefore, it should be mixed immediately before use with sufficient water, preferably in a dark container.

Various flavoring and thickening agents have been added to increase the palatability of activated charcoal. Addition of sorbitol to activated charcoal results in a product with a sweet taste that enhances patient compliance. Sorbitol produces catharsis, which enhance transit time of the activated charcoal-complex through the intestinal tract.

Activated charcoal is pharmacologically inert and not absorbed systemically. Large doses cause occasional constipation but may be used safely.

For maximal effectiveness, activated charcoal should be administered within 30 min of poison ingestion.

## Cathartics

Saline cathartics are preferred by most experts when catharsis is desired to remove toxic substances from the GI tract. Whenever contact time between the poison and absorption sites is reduced, the potential for toxicity will likewise be lessened.

Catharsis should not be attempted when the poison is strongly corrosive, the patient has electrolyte disturbance, or bowel sounds are absent. Aside from a few exceptions, including castor oil for phenol intoxication and mineral oil for fat-soluble vitamin overdoses, no stimulant or lubricant cathartic or laxative other than saline catharsis should be recommended.

The use of sorbitol at doses of 1 to 1.5 g/kg as a cathartic has recently been advocated over other osmotically active drugs. It may be a superior cathartic to both magnesium and sodium sulfate.

## Whole bowel irrigation

The new therapy that looks promising for gastric decontamination is whole bowel irrigation. The procedure is also used to cleanse the entire gastrointestinal tract before surgery. The solution most commonly used is a sodium sulfate and polyethylene glycol electrolyte solution (Colyte) that is not absorbed and does not lead to fluid or electrolyte imbalance.

## Demulcents ملطف

Many plants and chemicals cause oral and gastric mucosal irritation but no serious toxicity. Management of these acute ingestion may include ice cream, milk, or other soothing demulcent to reduce irritation. Egg white up to a dozen for an adult, which serve as a source of readily available protein have been given for corrosive intoxications and can be unofficially classed as a demulcent.

## Topical decontamination

Numerous lipid-soluble chemicals can be absorbed through the skin and cause systemic toxicity within minutes. After dermal exposure, all contaminated clothing should be removed. Skin should be thoroughly flushed with water with mild soap.

No cream, ointment, or occlusive bandages should be placed over the contaminated area. These would have to be removed before a physician could treat the area.

When ocular contamination occurs, irrigation with lukewarm فاتر water must be immediately instituted and continued for at least 15 to 20 min. The victim should seek medical attention immediately after irrigation.

## Methods to increase elimination of toxic agents

Other methods of enhancing the elimination of a toxic agents include forced diuresis and pH alteration, peritoneal dialysis, hemodialysis, hemoperfusion, and the use of specific antibodies. After gastric decontamination, the next logical step in the management of a poisoned patient is to address methods for elimination the toxic agent that has been absorbed into the blood.

## Forced diuresis and pH alteration

The use of mannitol or furosemide in over-doses was fraught مشحن with complications, such as pulmonary and cerebral edema. This method of enhanced renal elimination is no longer recommended.

Many toxic compounds are weak acids or weak base and in solution become ionized. The degree of ionization depends upon the dissociation constant (Ka) of the compound and the pH of the medium.

The goal of urinary pH manipulation is to enhance renal excretion of a compound by increasing the amount of the ionized (polar) form in the kidney. As toxic agents pass through the kidney, they are filtered, secreted, and reabsorbed across the tubular membrane. The ionized (polar) form is trapped in the renal tubule and excreted; the non-ionized form is reabsorbed in the blood. The purpose of pH manipulation is to present to kidney the compound in its ionized (polar) form so that renal elimination of that compound is enhanced. Ideally, increased elimination of weak acids will occur when urinary pH is more alkaline. Conversely, enhanced elimination of weak bases will occur when urinary pH is acidic.

Alkaline diuresis is achieved by administration of sodium bicarbonate. The potential uses of urine alkalinization have been with weak acid, such as salicylates, and phenobarbital. Acid diuresis is possible by using ammonium chloride, to increase the elimination of weak bases, such as amphetamines, phencyclidine, and quinidine. It is no longer uses.

## Dialysis and hemoperfusion

The following procedure are limited in scope and not routinely performed for every toxic ingestion. They are used as adjuncts to management of severely intoxicated patients.

Dialysis and perfusion methods should never replace the use of more specific treatment or antidotes.

Dialysis governed by the laws of osmosis. A diffusible chemical dissolved in water partitions across a semipermeable membrane and the solution moves from an area of higher concentration (i.e., the blood) to one of lower concentration (i.e., a dialyzing solution).

## Peritoneal dialysis

Peritoneal dialysis is the most easily performed method and is associated with the lowest risk for complications. However, it is also the least effective method for removing most poisons.

The procedure is undertaken by inserting a tube through a small incision made in the mid-abdominal area into the peritoneum. The peritoneal membrane serves as the semipermeable (dialyzing) membrane. In this way, the dialyzable chemical diffuses from blood across the peritoneal membrane into the dialyzing fluid (move from an area of higher to lower concentration).

The dialysis solution normally consist of a balanced electrolyte solution, although various solutions from different manufacturers vary in composition. The osmotic pressure of the fluid is maintained above that of extracellular fluid with dextrose.

## Hemodialysis

Two catheters are inserted into the patient femoral vein, about 2 inches apart. Blood pumped from one catheter through the dialysis unit, across the semipermeable membrane and back through the other catheter. The procedure is usually continued for 6 to 8 hr. the solubilized chemical diffuses across the semipermeable membrane into the dialysis solution. Clearance of the toxic agent is based on difference in osmotic and concentration gradients.

## Hemoperfusion

Hemoperfusion is significantly more effective than peritoneal dialysis and hemodialysis for removing intoxicating compounds, particularly those that are lipid soluble or protein bound or those that, for other reasons, are poorly dialyzable.
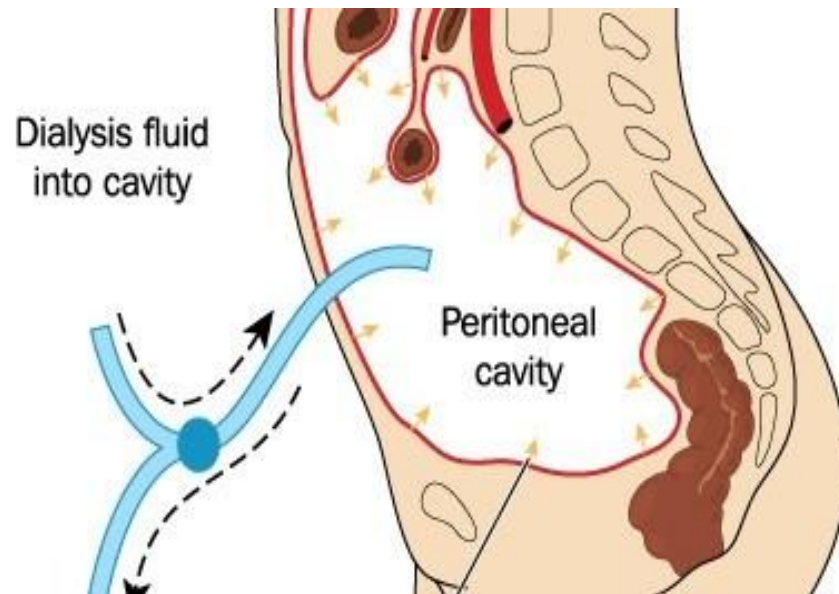
Regardless of the type of adsorbent used, blood is withdrawn via an arteriovenous or venovenous shunt and passed directly over the adsorbing material contained in sterile columns. The procedure is simple, and columns are commercially available.
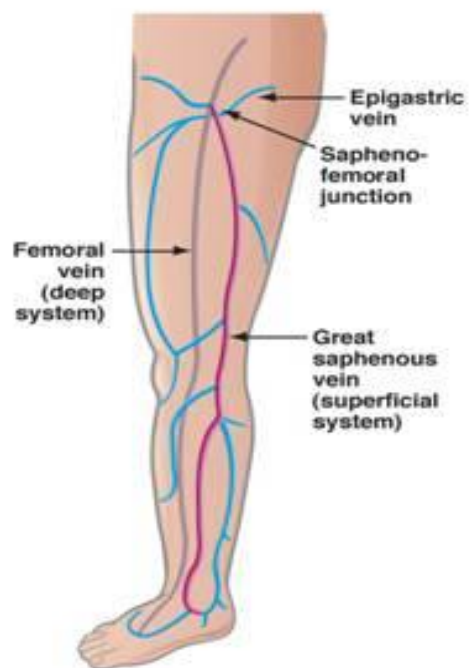
## Specific antidotes

## Classification of specific antidotes

1- Chemical antidotes: react with the poisonous chemical to produce a compound of lesser toxicity or one that is absorbed to lesser degree than the parent compound. Calcium salts react with oxalic acid to yield poorly soluble compound, Calcium oxalate, which passes through the intestine without being absorbed.

2- Receptor antidotes compete with the poison for receptor sites. Examples include naloxone reversal of morphine-induced respiratory depression and cholinergic blockade of atropine.

3- Dispositional antagonism: involves alteration of absorption, metabolism, distribution, or excretion of toxic agents to reduce the amount available to tissues. In acetaminophen overdose, for example, a toxic metabolites causes hepatotoxicity. Conversion of the toxic intermediate to a nontoxic form proceeds by conjugation with glutathione, a sulfhydryl (-SH) group donor. N-Acetylcysteine is also a source of sulfhydryl groups, which serve the same function as endogenous glutathione.

4- A functional (physiologic) antagonism acts on one biochemical system to produce effects that are opposite from those produces on another system. For example, during an anaphylactic reaction after administration of a drug, the individual experiences severe breathing difficulties, due in part to intense bronchoconstriction. Epinephrine reversed this effects, and breathing is normalized.
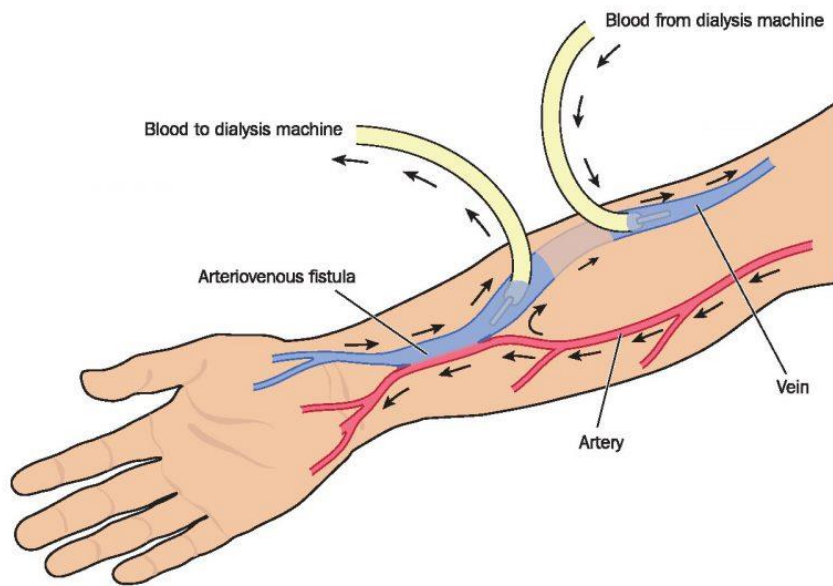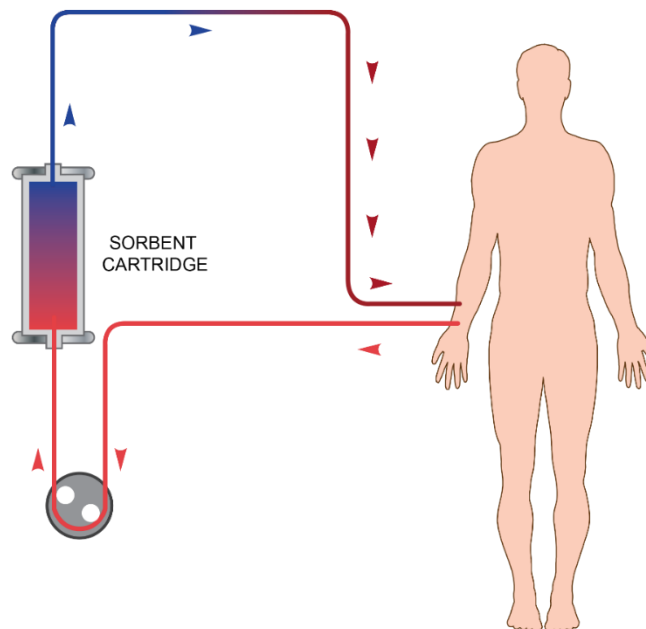
# Peritoneal dialysis



Dialysis fluid into cavity

Peritoneal cavity

# Hemodialysis



Epigastric vein

Sapheno-femoral junction

Femoral vein (deep system)

Great saphenous vein (superficial system)

# Hemodialysis



# Hemoperfusion

## Toxicity testing

The toxicity of a chemical can be detected and evaluated by several tests in laboratory animals. These tests include

**a- General tests**

1. Acute poisoning: A single or multiple exposures of the animal to the chemical under study within 24 hr resulting in acute signs of poisoning which may end in death of the test animal.

2. Sub-acute poisoning: Repeated exposure of the animal to the chemical for less than 30 days. The test chemical is administered daily or other specified intervals. Survivals time is usually longer than that of the acute poisoning.

3. Sub-chronic poisoning: repeated exposure of the animal to the chemical for 30-90 days. Additive tissue damage should be expected with this type of toxicity testing.

4. Chronic poisoning: Repeated exposure of the animal to the chemical for more than 90 days for up to a year or two, or even the life span of the test animal.

   The preferred route of administration of the test substance is orally or parenterally. In chronic studies, however, the oral route is usually selected. On the basis of data obtained from the acute toxicity testing (LD50), the toxic agents can be rated according to the severity of toxicity as follows:

| Class | Oral LD50 (mg/kg) in rats | Example |
|-------|---------------------------|---------|
| Super toxic | < 0.1 | TCDD |
| Extremely toxic | < 1 | Parathion |
| Highly toxic | 1-50 | Arsenic |
| Moderately toxic | 50-500 | DDT |
| Slightly toxic | 0.5-5 g | Nitrate |
| Practically non-toxic | 5-15 g | Salt |
| Relatively harmless | > 15 g | Corn |

TCDD: Tetrachlorodibenzo-p-dioxin, DDT: Dichloro diphenyl trichloroethane

Furthermore, the chronically factor can be calculated as follows

C. F. = Acute LD50/90-Day LD50

| Table: LD$_{50}$ Values of Various Substances | | |
|---|---|---|
| Substance | Animal Route | LD$_{50}$ (mg/kg) |
| Water | rat, oral | 90,000 |
| Sucrose (table sugar) | rat, oral | 29,700 |
| Glucose (blood sugar) | rat, oral | 25,800 |
| Monosodium glutamate (MSG) | rat, oral | 16,600 |
| Cadmium sulfide | rat, oral | 7,080 |
| Ethanol (grain alcohol) | rat, oral | 7,060 |
| Methanol | human, oral | 810 |
| Sodium chloride (table salt) | rat, oral | 3,000 |
| Metallic arsenic | rat, oral | 763 |
| Arsenic trisulfide | rat, oral | 185-6400 |
| Sodium cyanide | rat, oral | 6.4 |
| Hydrogen cyanide | mouse, oral | 3.7 |
| Ibuprofen | rat, oral | 636 |
| Aspirin | rat, oral | 200 |
| Caffeine | rat, oral | 192 |
| Cocaine | mouse, oral | 96 |

| | | |
|---|---|---|
| Nicotine | rat, oral | 50 |
| Heroin (diamorphine) | mouse, intravenous | 21.8 |
| Methamphetamine | rat, intraperitoneal | 57 |
| Mercury(II) chloride | rat, oral | 1 |
| Strychnine | human, oral | 1-2 |
| Sarin | mouse, subcutaneous injection | 172 microgram/kg |
| Ricin (from castor oil plant) | rat, oral | 20-30 |
| Botulinum toxin (Botox) | human, oral injection, inhalation | 1 ng/kg |

## B- **Special toxicity tests**

These include specified toxicity tests on certain tissues or systems in the body of the laboratory animal.

## Drug residues

Treatment of animals with drugs may result in the deposition of drug residues or its metabolites in tissues. Drug residues may result from feed additives. Environmental contaminants may also appear in animal tissues or products. Residues are expressed as ppm, ppb, ppt.

**Acceptable daily intake (ADI)**
The amount of a drug or its metabolite when consumed during the entire life-time of a person that appear to be without risk to health.

**No-effect-level (NOEL)**
It is the maximum level of the drug that does not induce adverse effect. It is fed to the most sensitive laboratory animals (e.g. rats) for 2 years.
A rat consumes 15 g diet/day.
e.g. 100 ppm = 100 mg/kg feed.
Total intake is 1.5 mg/rat (200 g) or 7.5 mg/kg body weight.

**Acceptable daily intake (ADI) for human** is derived by taking 1% of the NOEL.
$0.01 \times 7.5$ mg/kg = 0.075 mg/kg body weight, the ADI level in human.
**Tolerance level**
Maximum allowable concentration of a chemical in feed.

**Negligible tolerance**
Insignificant toxicologically chemical residue.

**Finite tolerance**
Measurable concentration of a chemical residue that is permitted infeed.

**Zero tolerance**
No drug residue is allowed in feed, because of extreme toxicity or carcinogenicity.

**Withdrawal period**
It is the time required for a chemical residue to reach safe concentration as defined by the tolerance. It indicates the time of animalremoval from medication until the time of slaughter. It varies according to doses of the drug, dosage form, route of administration and animal species.

# Cardiovascular drugs
## Digitalis toxicity

Digitalis glycosides are life-saving drugs when they are used in therapeutic doses in the treatment of congestive heart failure, and for management of certain supraventricular rhythm disturbances.

## Pharmacokinetics

The half-life of digoxin is about 1.5 days. Renal excretion is the major route of elimination. Digoxin has a large volume of distribution, which limits the usefulness of dialysis.

## Mechanism of toxicity

A toxic dose of digitalis interferes with transport of sodium and calcium ions. The glycosides bind with high affinity to an inhibitory site on the protein on the Na K-ATPase structure that faces the outside of the cell. Consequently, sodium, and potassium ion transport are blocked as long as the drug molecule remains in place. Since potassium ion transport back into cells is blocked, its concentration in the extracellular fluid increases. This is why serum potassium ion concentration is a good indication of the extent of digitalis poisoning. The changes in sodium ion fluxes across cardiac cell membrane result in disturbed impulse conduction. Accumulation of calcium intracellularly produces a positive inotropic action. An overdose of digitalis causes a reduction in resting membrane potentials, and cardiac pace maker cells cannot function properly. The outcome is asystole with complete loss of all cardiac function.

The electrophysiologic changes result in a variety of cardiac arrhythmias. Arrhythmias may be produced by direct ionic membrane changes, as well as autonomic neuronal effects.
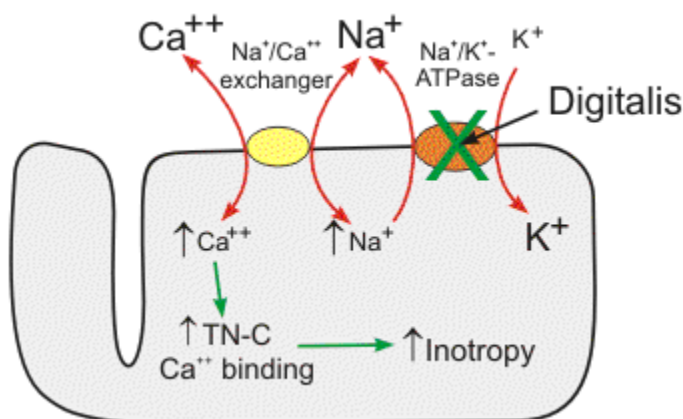
**Characteristics of poisoning**

Digitalis toxicity may appear after acute or chronic administration of therapeutic doses or massive intentional or accidental overdose.

Early manifestation of intoxication that occur in approximately 50% of all cases generally involve the GI tract. Complaints of anorexia, nausea, vomiting, and abdominal pain are common. Blurred vision, loss of visual acuity, and green-yellow halos have been described as early appearing symptoms.

CNS effects include a variety of neuropsychiatric disturbances. Digitalis intoxication can provide a large number of dysarrhythmias. These include bradyarrhythmias, tachyarrhythmias, or a combination of both.

**Management of poisoning**

Management involves removal of ingested drug, maintenance of a normal potassium concentration, reversal of arrhythmias. More recently it may include the use of specific antidote, digoxin immune Fab.

After massive overdoses of digitalis, efforts to decontaminate the GI tract should be under taken. The stomach should be lavaged to remove unabsorbed drug, although vomiting may already have accomplished this. Cardiac glycosides bind to activated charcoal, cholystramine, and cholyestipol.

Hypokalemia is more common after chronic digitalis toxicity. Massive acute overdoses often cause hyperkalemia. Hyperkalemia may require treatment with insulin, dextrose, bicarbonate, and sodium polystyrene sulfonate.

The patient should be monitored continuously with frequent electrocardiogram and electrolyte determinations.

When hypokalemia is encountered with tachy- or bradyarrhythmias, continuous potassium replacement alone may be sufficient. Even in the absence of hypokalemia, potassium administration may correct arrhythmias by restoring intracellular concentrations. Potassium administration in a person with digitalis-induced hyperkalemia can result in heart block terminating in sinus arrest. For atrial and ventricular arrhythmias that do not respond to potassium therapy. The treatment of choice includes lidocaine.

Beta-blockers, such as propranolol, are useful to suppress supraventricular and ventricular arrhythmia induced by digitalis toxicity.

# Beta-adrenergic blockers

These drugs have significant pharmacologic and pharmacokinetic differences. The three major pharmacologic considerations include difference in cardioselectivity, intrinsic sympathomimetic activity, and membrane stabilizing activity. The pharmacokinetic properties of importance include lipid solubility, route of metabolic elimination, plasma half-life, degree of protein binding, and volume of distribution.

## Mechanism of toxicity

Toxic effects of acute overdose with beta adrenergic blockers are predictable and result from the drug binding to and inhibiting beta adrenergic receptors throughout the body. The principle manifestations of poisoning include bradycardia, and hypotension. In overdose, the membrane stabilizing or quinidine-like action of some beta-adrenergic blockers predominate. This is responsible for the severe myocardial depressant actions leading to heart block, and possibly CNS effects such as sedation and seizures. High doses of beta-adrenergic blockers with intrinsic sympathomimetic activity (ISA) can cause tachycardia and hypertension as a result of their partial agonist effect.

## Characteristics of poisoning

Underlying pathology may influence the toxicity of beta-adrenergic blockers significantly. Bronchospasm and pulmonary edema, for example may be more prominent in patients with chronic obstructive pulmonary disease.

An overdose causes a diminution of myocardial contractility, producing bradycardia and severe hypotension leading to cardiogenic shock. Cardiac changes are not reported uniformly in all beta adrenergic blocker poisonings. They do occur most frequently with drugs that have membrane stabilizing action. Electrocardiographic changes are more prominent at serum drug concentrations that 50 to 100 times greater than needed for beta receptor blockade.

## Management of poisoning

Gastric decontamination after a large ingestion may be indicated. Gastric lavage is usually preferred over emesis because of the possibility of beta-blocker seizures. Activated charcoal can be given repeatedly during the first 24 hours to minimize enterohepatic cycling. Other areas of general management include giving glucose for hypoglycemia, diazepam for convulsions, and monitoring potassium levels.

If the patient is compromised hemodynamically, atropine may be given. If vagal blockade is unsuccessful, isoproternol, or a specific beta-1 agonist, can be given cautiously. The hypotensive patient may respond to

fluid in the absence of pulmonary edema. Presser agents, such as dopamine, or norepinephrine, may be useful. The treatment of choice in the hemodynamically compromised person appear to be glucagon.

Hemoperfusion or hemodialysis may be considered in cases involving nadolol, or atenolol, especially if there are signs of renal failure.

# Developmental Toxicology
# Thalidomide Catastrophe

- In 1979, the FDA established five letter risk categories - A, B, C, D or X - to **indicate the potential of a drug to cause birth defects if used during pregnancy**. The categories were determined by assessing the reliability of documentation and the risk to benefit ratio.

**FDA Pregnancy Categories**

**Category A**

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

**Category B**

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

**Category C**

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

- **Category D**

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

- **Category X**

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

# TERATOGENIC DRUGS

| Drug | Effect on Foetus/Offspring |
|---|---|
| ACE Inhibitors | Foetal loss<br>Growth retardation |
| Anticancer Drugs | Foetal death<br>Hydrocephalus<br>Multiple defects |
| Alcohol | Foetal alcohol syndrome<br>Growth retardation<br>Low IQ baby |
| Aspirin | Premature closure of the ductus arteriosus |
| Phenytoin | Cleft lip/palate<br>Microcephaly |
| Thalidomide | Phocomelia<br>Multiple defects |
| Warfarin | Eye and hand defects<br>Growth retardation |

# Teratogenicity of thalidomide

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- The first comprehensive regulatory law that required pre-marketing testing was passed in the USA in 1938, following the death of about 107 people due to the use of diethylene glycol
- Other countries did not take on board the lesson provided by the USA, and it took the thalidomide disaster to make governments all over the world initiate comprehensive control over all aspects of drug introduction, therapeutic claims and supply.

- In 1960–1961 in (West) Germany, the incidence of phocomelia in newborns was noted. The term means 'seal extremities' and is a deformity in which the long bones of the limbs are defective and substantially normal or rudimentaryبدائي hands and feet arise on, or nearly on, the trunk, like the flippers of a seal; other abnormalities may occur.

- Phocomelia is ordinarily exceedingly rare.

- Thalidomide was recommended for use in pregnant women, although it had not been tested in the appropriate animal model.
- The worst had happened: a trivial new drug was the cause of the greatest disaster in the short history of modern scientific drug therapy.
- Many thalidomide babies died, but many live on with deformed limbs, eyes, ears, heart and alimentary and urinary tracts. The world total of survivors was probably about 10000.

- In the UK, two direct consequences العواقب النباشرة were the development of a spontaneous adverse drug reaction reporting scheme and legislation to provide regulatory control on the safety, quality and efficacy of medicines through the systems of standards, authorisation, pharmacovigilance and inspection (Medicines Act 1968).

- A further landmark معلم معروف was the establishment of the Committee on Safety of Medicines in 1971 to advise the Licensing Authority in the UK.

- In 1995, the new European regulatory system was introduced.

Despite these protective systems, other drug disasters occurred.

- In 1974 the β-blocking agent practolol was withdrawn because of a rare but severe syndrome affecting the eyes and other mucocutaneous regions in the body (not detected by animal tests),

- In 1982 benoxaprofen, a non-steroidal anti-inflammatory drug, was found to cause serious adverse effects including onycholysisانحلال عضلي and photosensitivity in elderly patients.

- The association of serotonin-specific reuptake inhibitors with increased risk of suicidal behaviour in children and young people, and that of cyclo-oxygenase I and II inhibitors with an increased risk of cardiovascular disease.

THANK YOU FOR LISTENING

# Drug of abuse

## Opioids

When considering over doses of opioids (narcotics), heroin (diacetylmorphine) is probably the first drug that comes in mind, and we pictureنصور users as long term habitual drug abusers of low socioeconomic status. The association is actually unjustified, since victims of opioid overdose may be at any age and represent all social and economic levels, and the drug may be obtained by illicit means وسائل غير مشروعةor legally obtained by prescription.

The naturally occurring and semisynthetic opioid alkaloids are derivatives of phenantherine. The familiar dried exudate of the un-ripened seed pod وعاء البذور غير الناضجةof the Asian poppy plant, papaver somniferum, contains at least 25 different alkaloids. The phenantherine derivatives, morphine and codeine, are the major naturally occurring opioids.

Acetylation of morphine at C-3 and C-6 produces one of the most potent semisynthetic alkaloids, heroin.
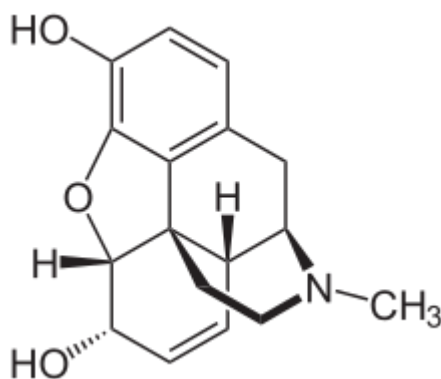


## Mechanisms of toxicity and characteristics of acute opioid poisoning

All opioid derivatives have the potential to produce severe toxicity that is dependent on the dose and route of administration. Clinical response of analgesia, euphoria, respiratory depression, and miosis are believed to result from occupation of the μ-receptors. A different type of analgesia results when the κ-receptors are involved, and the psychogenic effects,

such as dysphoria, delusion, and hallucinations, result from opioid action at the δ-receptors.

In acute overdose, respiration will be severely depressed to a rate as low as 2 to 4 per min. cyanosis becomes apparent and many victims have a frothy pulmonary edema. In humans, death from an acute opioid overdose is almost always from respiratory arrest.

Respiratory depression with acute overdose is further complicated by bradycardia and hypotension. Hypotension usually occurs in the later stages of poising and results from hypoxia.

Pinpoint pupils (miosis) are usually considered to be the classical sign of narcotic poisoning.

The body temperature usually decreases and the skin feels cold and clammyرطب. This is due to suppression of the hypothalamic heat-regulation mechanisms. Skeletal muscles also become flaccid رخو، لين and sometime the jaw relaxes. The tongue may even fail to block the airway. There is decrease urinary output which can be related to release of antidiuretic hormone (ADH).

Gastric motility and tone of both small and large intestine may be decreased, resulting in severe constipation.

Death even in an addict, is almost always due to respiratory failure, complicated by such factors as pneumonia, shock, and pulmonary edema.

## Management of toxicity

Since victims of opioid overdoses are often comatose with depressed respiration, the major treatment objective is to maintain vital functions. Therefore, the first step is to provide adequate respiratory assistance and cardiovascular support.

Opioid overdoses are treated readily with an ideal direct antagonists. The use of an antagonist brings about dramatic improvement in respiration within minutes. Overall, the antagonist will reverse CNS depression, analgesic, convulsion, psychotogenic, and dysphoric actions of opioids.

Naloxone was the first pure opioid antagonist, and it is considered the drug of choice for the treatment of opioid intoxications. Dramatic improvement in respiration is seen within minutes after it is administered.

Comatose patients must be aroused يوقظ as quickly as possible. If hypoxia persists and adequate tissue oxygenation is not achieved quickly, capillary damage followed by shock is likely to ensueيترتب على ذلك.

Patients with pulmonary edema are at special risk. Diuretics, digitalis, steroids, and antihistamine have all been recommended as supportive therapy. However, all have doubtful efficacy.

Respiratory depression lasts much longer than the antagonistic effect of naloxone. The patient must, therefore, be closely monitored for at least the next 24 to 48 hr. Naloxone should ideally be used only to return respiration to normal.

## Naturally occurring opioids

### Codeine

Codeine or methylmorphine, possesses analgesic and antitussive properties. It is less potent than morphine. Toxicity and death due to codeine alone are infrequently encountered. Acute toxic ingestions of codeine produce the typical trait صفة of symptoms seen with morphine: coma, meiosis, and respiratory depression.

## Synthetic opioids

### Diphenoxylate

Diphenoxylate is a mepridine congener used in combination with atropine in an antidiarrheal preparation. There is an extremely narrow dose range between therapeutic and toxic blood concentrations. Acute intoxications especially in children are characterized by anticholinergic effects. These may consist of hyperpyrexia, flushing of the skin, lethargy, hallucination, urinary retention, and tachycardia. This phase is followed by meiosis, respiratory depression, and coma due to the opioid activity.

### Fentanyl

Alpha-methyl fentanyl is 200 times as potent as morphine, and the minimum lethal dose is about 125 µg. 3-Methyl-fentanyl is 7000 times as potent as morphine, and the minimum lethal dose reported at 5 µg.

As with other opioids, the most significant acute toxic effect of fentanyl derivatives is respiratory depression, which is dose dependent and may last up to 30 min. The hemodynamic effects include bradycardia and hypotension. The remaining characteristics of toxicity include chest wall rigidity, nausea, vomiting, hypothermia, and seizures.

### Meperidine

Meperidine hydrochloride is a pure opioid agonist. It is the most commonly used opioid analgesic. Its structure is dissimilar to morphine, but similar to

fentanyl. When meperidine is prescribed for postoperative or chronic pain, it is often necessary to increase the dose to obtain the therapeutic response. However, a potential problem may result from cumulative doses of meperidine, which related to its pharmacokinetic properties.

## Pentazocine

It exert its major actions on the CNS and smooth muscle. CNS effects include analgesia, sedation, and respiratory depression. Psychiatric disturbance include dysphoria, depression, confusion and hallucination. The cardiovascular response to pentazocine differ from other opioids in that high doses cause increased blood pressure and heart rate, flushing, chills, and sweating.

## Propoxyphene

It is synthetic analog of methadone and if taken in overdose, causes all the classic signs of opioid poisoning. As with diphenoxylate containing products, most people do not consider the toxic potential of propoxyphene to be great. Too frequently, large quantities are being used for trivial بسيطpain without advising the recipient of the potential for toxicity.

One special concern is ingestion of a product that also contains acetaminophen. Clinical symptoms caused by propoxyphene overdose may completely overshadow those of a toxic acetaminophen ingestion.

## Cocaine

Central stimulation is one of cocaine's major pharmacological and toxic actions. Most cocaine use occurs by intranasal insufflation or inhalation of freebase cocaine, crack. A survey of cocaine users revealed that 61% were intranasal users, 21% smoked the free base form, and 18% were IV users. Most fatalities follow intravenous use. Cocaine death have also been associated with body packing.

## Mechanism of toxicity

Cocaine interferes with reuptake of norepinephrine at adrenergic nerve endings. Cocaine has also been shown to block reuptake of dopamine and interfere with serotonin activity.

## Characteristic of poisoning

Feeling of euphoria or dysphoria may occur. Motor coordination is not usually hampered اعاق at lower doses. With large doses, stimulation

extends to the lower motor centers and cord reflexes. Muscular twitching is noted first and may be followed by clonic-tonic convulsions. Death from high doses is usually a result of medullary depression producing respiratory failure.

The most prominent cardiovascular feature is sinus tachycardia which may produce ventricular arrhythmia.

Vasoconstriction, combined with increased heart rate, produces hypertension. Hyperpyrexia may occur and be a combination factor in cocaine death.

The effect of cocaine on the respiratory system follows the same progression: initial stimulation resulting in tachypnea, followed by dyspnea and respiratory failure.

## Management

Diazepam is the drug of first choice to control cocaine-induced seizures. When seizure control is inadequate phenobarbital may be substituted.

Cardiovascular effects must be treated aggressively. Propranolol, a beta-adrenergic blocking agent, will normally reverse and control hypertension and tachycardia.

If the victim is in the depression stage of poisoning (hypotension), attention must be directed immediately toward raising the blood pressure. Intravenous fluids and vasopressors such as dopamine are indicated at this point.

Hyperthermia must also be controlled. Cocaine-induced psychosis with hallucination paranoia, and hyper-excitability requires treatment. Neurologic agents have been used with success. More recently, lithium has been used.

## Marijuana

Marijuana is a mixture of crushed leaves, flowers, and stems of the Indian hemp قنب plant, cannabis sativa. The principle active ingredient is delta-9-tetrahydrocannabinol (THC). The content of THC in marijuana varies broadly in the United States, ranging from 0.5 to 11% depending on methods of cultivation. Sinsemilla (without seeds) refers to a mixture of flowering tops and leaves of cultivated, unfertilized female plants. THC content in Sinsemilla may range from 8% to 11%.

THC is rapidly absorbed into the blood after inhalation, producing subjective effects within seconds to minutes that last at least 2 to 3 hr. After

a single usage, only 5% to 10% of an oral dose of THC is absorbed. Onset of effects may be delayed for 30 min, but last as long as 5 hr or more.
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## Characteristics of marijuana poisoning

Low doses of THC (2 mg) will generally produce a sense of relaxation, mild euphoria, and increased auditory, visual, and gustatory ذوق perception ادراك حسي. Periods of hilarity مرح صاخب may be followed by silence. With moderate doses (5-7 mg) a progression to disturbance in thought processes and time perception, impairment in short-term memory, and ataxia may be prominent. High doses (15 mg) may induce feeling of depersonalization, disorientation, paranoia, and marked sensory distortion تشويه.

Cardiovascular effects may include dose-related sinus tachycardia, but blood pressure is usually not significantly affected. Impaired pulmonary function is evidenced by bronchitis, pharyngitis, cough, and an asthma-like condition. Marijuana smoking may cause cancer due to its high tar content.

## Management

Management of marijuana-induced reactions is purely supportive and symptomatic. Ingested material should be removed from the stomach with emesis, lavage, or activated charcoal. If the patient is disoriented مشوش or experiencing hallucinations or panic reactions, a prolonged talk down كلام بهدوء period may be necessary. Since acute toxic reactions due to marijuana alone are rare, whenever a patient presents with serious manifestations, consideration should be given to other drug such as LSD, or cocaine being at fault.

# Central nervous system stimulants

## Amphetamine like drugs

Numerous derivatives of amphetamine have been over the years to modify a variety of medical conditions. Today, they are approved in the management of narcolepyخدر , hyperkinesia (hyperactivity) in children, and short-term treatment of obesity.

### Mechanism of toxicity

Amphetamine induces CNS stimulation mainly by causing release of catecholamines (epinephrine, norepinephrine, and dopamine) into central synaptic spaces and inhibiting their reuptake into nerve endings.

One problem frequency encountered by amphetamine users is tolerance to some of the central effects, such as the anorexiant and euphoric actions. Therefore, users may need to increase the dose. If use is continued in these individuals, the convulsive threshold may actually be lowered, and fatalities become a greater problem.

### Characteristic of poisoning

Amphetamine causes a variety of dose related signs and symptoms. Most toxic effects are extension of pharmacological actions.

Amphetamine-induced psychosis with euphoria and hallucinations is common. Hallucinations are generally perceivedمحسوس as unpleasant. These may be auditory in nature (mostly in patients using amphetamines chronically), or visual (more common after a single large dose). Tactile hallucinations are experienced occasionally.

Respiratory and cardiovascular functions are stimulated. Sympathomimetic effects include tachycardia, hypertension, flushing, and diaphoresisتعرق غزير.

Hyperpyrexia may be significant, with temperatures above 109 ºF (42.8 C) reported. Temperatures this high are incompatible with life and are a contributing cause of death.

### Management

Amphetamine-poisoned patients often present with acute psychosis, delirium هذيان, or extreme anxiety. Phenothiazines have been recommended for treatment of amphetamine-induced psychosis, which is due to excess dopamine. Chloropromazine has also been shown to reverse hyperthermia, convulsions, and hypertension associated with amphetamine toxicity without causing depression.

Management of hyperthermia may include use of a hypothermic blanket or placing the patient in a cool, quit room. Salicylates may be helpful in temperature reduction.

# Methylxanthine derivatives

Three methylxanthine alkaloids are commonly encountered from natural resources: theobromine, theophylline, and caffeine. Cocoa and chocolate contain theobromine and some caffeine, Tea contains caffeine and some theophylline. Coffee and many cola-flavored beverages are rich sources of caffeine.

In addition to their presence in foods and beverages, theophylline and caffeine are used in drug therapy. Methylxanthines stimulate the CNS, induce diuresis, relax smooth muscle (notably bronchial muscles, and stimulate cardiac functions. Caffeine also augments the analgesic properties of salicylates and is contained in numerous analgesic products. Theobromine possess similar, but weaker pharmacological activity on CNS.

## Mechanism of Toxicity

1. Increased calcium release from intracellular sites
2. Accumulation of cyclic nucleotides, especially cyclic AMP (cAMP)
3. Adenosine receptor blockade.
   Toxicity probably results from more than one mechanism. Direct stimulation of the chemoreceptor trigger zone appears to cause the nausea and vomiting.

## Characteristics of poisoning

Theophylline has a narrow therapeutic margin, 10 to 20 µg/mL because numerous factors including other drugs can stimulate or depress theophylline clearance, maintaining therapeutic blood concentration can be difficult. Rapid intravenous administration of theophylline or aminophylline (theophylline ethylenediamine) can result in death due to cardiac arrhythmias.

Other manifestations of overdose include nausea and vomiting, headache, dizziness, palpitations, and tachycardia, hypotension, and precordial pain. Also, patients have reported severe restlessness and agitation. Focal and generalized seizures may appear occasionally.

## Management

Theophylline-induced seizure are difficult to manage. Diazepam is often recommended as first-line therapy, but it often fails to control the problem. Still diazepam should be given first. If fails to control seizures, phenobarbitone should be administered.

Arrhythmias can usually be controlled with propranolol or verapamil. These block the SA and AV nodes, and also restore coronary blood flow by reversing theophylline induced hypotension.

# Camphor

Camphor-containing products are not generally considered by the laityالناس to be toxic. Indeed, camphor has long been used externally as a rubefacient, mild analgesic, antipruritic, and counterirritant.

Camphorated oil has been the largest single cause of camphor-related poisonings. Most poisonings have occurred because victims mistook it for castor oil, or other

remedies that either sounded like or looked like camphorated oil, and ingested an unsuspected toxic dose.

**Characteristics of poisoning**

Signs and symptoms of camphor poisoning may appear within 5 to 15 min after ingestion, or be delayed for several hours on a full stomach. Because it is highly lipid soluble, camphor enters the CNS quickly.

**Management**

Camphor must be removed from the stomach as quickly as possible. Immediate emesis or gastric lavage is indicated (before convulsions and generalized stimulation occur). Activated charcoal should follow. Lavage should be continued until the odor of camphor is no longer detected. It has been suggested that whenever the quantity ingested is unknown, it should be assumed the amount was greater than 1 g and the patient should be vigorously treated.

Barbiturates have long been used to control convulsions, but diazepam is generally preferred because it produces less respiratory depression. Hemodialysis will hasten removal of camphor from the blood. Succinylcholine may be used to help control muscular rigidity and spasm. As with any other CNS stimulant the patient must be kept quiet and at minimum sensory input.

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# Central nervous system depressants

## Barbiturates

Short-acting barbiturates have a duration of action of 4 to 6 hr, and include pentobarbital. Long-acting barbiturate, such as phenobarbital and barbital, have a duration of action of 12 to 24 hr.

The short duration of action of certain barbiturates cannot be equated يساوي with decreased toxicity potential. In fact, just the opposite is true. Shorter-acting barbiturates are more lipid soluble. Hence they reach higher CNS concentrations and cause greater depression than phenobarbital. Furthermore, toxic blood concentrations of phenobarbital are more readily decreased by hemodialysis and alkaline diuresis than similar blood concentrations of short acting barbiturates.

### Mechanism of barbiturate toxicity

Barbiturates depress the polysynaptic neuronal pathways primarily, with monosynaptic pathway affected to lesser extent. This action is believed to be due to direct gamma-amino-butyric acid (GABA)-like effect, or to stimulation of GABA release. GABA is an inhibitory neurotransmitter within the CNS. When released, central depression is noted.

Respiratory depression is the major toxic event that follows barbiturate ingestion and usually causes early death.

Hypothermia is another potentially serious problem that follows toxic ingestion of barbiturates. Lowered body temperature results from direct depressant action on the thermo-regulatory center. It potentiates acidosis, hypoxia and shock.

Sympathetic ganglia are depressed with larger doses. This may help explain why toxic barbiturate doses reduce the blood pressure.

Other clinical toxicity of barbiturate include decreased gastrointestinal motility and tone, which may lead to increased drug absorption.

### Characteristics of barbiturate poisoning

Short-acting barbiturates are highly lipid soluble and potentially more than long acting barbiturates, which are less lipid soluble. Lethal doses of short–acting barbiturates produce death in a short period of time. In suicides, victims are often found dead at the scene or they die shortly thereafter. In contrast, patients who overdose on long-acting barbiturates generally die later in the hospital.

## Benzodiazepines

Benzodiazepines have a high therapeutic index and are the safest of all sedative-hypnotic drugs. In other words, the range between therapeutic dose or toxic or lethal dose is extremely wide. Increasing dosage, even to massive amounts, will not cause general anesthesia, as opposed to other sedative drugs. Consequently, their overall

potential for toxicity is low, and patients with benzodiazepine overdose present with fewer problem.

**Mechanism of benzodiazepine toxicity**

Most toxic effects of benzodiazepines result from their sedative action on the CNS. At extremely high doses, neuromuscular blockade may occur.

Within the CNS, benzodiazepines are selective for polysynaptic pathways. They inhibit presynaptic transmission by stimulating the inhibitory neurotransmitter, GABA.

**Characteristics of benzodiazepine poisoning**

Effects on motor performance are more prominent than cognition. On occasion, severe paranoia, psychosis, hallucinations, and hypomania behavior are noted.

# Chloral hydrate

Chloral hydrate is converted to its active metabolite, trichloroethanol. Chloral hydrate and its metabolite are lipid soluble and readily enter the CNS. Poisoning resemble barbiturate intoxication. The corrosive action of chloral hydrate may cause gastritis, nausea, and vomiting.

# Antihistamines

With introduction of antihistamines in the late 1940's, it was realized that these drugs produces a variety of effects centered around CNS depression. Sedation is the most common side effects of most antihistamines in adults. In overdose, CNS depression leading to coma may result. However, additional symptoms that resemble anticholinergic action may also be present and may be more significant than the degree of depression. These include mydriasis, flushing, fever, dry mouth, and blurred vision. Children usually experience central stimulation, hallucinations, tonic-clonic convulsions, and hyperpyrexia, rather than depression.

# Management of CNS depression overdose

The highest priority in treating any victim of depressant poisoning is to stabilize respiratory and correct anoxia نقص الاوكسجين. If the brain suffers damage from insufficient oxygenation other procedure will be little benefit.

Oxygen should be given and the patient ventilated mechanically, if needed. A cuffed endotracheal tube should be used in Stage 4 coma to decrease risk of aspiration pneumonia during lavage. To help prevent hypostatic pneumonia, the victim should be turned frequently.

Since circulatory collapse is a major threat after ingestion of massive doses of CNS depressants, cardiovascular function must be assessed quickly and deficiency corrected.

Renal failure is the cause of one-sixth of all death. Therefore, kidney function must be monitored constantly. Signs of uremia may be an indication for hemoperfusion or hemodialysis.

**Prevent further absorption of the poison**

Ipecac-induces emesis should be considered. In a comatose individual, gastric lavage is appropriate. Activated charcoal adsorbs barbiturates and most common CNS-depressant drugs. A slurry can be instilled into the stomach though a nasogastric tube.

**Increase excretion of absorbed drug**

Barbiturates are weak acids. Thus alkalinization will promote ionization of at least half the drug in the glomerular filtrate and cause it to be excreted more readily.

Multiple doses of activated charcoal starting 10 hr after phenobarbital ingestion in healthy individuals significantly reduce blood concentrations.

Hemodialysis is variably effective in removing significant amounts of CNS depressant from blood in cases of toxic/lethal ingestion.

**Benzodiazepine antidote**

Flumazenil is an antagonism that can reduce or terminate the sedative, anxiolytic, anticonvulsant, ataxic, anesthetic, and muscle relaxant effects of benzodiazepines in a dose related manner.

# Drug toxicity

# Over the counter drugs

## Non-steroidal anti-inflammatory drugs

## Salicylates

Aspirin poisoning may affect people of all ages. Children are most susceptible and are usually the victims of accidental ingestions. Adult salicylate toxicity is normally due to chronic misuse or intentional ingestions of large quantities. Children present the greatest risk of developing serious toxic complications after salicylate poisoning.

**Mechanism of toxicity**

1- CNS effect of salicylate intoxication
   The respiratory center is stimulated either:
   - Indirectly by an increase in $PCO_2$ production, salicylates enhance oxygen consumption by increasing the cellular metabolic rate, this results in hyperthermia with accumulation of $CO_2$ which then causes hyperpnea.
   - Directly by producing both hyperpnea and tachypnea (increase depth of respiration and increase rate of respiration, respectively). The increased respiration rate causes a greater than normal amount of $CO_2$ to be expired by the lungs. As a result, there is less plasma $CO_2$ (alkalosis).

2- Metabolic effects of salicylate intoxication
   - The kidney attempts to compensate for the acid-base imbalance by excreting more $HCO_3$, and retaining $H^+$ and nonbicarbonate anions. Usually this mechanism operates to correct the acid-base imbalance. In salicylate toxicity this may add to the latent metabolic acidosis.
   - The second action of salicylate toxicity results from uncoupling of oxidative phosphorylation, which ultimately produces metabolic acidosis. Uncoupling of oxidative phosphorylation result in a decrease in ATP production. Cells attempt to compensate by increasing glycolysis.
   - The body also uses its glycogen stores to obtain energy. Eventually, these are depleted and the body switches to lipid metabolism to meet energy demands. Although this is an efficient mechanism, it leads to excessive free fatty acid in the liver, producing increased ketone bodies, which can cause ketoacidosis.
   - Inhibition of amino acid metabolism, resulting in accumulation of amino acids.

   Salicylates also interfere with normal blood glucose concentration. Eventually, however, there is depletion of glucose stores with resultant hypoglycemia.

Hypoglycemia may be of greater significance in chronic salicylism, or during the latter stages of acute salicylate toxicity.

Ingestion high doses of salicylate result in switching salicylate metabolism from first to zero-order kinetic. That is, the rate of degradation is independent of dose and an increase in dose results in a greater increase in serum and tissue salicylate concentrations especially, the CNS. This result of decreased plasma protein binding of salicylate at high doses.

**Characteristics of poisoning**

The major toxic manifestations of salicylate poisoning result from stimulation of CNS. These may include nausea, vomiting, tinnitus, headache, hyperpnea, and neurologic abnormalities, such as confusion, hyperactivity, slurred speech, and generalized convulsions. Salicylate results in hyperventilation, decreased $PCO_2$, and respiratory alkalosis.

**Management of poisoning**

Management strategies involve removal of aspirin from the GI tract, and correction of metabolic acidosis, dehydration, hyperthermia, hypoglycemia, and hypokalemia.

The general sequence for managing salicylate toxicity should begin with gastric decontamination. In children, emesis is easier to accomplish and probably more effective.

Dehydration is common in salicylate poisoning and appropriate fluid replacement is critical. This may be managed by administration oral fluids. When toxicity is within the moderate to severe range, dehydration is usually treated with parenteral fluids.

Sodium bicarbonate is given to help correct metabolic acidosis associated with moderate to severe toxicity, and to produce an alkaline urine that will promote movement of salicylate from intracellular site to plasma to enhance excretion by the kidney.

Potassium chloride is added to correct hypokalemia and help prevent alkalosis from sodium bicarbonate administration. Alkaline diuresis is only effective in removing salicylate from the body when potassium depletion is corrected.

Fever can be reduced by cold or tepid water. Other symptomatic treatment include diazepam for seizures, calcium supplements for hypocalcemic tetany, and vitamin k for coagulation defects.

# Ibuprofen

Ibuprofen can be predicted to be safe. After absorption it is quickly metabolized with an elimination half-life of approximately 2 hr. A single therapeutic dose is completely eliminated within 24 hr. An acute overdose does not prolong the elimination half-life of ibuprofen.

**Mechanism of toxicity**

Acute renal failure is believed to result from decreased production of intra-renal prostaglandins. This in turn decreases the renal blood flow and glomerular filtration rate.

**Characteristics of poisoning**

Patients have either no symptoms, or mild manifestations of gastrointestinal irritation, such as nausea and vomiting. Drowsiness, lethargy, and mild coma have been reported but generally resolve in 24 hr even with large doses.

**Management of poisoning**

Treatment of acute overdoses of ibuprofen and similar NSAIDs should consist of basic poison management, including symptomatic and supportive care.73% of the patients received emetic or gastric lavage. Another 20% were given oral fluids. The remainder required no treatment. Activated charcoal will adsorb NSAIDs including ibuprofen.

# Acetaminophen

Acetaminophen, like aspirin, is safe when taken as directed. In acute overdose, unlike aspirin, acetaminophen does not cause early neurologic or other warning signs of toxicity (e.g. tinnitus). Patients present in otherwise good health, and by the time the potential for toxicity is realized (by either the victim or attending physician), irreversible liver damage may have already occurred.

**Mechanism of toxicity**

Acetaminophen is absorbed rapidly from the stomach and upper GI tract. Most of the drug is metabolized by conjugation with glucuronide and sulfate. An intermediate metabolite formed via this system is a highly reactive acylating compound, N-acetyl-p-benzoquinonimine (NAPQI). NAPQI binds covalently to hepatocyte proteins causing hepatocellular necrosis. At therapeutic doses, glutathione inactivate NAPQI by conjugation and subsequent transformation to acetaminophen-3-mercapturic acid. Which is already excreted. When a massive overdose is ingested, live enzymes are saturated and the supply of glutathione is inadequate to detoxify NAPQI. The concentration of toxic metabolite, therefore, increases and can bind covalently to sulfhydryl groups of hepatic cellular proteins, resulting in centri-lobular necrosis.

**Characteristics of poisoning**

Except for signs of hepatotoxicity that may not appear for days after ingestion, acetaminophen causes few remarkable signs or symptoms.

**Stages of poisoning**

Stage 1 may appear quickly and persist 24 hr or more (anorexia, nausea, and vomiting). Stage II, a period of apparent recovery. Destruction of hepatocytes is inevitable during this phase. As noted by increased serum glutamate-oxalactic transaminase (SGOT, AST), liver damage has already began.

Stage III may manifest within 72 to 96 hr after ingestion. It is characterized primarily by elevated plasma lactic dehydrogenase (LDH), SGOT, and bilirubin. Prothrombin time may be increased, and case reports have described hemorrhage tendencies after acetaminophen toxicity.

Eventually the liver damage may cause jaundice and other sequelae depicted. Myocardial tissue damage and renal failure have been reported.

Plasma acetaminophen concentration are the most important predictor for assessing the probability of developing hepatic damage.

Stage IV, the period of resolution of hepatic injury ensues, and liver function tests generally return to normal.

**Management of poisoning**

Early in the management protocol, as soon as poisoning has become evident, gastric decontamination should be undertaken to reduce the quantity of acetaminophen present within the GI tract. Decontamination includes ipecac-induced emesis, lavage, activated charcoal and a cathartic.

In many instances, by the time N-acetyl cysteine is administered, several hours have already elapsed since activated charcoal was given. As long as the initial dose of N-acetyl cysteine is given within the first 10 to 16 hrs after ingestion of acetaminophen, the regimen should be beneficial. Also, not all studies show that activated charcoal significantly reduces N-acetyl cysteine blood concentrations and, thus concomitant use of activated charcoal and N-acetyl cysteine may be effective.

N-acetyl cysteine and methionine afford antidotal activity mainly by restoring intracellular glutathione concentrations. Both compounds require prior conversion to cysteine. Besides enhancing synthesis of glutathione, N-acetyl cysteine and methionine also serve as a source of inorganic sulfur. This may promote increased conversion of acetaminophen on its sulfate metabolite, as well as reduce formation of other metabolites including the toxic intermediate, NAPQI.

# Vitamins

Accidental poisoning by vitamin products currently rank يصنف as a major cause of poisoning in children under the age of five, similar toxicity also occurs in adults, and reports of such poisonings have increased since the advent قدوم of the megadose concept of dosing vitamins. Fortunately, few deaths have been reported.

**Megadosing**

Toxic manifestation of vitamin over-ingestion are more commonly seen with fat-soluble vitamin A and D. Fat-soluble vitamin K has been frequently reported to induce toxicity, probably because it is not available for self-administration in OTC products. Vitamin E is practically nontoxic, at least according to current knowledge. For the most part, excessive intake of the water-soluble B complex group and vitamin C is eliminated by the kidney. Although they produce minor adverse reactions and may cause drug interactions or modify laboratory values, these are not generally life-threatening. An exception is vitamin C which can induce renal toxicity in a small number of susceptible individuals.

# Vitamin A

Hypervitaminosis A has occurred in patients receiving large doses of vitamin A or other vitamin A analogs such as isotretinoin and tretinoin to treat skin diseases, such as ichthyosis داء السمكة, acne, and Drier's disease (a genetically transmitted disease in which the skin becomes extremely crusty قشري). Large doses of vitamin A taken during pregnancy are teratogenic, causing a variety of fetal malformation تشوه.

## Mechanisms of poisoning

A retinol-binding protein is involved in transport of the vitamin to peripheral tissues. Clinical manifestation of hypervitaminosis A occur when this protein becomes saturated with the vitamin. Cellular membrane are then exposed to unbound vitamin, which leads to degradation of the membrane structure. This mechanism may be responsible for increased cerebral spinal fluid pressure and other CNS manifestations that characterize vitamin A toxicity.

Vitamin A is normally stored in hepatocytes. When massive doses are consumed, the Ito cells (lipocytes) take up the vitamin. It is believed that this transforms, the Ito cells into fibroblasts that can produce collagen, which in turn causes subsequent hepatic pathology.

## Characteristics of poisoning

Vitamin A-induced symptoms of toxicity are:
Gastrointestinal: nausea/vomiting, anorexia, Diarrhea
Central nervous system: headache, irritability and restlessness, fatigue
Skin: Dry, pruritic skin, rash
Muscle and joints: myalgia, muscle fasciculation, tender
Bone: hyperostosis

## Management of poisoning

Treatment of vitamin A intoxication includes immediate discontinuation of the substance. Most signs and symptoms will disappear within a week or two. If symptoms are ignored and the vitamin is not withdrawn, irreversible hepatic damage, including cirrhosis, may result.

Vitamin E is reported occasionally to protect against hypervitaminosis A.

# Vitamin D

Vitamin D is the most toxic of all vitamins. A large number of toxicity have been reported in people using vitamin D to treat arthritis, muscle cramp, cold hand and feet, and a variety of other real or imagined disorders. The vitamin is used occasionally in excess to treat various nutritional disorder in persons of all ages. Because excessive and repeated doses are frequently taken, reports of toxicity have increased in recent years.

**Mechanisms of poisoning**

Vitamin D toxicity are caused by its action to elevate the concentration of plasma calcium. 1,25-dihydroxycholicalciferol exerts activity at several sites, including intestinal epithelium to promote calcium absorption.

**Characteristics of poisoning**

Symptoms of vitamin D toxicity are largely suggestive of hypercalcemia. Deaths occurring after acute toxic doses are usually attributed to this finding. Toxic effects from chronic use are due to deposition of calcium in soft tissues, especially the kidney and heart. Aortic valvular stenosis (narrowing) and nephrocalcinosis with calcification other soft tissues are characteristic finding. Renal function may be severely and irreversibly impaired. Cardiac rhythm may become abnormal after prolonged deposition of calcium salts within the heart's myofibrils.

**Management of poisoning**

Hypervitaminosis D treatment consist of immediately discontinuing vitamin intake, reducing calcium intake, administering glucocorticoids, and assuring a generous fluid intake.

# Vitamin K

Vitamin K is not a component of over the counter remedies. Thus there are few cases of toxicity reported in the literature.

**Characteristic of poisoning**

The major toxicity is associated with water soluble synthetic analogs such as menadione. These derivatives are oxidants and may cause erythrocytic membranes to rupture with resultant cell hemolysis, and jaundice.

# Vitamin E

At present, vitamin E is believed to have a low toxicity profile. Undesirable side effects of megadoses of vitamin E include headache, nausea, fatigue, dizziness, and blurred vision, gastrointestinal disturbance.

# Vitamin C

Serous toxicity to vitamin C is uncommon. However, numerous untoward effects may occur when it is taken in overdose, or by persons susceptible to larger-than-normal doses.

It is often reported that large doses of vitamin C destroy substantial amounts of vitamin $B_{12}$, and therefore reduce its concentration in the blood.

**Kidney stone formation**

Ascorbic acid increases renal excretion of oxalate, uric acid and calcium. These may increase the potential for stone formation in the kidney and bladder. This potential seems to be governed by general factors, and only occurs in a small segment of the population.

# Vitamin B$_1$

Symptoms from parenterally administered vitamin B1 (thiamine) ranged from nervousness, convulsions, weakness, trembling, headache and neuromuscular paralysis to cardiovascular disorders

With the subsequent decline in use of thiamine in its parenteral form, there have been fewer toxicities reported and it is longer considered to possess a major toxicological threat.

# Niacin

In single doses of 50 mg niacin (nicotinic acid), intense flushing and pruritus have been reported. When the practice of giving niacin in doses ranging upward to 30 g or more a day advocated, more serious toxicity was noted.

The most common serious toxicities reported for niacin include abnormal liver function and jaundice.

# Vitamin B$_6$

Vitamin B$_6$ (pyridoxine)-induced reactions are rare. Convulsive disorder have occurred due to both vitamin excess as well as a deficiency state.

# Vitamin B$_{12}$

Vitamin B$_{12}$ (cyanocobalamin) is associated on rare occasion with allergic reactions to the injectable products, Symptoms of edema of the face, urticarial, shivering, bronchospasm, rash, dyspnea, aphonia فقدان الصوت, and anaphylaxis has appeared, but only after years of continuous vitamin administration.

# Folic acid

Long-term folic acid therapy increased seizure frequency in some epileptic patients and may precipitate vitamin B$_{12}$ deficiency neuropathy in some cases of megaloblastic anemia.

# Chemicals and Environmental Toxins

# Hydrocarbons

## Classification of hydrocarbons

Hydrocarbons compromise a broad group of organic compounds that contain only hydrogen and carbon. They may be divided into two large categories: aliphatic (straight chain) or aromatic (benzene ring) compounds. Another group, which is of great toxicological significance, consist of halogenated aliphatic and aromatic hydrocarbon.

## Mechanism of toxicity

The two most common routes of exposure for hydrocarbons are inhalation and ingestion. Ingestion is the more common route of exposure encountered in acute accidental hydrocarbon poisoning. When ingested, hydrocarbons produce toxic effects at several sites including the pulmonary, CNS, gastrointestinal, hepatic, and cardiovascular systems. Among these, the most serious damage occurs to the pulmonary system. Aspiration pneumonitis is the greatest cause of morbidity and mortality with these compounds. Halogenated hydrocarbons particularly those containing fluorine sensitize the heart to catecholamine and induce arrhythmias in susceptible individual

## Pathogenesis

The physicochemical properties of hydrocarbons are also important factors responsible for the increased incidence of aspiration among certain hydrocarbons. The risk of aspiration and lung damage is directly proportional to volatility and indirectly related to surface tension and low viscosity. That is, hydrocarbons that are most likely to be aspirated are highly volatile and have low surface tension and viscosity. These properties permit the hydrocarbon to "creep" up يرتفع the wall of the esophagus and enter the trachea. Hydrocarbons are also gastric irritants, and spontaneous vomiting sometimes occurs during which there is greater chance for entry into the trachea.

As the hydrocarbon enters the lung, it causes severe local irritation resulting in inflammation, edema, and hemorrhage bronchopneumonia.

## Management of hydrocarbon poisoning

One of the early determinations that must be made is to identify the specific hydrocarbon ingested and determine its potential for aspiration and systemic toxicity.

Gastric decontamination is not recommended for most accidental petroleum distillate ingestions because of the risk of pulmonary aspiration.

Evacuation is indicated for hydrocarbon ingestion involving large quantities of petroleum distillates, turpentine, aromatic hydrocarbons, or halogenated hydrocarbons.

Emesis indicated for ingestion of hydrocarbon containing heavy metals, camphor, or insecticides.

Much of the management of hydrocarbon ingestion is symptomatic and largely supportive. This includes providing oxygen and fluids, and controlling fever with antipyretics.

Antibiotics are indicated if infections occur but should be given only at that time. Most pulmonary complications are nonbacterial. Glucocorticoids may actually increase the patient's chance of development pulmonary bacterial infection by lowering the immune system response.

# Household toxins

The toxic agents present in household chemicals are quite varied. For a variety of technological and legal reasons, formulations change rapidly or differ by region. Thus, the date of manufacture and place of production are of importance in establishing the toxic substance. Most poisoning due to these substances are truly accidental and are most common in children.

## Soaps, Detergents and Shampoos

**Soaps and detergents** constitute the largest class of household products found in greatest quantity around the household. Most soaps are relatively nontoxic and possess an emetic action that is possibly as effective as syrup of ipecac. Soap-induced emesis is mediated through a direct effect on the GIT, rather than systemic action. Ingestion of many soap products is not dangerous because soap is self-eliminating and very few symptoms, other than upset stomach will be experienced.

**Bar soaps** have a low order of toxicity. The most prominent symptoms produced by ingestion are usually nausea and vomiting, although diarrhea can appear and may become severe.

Ingestion of strong detergents may cause a variety of reactions, depending on the specific products. **Detergents** contain a wide variety of inorganic and organic ingredients, among which are *surfactants and wetting agents*. Surfactants may be anionic, cationic or nonionic. Most household detergents contain anionic or nonionic surfactants. Cationic detergents have a greater toxicity potential compared to anionic and nonionic detergents. The latter produce local irritation, whereas cationic detergents may inciteيحرض sever irritation and possibly systemic effects. *Builders* are added to detergents to improve cleaning action of the product. Commercially used builders may include carbonates, silicates, aluminosilicate, sulfates and phosphates. The major problem of toxicological concern from ingestion of most detergents products is the builder. Because of their high alkalinity, it may produce sever ocular irritation and oral and gastrointestinal burns.

**Granular soaps and detergents** have a low order of toxicity. The exception is automatic dishwashing machine detergents which are highly alkaline and produce corrosive action.

**Shampoos** have a low order of toxicity, although gastric irritation may cause a greater incidence of nausea and vomiting. Addition of antidandruff agents to shampoos increase the products toxicity.

### Managements

Management of soap, detergents or shampoos ingestion should involve immediate dilution with water or milk. Spontaneous emesis should be expected, induction of emesis is seldom necessary. When highly alkaline products such as aromatic dishwasher detergents are ingested, managements for a corrosive substance should be followed. If vomiting or diarrhea becomes prominent, symptomatic treatment and fluid replacement may be necessary.

## Ammonia and Ammonium Solutions

Ammonia, oven cleaners and drain cleaners are highly alkaline and extremely corrosive. Household ammonia ranges from 5% to 10% ammonia but an industrial strength solution is greater than 50%. Inhalation of ammonia gas produces irritation of the upper respiratory tract, often cause cough, dyspnea and pulmonary edema. Contact with skin or eyes produces sever pain and corrosive damage. Ingestion of ammonia solution resembles that of a typical alkaline corrosive. Treatment is the same as for alkaline corrosive substances.

## Bleach

Most bleach products are solutions of 3% to 6% sodium hypochlorite (NaOCl) in water. The pH is approximately 11 which makes them highly alkaline. Bleach ingestion produces severe irritation and corrosion of mucous membranes with pain and inflammation. The amount of bleach actually ingested is usually small, probably due to its extremely bad taste and bleach solution are spontaneously vomited. Therefore, severe toxicity is often avoided.

### Management

Of ingestion includes dilution with water or demulcents, such as milk or antacids. Neutralization with acidic solutions and ipecac-induced emesis are contraindicated. Bleach should not be mixed with strongly acidic or alkaline cleaning agents in an unvented area, although this is apparently common practice in some households. When bleach reacts with either acid or alkali, either chlorine or chloramines gas may be released. Both can cause lacrimation and irritation to the mucous membranes and respiratory passages if inhaled in sufficient concentrations. In high concentrations, both could cause asphyxiation.

## Disinfectants

## Quaternary Ammonium Compounds (QACs)

They are cationic surfactants used in a wide variety of products, such as disinfectants, bactericides, deodorants and sanitizers. QACs are all potentially toxic. Toxicity varies

with a specific compound, the concentration of the product, dose ingested and the route of administration. All QACs produce similar symptoms through a similar mechanism.

Concentrations above one-percent produce superficial necrosis of mucous membranes, causing GIT erosion, ulceration and hemorrhage. Edema of the glottis and brain has been reported as well as damage to the heart, liver and kidney.

All QACs cause disinfection only to chemically clean areas. In the presence of any trace of soap, they are inactivated. Thus, soap is a suitable means for preventing damage from QAC poisoning, from either skin contamination or oral ingestion. Ingestion of a cleaning agent greater than 5% to 10% of QACs should be treated as a corrosive alkaline ingestion.

# Moth Repellents

## Naphthalene

May be taken by children when air freshener discs or old fashioned mothballs are eaten. About 2 g is a fatal dose for a small child, as absorption occurs rapidly. Hemolysis with subsequent renal failure is the chief danger. Liver necrosis may also occur. Paradichlorbenzene which is the main ingredient of many modern moth repellants is considerably less toxic.

**Clinical features**

1. GIT: nausea, vomiting and diarrhea. Jaundice and liver failure may follow.
2. Hematologic system: anemia due to hemolysis.
3. Renal disorders: oliguria, hematuria and proteinuria.
4. CNS: cerebral stimulation with agitation leading to coma and convulsion.

**Treatment**

1. Gastric aspiration and lavage.
2. Alkalinize the urine with oral sodium bicarbonate, or if this is not retained, intravenous sodium bicarbonate.
3. Hydrocortisone six-hourly intramuscularly.
4. Blood transfusion if hemolysis is sever.
5. Oliguria or anuria may require intensive medical treatment and hemodialysis, if this is ineffective.

# Corrosives and chemical burns

**Clinical presentation**

Sites commonly affected by corrosive ingestion are the oropharynx, esophagus, and stomach, although injury may occur far as the proximal jejunum.

Systemic toxicity may sometimes accompany severe gastrointestinal injuries and is usually secondary to tissues inflammation, necrosis, perforation, acidosis, and

infection. Fluid and electrolyte shifts accompanying extensive burns can results in hypovolemic shock. Some corrosive also cause systemic toxicity when absorbed.

Patients usually present with oral, throat, or abdominal pain. Dysphagia, drooling, and vomiting. Hoarseness, hematemesis, and melena occur less frequently. Tachypnea can occur from aspiration of the corrosive with resultant pneumonitis or as a compensation for a metabolic acidosis.

Superficial burns of the oropharynx are covered with a pale membrane, and deeper burns are black, hemorrhagic, or friable. Full thickness injuries to the esophagus or stomach are at risk for perforation and fistula formation into the trachea, mediastinum, or peritoneum.

Ocular injury most commonly results from splash رش exposure at home or in the work environment. The severity of these injuries ranges from transient irritation to severe disabling ocular damage and blindness. Manifestation include immediate eye pain, photophobia, blepharospasmتشنج الجفن, lacrimation, conjunctival injection or hemorrhage, and decreased visual acuity. Intraocular pressure rises and if the penetration is deep retinal damage occurs.

Dermal exposure usually results in immediate pain at the affected site but onset of pain can sometimes be delayed for several hours. Chemical burns rarely blister, and the affected skin is usually dark, insensate, and firmly attached regardless of the burn depth. With time, the skin hardens and cracks, exposing the underlying dermis or subcutaneous tissue. Healing of chemical burns usually takes longer than for thermal burns.

**Management**

Any patient with evidence of significant upper airway obstruction such as severe respiratory distress, or inability to speak should undergo immediate endotracheal intubation. Emesis is contraindicated because it re-exposes the esophagus to the corrosive agent and increases the risk of aspiration. For this reason antiemetic should be given to patients with persistent nausea or vomiting. Dilution with oral fluid may be beneficial and should be within minutes of exposure in patients with a normal and mental status without significant nausea, vomiting, or pain and who are able to speak and co-operate.

Concomitant antibiotics are recommended whenever steroids are being used. Antacids, sucralfate, $H_2$ blockers and analgesics can provide symptomatic relief. The patients may be given oral fluid when they are able to swallow their own secretion. Those patients with severe injuries should receive intravenous fluids and nothing by mouth.

Surgical exploration is indicated if perforation is confirmed by radiographs or endoscopy when there is persistent hypotension or in the presence of abdominal rigidity.

Irrigation of the eye is performed immediately at the time of exposure in the home or workplace and continued in route to the hospital. If the patient has significant pain, irrigation must again be performed in the emergency department. Irrigation will be aided greatly by the application topical anesthetic solution and the use of eyelid retractors. Intravenous analgesics or sedative may also be required. Acceptable irrigation solution include tap water, normal saline, or ringer lactate.

Standard treatment for corneal injury includes topical antibiotics, steroids, cycloplegic, and mydriatics. Topical timolol and oral acetazolamide may be required, if intraocular pressure is elevated.

Initial management of dermal injuries is also directed at rapid decontamination. Copious irrigation of the skin surface with water is the decontamination method of choice for most exposures. All contaminated clothing, footwear, jewelry, and contact lens should be removed from the victim. It must be emphasized that immediate irrigation with water should never be delayed to search for an alternative irrigation solution. Irrigation should continue for at least 20 minutes. A longer period of irrigation lasting up to several hours.

# Organic builders

## Antiredeposition agents

Anti-redeposition agents **prevent soils** that have been dislodged from fabric from being **redeposited**.
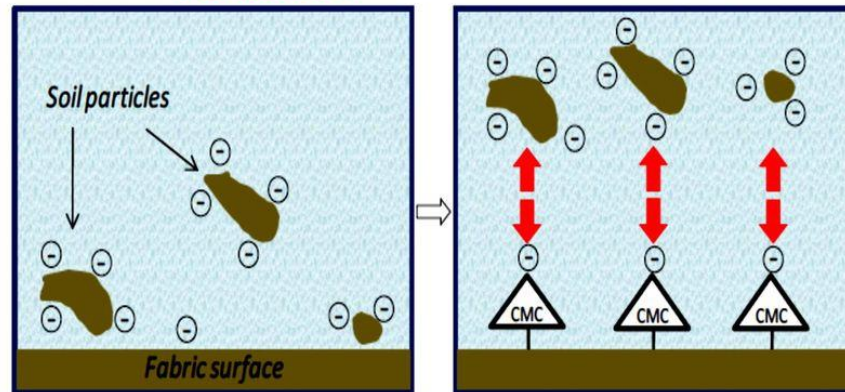


Anti-redeposition agents increase the negative charge on the fabric surface, so that the surface repels soil particles because these are also negatively charged

# Plants

Plant ingestion is a common cause of poisoning exposure in children under age of 5 in the United States, and a significant cause of toxicity in adults.

Studies have shown that many products of plant origin are available in numerous retail outlets سوق التجزءة and these are potentially toxic if misused. Moreover, children often see the bright berries of many plants and, perhaps believing they are fruits or confections, consume them. Sometimes the green, leafy foliage اوراق الشجر of some plants are items growing in the family garden.

In some cases, an actual plant part may not need to be ingested. Drinking water from a vase مزهرية containing plant stems may be sufficient to cause serious toxicity. In other instances, plants that are considered to be harmless have been treated with toxic insecticides, herbicides, or fertilizers may be consumed.

Poisonous species are those that contain components that, when small quantities are ingested, cause specific biochemical alteration or physiological symptoms.

Not all parts of some poisonous plants are toxic and the toxic principles may be present in the plant only during certain seasons or stage of growth. Slight variation in methods used to prepare plants for intentional consumption may make a tremendous difference in whether or not the final preparation is safe or toxic. The specific plant or plant parts ingested, therefore, must be identified before one can formulate an opinion on its toxicity and the best way to manage the ingestion.

**Management of the plant-poisoned patient**

All plant ingestions must be considered potentially toxic until shown otherwise. Identification of the plant is often the most difficult task. The parent of a child who has ingested a plant may be completely unaware of its identity, or where the child found it.

For most plant ingestions, management consists of demulcent therapy. Many plants contain constituents that are extremely irritating to the oral mucus membranes, but not damaging to other tissues. Ice cream, milk, or a frozen confection will soothe most irritations of the GI tract associated with plant ingestions. The victim should be observed closely over the next 12 to 24 hr to assure that no additional symptoms appear as a result of delayed absorption or delayed toxic effects.

If the plant in question has been identified as toxic or has toxic potential or enough of a plant has been ingested to cause concern, gastric decontamination should be considered. Ipecac-induced emesis is the preferred method.

Many plants have a powerful emetic action of their own may cause profuse, spontaneous vomiting. If this occurs, the vomitus should be examined. Demulcent may be given at this time if needed.

Gastric lavage is limited in value for decontamination the stomach after a plant ingestion. Most undigested plant parts will not fit though the opening of even the largest orogastric tube. However, after the ipecac-induced emesis, gastric lavage may be performed to wash out any remaining poison and may be useful as long as ingestion occurred within the past 5 to 6 hr.

Activated charcoal is generally not an acceptable alternative to syrup of ipecac in gastrointestinal decontamination of a poisonous plant Adsorption of the toxic principles onto activated charcoal is dependent on these components existing as a fine powder or in solution. A leaf, berry or other coarse plant part that contain toxic principles probably will not release them until it is sufficiently digested. It is better to remove the entire plant part, if at all possible. Activated charcoal may be given after ipecac-induced emesis or gastric lavage to adsorb residual poison.

Saline cathartics may be given to hasten removal of ingested plants and after administration of a slurry of activated charcoal.

# Common poisonous plants

## Arum-family plants

Of all the houseplants, those of the Arum family are responsible for most frequently encountered plant ingestions or exposure. These plants include caladium or fancy leaf, elephant's ear and philodendron.

These plants all possess large leaves that contain tiny needle-sharp crystals of calcium oxalate, arrange parallel in compact bundles called raphides or in star like clusters called druses. Biting into a leaf results in pain as these crystals pierce يثقب the sensitive membranes of the mouth and lips. A second bite is usually avoided and significant systemic toxicity is rare.

Ingestion of plants from the Arum family results in localized edema, pain, and irritation. Occasionally, the tongue swells to the point that swallowing and speaking become difficult. If swelling of the tongue, pharynx, or larynx become severe enough as to hamper يعيق breathing or induce choking خانق, emergency medical treatment is necessary to maintain a patent airway.

Management of ingestions of Arum family plants is supportive and symptomatic.

## Christmas plants

Another group of houseplants reported to entice children includes a variety of plants commonly seen around the holidays such as poinsettia, holly, mistletoe, and Jerusalem cherry.

Jerusalem cherry (solanum pseudocapsicum) has bright orange cherry-like ornamental berries that contain the extremely toxic substance solanine. Solanine is a glycoalkaloid found also in the nightshade plants which produce intense gastrointestinal symptoms. The glycoalkaloid is hydrolyzed by gastric acid to alkamine, which has toxic action upon the cardiovascular and nervous system to cause circulatory collapse and respiratory distress, as well as drowsiness and restlessness.

All ingestions of Jerusalem cherry or any other Solanacene plant must be treated aggressively. Spontaneous vomiting will most likely occur. If it does not, however, gut decontamination, using syrup of ipecac, Lavage, activated charcoal, and cathartics

should be considered. In addition, good supportive and symptomatic care is required. Poinsetti is nontoxic.

# Cardiotoxic plant

Ingestion of foxglove or oleander resembles digoxin poisoning, with gastrointestinal and cardiac symptoms predominating. Intoxication requires serial monitoring of the electrocardiogram and serum potassium, since hyperkalemia may be present. Ingestion of even small quantities of these plants must be treated aggressively. Gastric decontamination with syrup of ipecac followed by serial doses of activated charcoal and supportive care is recommended.

# Caster bean

The plant (Ricinus communnis) is grown for its oil and as ornamental زخرفي shrub. Castor beans (seeds) are quite attractive to children, and ingestion of a single chewed seed may be fatal. Un-chewed seed often pass through the GI tract without causing clinical problems.

Castor beans contain the deadly phytotoxin ricin. Ricin consist of two polypeptide chains, one of which binds to intestinal cells and the other is an inhibitor of protein synthesis. Ordinarily inactivated by heat during production of castor oil, ricin may cause gastrointestinal hemorrhage. The primary target organs for inhibition of protein synthesis include the kidney, liver, and pancreas.

Symptoms of poisoning include intense gastrointestinal irritation, with burning in the mouth and throat. Muscle weakness, general malaise, reduced reflexes, convulsions, and dyspnea are also reported.

# Rhubarb

The leaf, but not the stem, of the rhubarb plant (Rheum rhaponticum) contain oxalic acid. The leaf is occasionally used to embellish تجميل salads, or cooked as a side dish. Heating does not destroy the toxic principle. Once absorbed it combined with calcium from the blood to form the insoluble substances calcium oxalate, which may crystalize in the renal tubules. If severe, this precipitate may block the tubules to cause acute renal failure. A single bite of rhubarb leaf is usually not sufficient to cause systemic toxicity, but multiple bite may be.

Symptoms of oxalic acid poisoning include nausea and vomiting, weakness, and muscle cramps.

Ingestion should be treated with emesis, followed with milk (a source of calcium) or calcium hydroxide solution (lime water). Calcium combines with oxalic acid in the GI tract to form insoluble calcium oxalate. Calcium salt may be administered intravenously to replace calcium that might be last from the blood. Intravenous accumulation of the precipitate in the renal tubules.

# Nightshade

Deadly nightshade (Atropa belladonna) is the plant to seriously avoid. Atropine at a concentration of 0.25% to 0.5% is found in this species, and can be lethal if ingested in sufficient quantity.

Symptoms of poisoning and their management are the same for jimsonweed.

# Jimsonweed

Jimsonweed (Datura stramonium), also known as thorn apple تفاح الشوك and angel's trumpet.بوق الملاك Unilateral mydriasis has been reported in farmers working with harvesting equipment, indicating poisoning. Children have been fatally poisoned by eating the flowers, and teenagers by ingesting a concentration made from infusion seeds in water.

The fruit pods that appear in the fall each contain 50 to 100 brown-black seeds. It is these seeds that are most toxic, with 10 seeds containing approximately 1 mg atropine. Other alkaloids include hyoscyamine, present throughout the plant in varying proportions. As little as 4 to 5 g of the leaves or seeds can be fatal.

Symptoms of jimsonweed poisoning include typical manifestations of anticholinergic poisoning, including blurred vision, CNS stimulation, euphoria, delirium, terrifying halucinations, tachycardia, hyperthermia, and coma.

Jimsonweed intoxication must be treated quickly. After decontamination, physostigmine salicylate is given intravenously. Physotigmine is a reversible cholinesterase inhibitor that promotes accumulation of endogenous acetylcholine.

# Cyanogenic plants

Several plants contain cyanogenic glycosides, such as amygdin in their leaves, stems, bark, and seed pits, but not in their pulpy, edible fruits. When ingested, the glycosides are hydrolyzed in alkaline medium to hydrocyanic acid. Mild ingestion may require only gastric decontamination and support care.

# Mushrooms

Poisoning by mushrooms is unpredictable, since different species may produce variable symptoms and require various treatment. Some are poisonous only if eaten raw, and others if ingested during certain stages of growth. Even differences in soil composition may significantly influence the potential to cause toxicity.
 Aminita mushrooms contain a mixture of thermostable cyclopeptides, including phalloidin, phalloin, and amanitin congeners المتجانسات.

### Characteristics of mushroom poisoning

Symptoms of poisoning vary widely among various species of mushrooms. Delayed onset of symptoms usually means that ingestion of A. palloides is likely. Most nonlethal mushrooms produce symptoms early after ingestion.

The characteristics of cyclopeptides in A. phalloides can be described in three stages. In the early stage 6 to 24 hr, there is generally an abrupt onset of severe abdominal pain associated with profuse, cholera-like diarrhea and emesis. The next 24 to 48 hr is usually marked by a period of apparent recovery. During this time, cellular destruction of the kidney and liver is ongoing. The third phase occurs about 3 to 5 days post-ingestion, and is characterized by hepatocellular damage and renal insufficiency. Circulatory failure manifests later, with the victim showing signs of

becoming jaundice and lapsing انتكاس into a hepatic coma within a week. Death occurs in 4 to 7 days of mushroom consumption.

**Management of mushroom poisoning**

Management of poisonous mushroom ingestion should consist of good supportive care, including fluid replacement and correction of metabolic disturbances.

For A. muscaria , if ingestion is suspected, administer ipecac and observe for signs and symptoms for at least three hours. For A. phalloides if the time since ingestion is less than 4 hr, ipecac- induced emesis may be beneficial. Since signs and symptoms are delayed, it is unlikely to detect poisoning before 4 hr. Activated charcoal and cathartics have been recommended.

Penicillin G and corticosteroids have also been used. Given intravenously, they may limit hepatotoxicity by competing with amanitin for binding on serum proteins, there by leaving more toxic free for renal excretion.

# Arum-family plants
# Elephant' ear

# Arum-family plants
## Caladium



# Arum-family plants
## Philodendron

# Christmas plants

## Jerusalem cherry

# Christmas plants

## poinsettia (non toxic)



# Cardiotoxic plant, Foxglove

# Caster bean



www.aliexpress.com/store/819566

# Rhubarb

# Nightshade



# Jimsonweed

# Mushrooms



Amanita phalloides, Grüner Knollenblätterpilz © www.mykonet.ch, Sepp Keller

# Venomous animals

Acute poisoning by venomous animals is common in tropical and subtropical climates. The precise chemical composition and pathophysiology of animal venoms is incompletely known and so the range of specific treatment is limited. The general principles of intensive supportive therapy should be followed in the management of these poisonings.

## Snakebite

There are over 3000 species of snake in the world, but only about 250 are venomous. Poisonous snakes may be divided into two types according to the types of fangs:
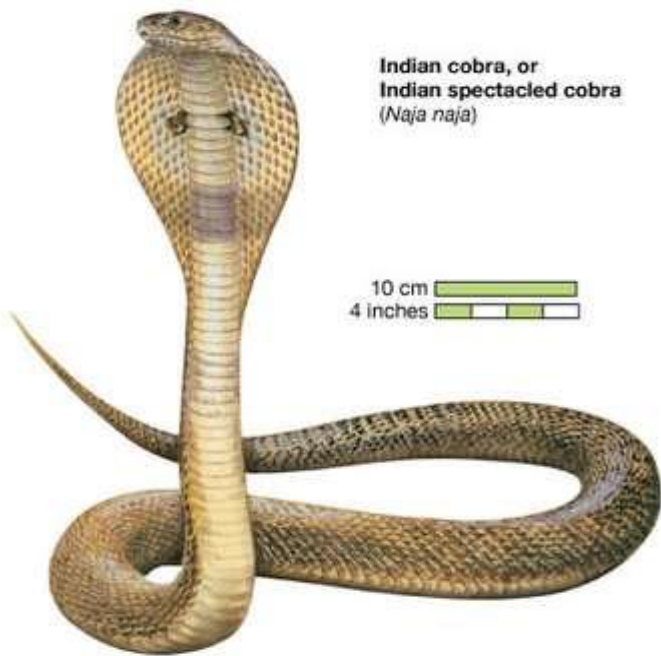
| Family | Common names |
|---|---|
| Viperides     (foldable fangs) | Rattlesnakes ام الاجراس |
| | Saw scaled vipers  (In Iraq) |
| | Desert horn Viper  (In Iraq) |
| Elapidae        (fixed fangs) | Cobras (in Iraq) |
| | Mambas |
| | Sea snakes |



**Saw scaled viper**

**Desert horn viper**



Indian cobra, or
Indian spectacled cobra
(*Naja naja*)

10 cm
4 inches

© Encyclopædia Britannica, Inc.

**Cobra**

**Rattlesnake**

Every year 30000 people die from snakebites in the world, the great majority being in India and South-East Asia. In Europe the mortality is less than I per cent of the total and in the United Kingdom deaths from this cause are rare.

Snake bites occur most often in children, who have disturbed the snakes as a result of curiosity, or in men, who have disturbed them in the course of their work.

Snake venomous contain <u>enzymes, non-enzymatic proteins and other substances such as acetyl choline and 5-hydroxytryptamine</u>. Apart from the direct effects of these compounds they also provoke tissue production of other inflammatory agents such as <u>kinins, histamines and slow reacting substance</u>.

The severity of the toxic effects of snake bite depend on the type and quantity of venom injected. This in turn depends on the age, size and sex of the snake and bites occurring at night are more venomous than during the day. In the case of hibernating snakes, the venom is particularly potent just after hibernation is over.

# Clinical features

Venomous snakes leave characteristically two or occasionally one fang mark, whereas bites from non-poisonous snakes produce a semi-circular set of tooth marks

1. **Local effects:** these may be of no more than a mild inflammatory reaction or slight bruising. Tissue necrosis is particularly likely, however, in bites from Viperidae and Crotalidae the necrosis occurs several days after the bite, but is preceded by marked pain and swelling.
2. **Systemic effects:** venom from Crotalidae, Viperidae and Elapidae may cause the following effects.
   **GIT:** nausea and vomiting.
   **CVS:** hypotension is common due to vasodilatation and hypovolaemia.
   **CNS:** drowsiness, muscular weakness, which may result in dipilopia and difficulty with speech and swallowing. In severe cases ventilatory paralysis may occur, and coma and convulsions may develop. Sensory function remains normal.
   **Haematological system:** increased blood coagulability may result from rattlesnake bite, whereas with the Malayan Pit Viper a prolonged coagulation defect with extensive ecchymosesكدمة and general bleeding tendency may occur due to a very low plasma fibrinogen.
   > Sea snake bite characteristically result in marked polymyositis. Muscle enzymes and plasma potassium levels are elevated and myoglobinuria with renal failure may occur. The muscle damage is so severe that patients may have marked weakness for several months.

   **Treatment**
   There are a number of popular misconception regarding the management of snake bite. There is no evidence that there is any value in the use of tourniquets or incision and suction of the injection site, and in unskilled hands these maneuvers may be even harmful.
   Cooling of the bite area, the administration of antihistamines and corticosteroids have all been advocated but none of these are

considered helpful now in snake bite. These methods of treatment, therefore, should be avoided. Recommended treatment consist of:

1. Careful cleansing of the wound with sterile saline or water.
2. Immobilisation is valuable treatment, particularly for the local effects.
3. Intensive supportive therapy.
4. Inject tetanus antitoxin, or if the victim has previously been inoculated against tetanus, a booster dose of tetanus toxoid.
5. Inject crystalline penicillin by I.M.
6. Sedation and analgesic may be required.
7. Antivenins .

As snake venoms are largely protein, they are antigenic. Many antivenins are polyvalent containing antibodies to several venoms. They are ineffective to certain viper and elapidine venoms, and often provoke serious allergic reactions which may be fatal. Their use, therefore, must be considered very carefully.

Antivenins are indicated only when systemic effects developed or when extensive local tissue damage is presented. A test dose should always be given before administrating the full therapeutic dose.

## Insect bites

Stings from ants, bees, wasps and hornets seldom cause severe toxic effects apart from local pain and swelling, unless the bite is on the mouth or tongue when the associated swelling may cause respiratory distress. Rarely deaths have been reported from very extensive stings or more commonly due to severe allergic reactions, especially to bee stings. Bee stings are alkaline, while wasp, and hornet stings are acid. If the local reaction is marked an antihistamine given systemically is helpful. In severe allergic reactions S.C. adrenaline 1:1000 (0.5ml) and hydrocortisone 100 mg I.V. may be life-saving.

# Spider bites

poisonous spiders live in warm climates. The black Widow spider and the Funnel Web spider are quite frequent causes of poisonous bites. They commonly inhabit تعيش outhouses المباني, basementsالسراديب and foundationsاساس of houses and outside lavatoriesالمراحيض, children and workmen are most often the victims. Death occurs in up to 6 per cent of cases, especially in young children.



**Deady Daesh spider (Black widow)**

## Clinical features

The initial bite may be unnoticed. Within about an hour, however, the following occur:

- Locomotor disorders: generalised muscular pains and stiffness, burning sensation of feet.
- Gastrointestinal system: nausea and vomiting. If there is marked abdominal rigidity a mistaken diagnosis of peritonitis may be made.
- Salivation.
- Metabolic disorders:  pyrexia and sweating.
- Leucocytosis, mild hypertension and a macular rash may also occur.

**Treatment**

1. Cleanse the bite with sterile saline or water.
2. Analgesics for relief of pain. 10-20 ml of 10 per cent calcium gluconate by slow IV injection.
3. If secondary infection occurs systemic antibiotics.
4. Intensive supportive therapy.
5. If the systemic features are severe administer the specific antivenin, if this is available.

Camel spiders can grow to be as large as dinner plates. It can traverse desert sand at speeds up to 25 MPH, making screaming noises as they run. It can jump several feet in the air. Camel spiders eat the stomachs of camels and lay their eggs there, hence the name "camel spider."

Camel spiders eat or chew on people while they sleep. Their venom numbs the area so people can't feel the bites: Camel spiders are not venomous, and though their bites are painful, they are not deadly to humans.



**Camel spider**

## Scorpions

These nocturnal creatures live in the tropics or sub-tropics. The sting is rarely fatal.

**Clinical features**

Marked local pain occurs after the sting. Subsequently sweating, numbness and hyperaesthesiae may develop. In severe cases, central respiratory and cardiac depression may be marked.

**Treatment**

1. Cleanse the sting.
2. Analgesic for the pain.
3. Intensive supportive therapy.


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**Androctonus crassicauda (In Iraq, Dangerous)**

# Venomous sea animals

## Sting rays السمك الادغ

These fishes live in warm seas and they present a hazard usually to bathers, who inadvertentlyدون قصد stand on the fish lying in the sand. The venom contains a thermolabile toxin. Fatalities are uncommon and usually result from extensive injury, especially if the sting sheath remains in the wound.

**Clinical features**

Usually the sting results in a jagged wound and severe local pain. Systemic features may develop and include hypotension, oculogyric crises and convulsions.

**Treatment**

Incision and suction of the wound should not be done.

1. Careful cleansing of the wound with surgical exploration if the sting sheath has been retained. The wound should be immersed in the hottest water bearable in an attempt to destroy the toxin. Local anaesthetic, systemic analgesic and corticosteroids are often helpful.
2. Intensive supportive therapy in severe cases.

# Jelly fishقناديل البحر



## Clinical features

Local pain is the main effect. <u>Physalia</u> are more sever and pain may be very marked and generalised muscle pains, colic, nausea and breathlessness with cyanosis may result. Death from physalia stings may occur rapidly within minutes or be delayed for some hours.

## Treatment

1. Any tentacles مجسstill adherent to the bather must be removed with care, by adhesive tape, and on no account should they be brushed off with a bare hand as the tentacles may be still capable of delivering a sting for many hours after removal from the water.
2. Analgesic for pain, local anaesthetic cream are effective.
3. Intensive supportive therapy.

# Analytical and Forensic Toxicology

## History

Ancient Egyptians and Grecians reported poisonings due to herbs, plants and food. Opium, arsenic and hydrocyanic acid were used throughout Europe during the middle ages. Everything could be a poison. However, the dose determines the poison.

## Analytical toxicology

Involves the application of tools of analytic chemistry to the qualitative and/or quantitative estimation of chemicals that may exert adverse effects on living organisms and other specimensعينات.

## Forensic toxicology

Involves the use of toxicology for the purpose of law: by far the most common application is to identify any chemical that may serve as a causative agent in inflicting death or injury on humans or in causing damage to property.

## Ideal poison characteristic

1. Test-less
2. Odorless
3. Colorless
4. Readily soluble
5. Delayed onset of action
6. Undetectable
7. Low dose lethality
8. Easily obtained
9. Mimics a natural disease
10. Chemically stable before administration
11. Decomposes after death
12. Found in environment

**Role of forensic toxicology**

The duties of a forensic toxicologist in postmortem investigation include the qualitative and quantitative analysis of drugs or poisons in biologic specimensعينات collected at autopsyتشريح الجثة and the interpretation of the analytical findings with respect to the physiologic and behavioral effects of the detected chemicals on the deceasedالمتوفيat the time of injury and/or death.

**Toxicological investigation of a poison death**

The toxicological investigation of a poison death may be divided onto three steps: (1) obtaining the case history and suitable specimen (2) the toxicological analyses, and (3) the interpretation of the analytical findings.

1- Case history and specimens

Today, thousands of compounds are readily available that are lethal if ingested, injected, or inhaled. Usually a limited amount of specimen is available on which to perform analyses; therefore, it is imperative الزاميthat before the analyses are initiated, as much information as possible concerning the facts of the case be collected. The age, sex, weight, medical history, and occupation of the decedent as well as any treatment administered before death, the gross autopsy finding, the drugs available to the decedent, and the interval between the onset of symptoms and death should be noted.

Specimens of many different body fluids and organs are necessary, as drugs and poisons display varying affinities for body tissues. It is paramount اساسيthat the handling of all specimens be authenticated and documented. Fluid and tissues should be collected before embalming, as this process will or chemically alter the poisons present, rendering their detection difficult or impossible. Although forensic toxicology laboratories typically receive blood, urine, liver tissue, and/or stomach contents for identification of xenobiotics, alternative samples are also used such as bone marrow, hair, vitreous humor, nail, and skeletal remain.

2- Toxicological analysis

Before the analysis begins, several factors must be considered including the amount of specimen available, the nature of the poison sought, and the possible biotransformation of the poison. In cases involving oral administration of the poison, the gastrointestinal (GI) contents are analyzed first because large amount of residual unabsorbed of poison may be present. The urine may be analyzed next, as the kidney is the major organ of excretion of most poisons and high concentrations of toxicants and/or their metabolites often are present in urine. After absorption from GI tract, drugs or poisons are carried to the liver before

entering the general systemic circulation; therefore the first analysis of an internal organ is conducted on the liver.

The analysis may be complicated by the normal chemical changes that occur during the decomposition of a cadaver. The autopsy and toxicological analysis should be stated as soon after death as possible. However, many poisons such as arsenic, barbiturates, mercury, and strychnine are extremely stable and may be detected many years after death.

Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) are the most widely applied methodology in toxicology and are generally accepted as unequivocal identification for all drugs.

3- Interpretation of analytical results

Once the analysis of the specimens is complete, the toxicologist must interpret his or her findings with regard to the physiologic and behavioral effects of the toxicants on the decedent at the concentration found. Specific questions may be answered such as the route of administration, the dose administered, and whether the concentration of the toxicant present was sufficient to cause death or alter the decedent's action enough to cause his or her death.

The presence of large amounts of drugs and/or poisons in the GI tract and liver indicates oral ingestion, while higher concentration in the lungs other than in other visceral organs can indicate inhalation or intravenous injection.

## Criminal poisoning of the living

Over the past few decades, forensic toxicologists have become more involvement in the analyses of specimens obtained from living victims of criminal poisonings. Generally this increase in testing is a result of two types of cases: (1) administration of drugs to incapacitate يجعله عاجز victims of kidnapping, robbery, or sexual assault and (2) poisoning as a form of child abuse.

## Forensic urine drug testing

Forensic urine drug testing (FUDT) differs from other areas of forensic toxicology in which urine is the only specimen analyzed and testing is performed for a limited number of drugs and metabolites. A confirmation analysis in FUDT certified laboratories is performed by GC-MS and LS-MS. FUDT results are reported only as positive or negative for the drug sought.

Many individuals who are subject to regulated urine testing have devised techniques to mask their drug use either by physiologic means such as the ingestion of diuretics or by attempting to adulterate the specimen directly with bleach, vinegar, or other products that interfere with the initial immunoassay tests. Thus, specimens are routinely tested for adulteration by checking urinary pH, creatinine, and specific gravity and noting an unusual color or smell.

**Human performance testing**

Forensic toxicology testing also include the determination of the presence of ethanol and other drugs and chemicals in blood, breath, or other specimens and the evaluation of their role in modifying human performance and behavior. The most common application of human performance testing is to determine impairment while driving under the influence of ethanol or drugs.

**Courtroom testimony**

The forensic toxicologist often is called upon to testify in legal proceedings as an 'expert witness'. An expert witness may provide two types of testimony: objective testimony and 'opinion'. Objective testimony by a toxicologist usually involves a description of his or her analytical methods and findings. When a toxicologist testifies as to the interpretation of his or her analytical results or those of others, that toxicologist is offering an 'opinion'.

**Role in clinical toxicology**

Analytical toxicology in a clinical setting plays a role very similar to its role in forensic toxicology. As an aid in the diagnosis and treatment of toxic incidents, as well as in monitoring the effectiveness of treatment regimens, it is useful to clearly identify the nature of the toxic exposure and measurement of the toxic substances that has been absorbed. Frequently, this information, together with the signs and symptoms observed to the anticipated متوقع effects of the toxic agent. This may permit a clinical judgment as to whether the treatment may be vigorous and aggressive or whether simple observation and symptomatic treatment of the patient are sufficient.

**Role in therapeutic monitoring**

A dosage amount was selected and administered at appropriate intervals based on what the clinician had learned was generally tolerated by most patients. If the drug seemed ineffective, the dose was increased; if toxicity developed, the dose was decreased or frequency of dosing was altered. At times, a different dosage form might be substituted. Establishing an effective dosage regimen was particularly difficult in children and the elderly.

The factors responsible for individual variability in responses to drug therapy include the rate and extent of drug absorption, distribution, and binding to body fluid, rate of metabolism and excretion, pathologic condition, and interaction with other drugs.