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Assignment
Questions
1. With relevant examples, describe the classification of poisonous substance
2a. A hydrophobic substance Q was orally administered on an individual. Discuss from the point of entry, the fate of the said substance.
b. what would have been different if the substance had been hydrophilic in nature
3a. In a tubular form list 20 poisonous substance and their respective antidotes.
b. explain ways by which the clinical effects of poisons can be studied.
Answer

1. Classification of poisonous substance.

A) According to the site and mode of action

a. local Action

i. Corrosive: -Strong Acid: mineral acid: eg H_2SO_4, HCl
Organic acid:Carbolic, oxalic,acetic,salicylic

- Strong alkali: Hydrates and carbonates of sodium, potassium and ammonia
- Metallic salts: Mercuric Chloride, KCN,

ii. Irritant

- Agricultural
- Inorganic: +Nonmetallic: P, Iodine, Cl, bromine
  +Metallic: Arsenic, Antimony, Pb, Cu, Zinc
  +Mechanical: Glass, Diamond dust, Hair
- Organic: +Animal: Snakes, insects Cantharides
  +Vegetable: Abrus, Castor, Croton,Calotropis

b. Systemic Action

i. Cerebral

- Somniferous: opium and its alkaloids, Barbiturates.
- Inebriant (Intoxicant): Alcohol, ether, Chloroform.
- Psychotropic: AD: TCAD, Amphetamines, Caffeine, MAOI
  Neuroleptics: Phenothiazenes, thioxanthenes
  Hallucinogens: LSD, Phencyclidine, psilocybe
- Deliriant: Dhatura, Belladona, Hyocyamus, cannabia Indica.
- Hallucinogens

ii. Spinal

- Strychnos Nux Vomica
- Gelsemium

iii. Peripheral Nerves

- Local Anaesthetics: Cocaine, Procaine.

- Relaxants (curare)

iv. CNS DEPRESSANTS

- Alcohols
- General anaesthetics
- Opioid analgesics
- Sedative hypnotics

Sedatives are those drugs that decrease activity, moderate excitement and exert a calming effect. Hypnotics produce drowsiness and facilitate a state of sleep, resembling natural sleep. Examples are: Barbiturates, Benzodiazepines, Non barbiturates, Alcohols, Propanediols, Glutethimide, quinazolines, methaqualone

v. Cardiac Poisons: KCN, NaCN, Digitalis, Aconite, Nicotine, Quinine, Oleander

vi. Asphyxiants: Carbon Dioxide, CO, hydrogen sulphide

c, Miscellaneous: Food Poisons.

B. Classification of poison according to motive or nature of use

1. Homicidal: Arsenic, Aconite, Digitalis, Abrus Precatorius, Strychnos nux vomica.
2. Suicidal: Opium, Barbiturate, Organophosphorus, carbolic acid, copper sulphate.
3. Accidental: Aspirin, organophosphorus, copper sulphate, snakes bite, Ergot, CO, CO_2, H_2S.
4. Abortifacient: Ergot, Quinine, Calotropis, Plumbago.
5. Stupefying agent: Dhatura, cannabis, chloral hybrate.
6. Agents used to cause bodily injury: Corrosive acids and alkalies.
7. Cattle Poison: Abrus precatorius, Calotropis, plumbago.
8. Used for malingering: semicarpus anacardium
9. Arrow Poison: Abrus precatorius, Calotropis, Aconite, Strychnos nux vomica.
10. Aphrodisiacs

2a. The hydrophobic substance Q is a water insoluble substance and the route of administration is oral. The fate of the substance Q start with absorption and assimilation into the bloodstream, distribution into the cell, metabolism and excretion.

Absorption is defined as the passage of a drug from its site of administration into the plasma.

ORAL ADMINISTRATION

Most drugs are taken by mouth and swallowed. Little absorption occurs until the drug enters the small intestine, although a few non-polar drugs applied to the buccal mucosa or under the tongue are absorbed directly from the mouth.

DRUG ABSORPTION FROM THE INTESTINE

For most drugs, the mechanism of absorption is the same as for other epithelial barriers, namely passive transfer at a rate determined by the ionization and lipid solubility of the drug molecules. Intestinal drug absorption depends on carrier-mediated transport rather than simple lipid diffusion.

The main factors that affect gastrointestinal absorption are:

- gut content (e.g. fed versus fasted)
- gastrointestinal motility
- splanchnic blood flow
- particle size and formulation
- physicochemical factors including some drug interaction

Bioavailability and bioequivalence

To get into the systemic circulation, for example from the lumen of the small intestine, a drug must not only penetrate local barriers such as the intestinal mucosa, it must also run a gauntlet of inactivating enzymes in the gut wall and liver, referred to as 'presystemic' or 'first-pass' metabolism or clearance. The term *bioavailability* is used to indicate the fraction (*F*) of an orally administered dose that reaches the systemic circulation as intact drug, taking into account both absorption and local metabolic degradation. Bioavailability relates only to the total proportion of the drug that reaches the systemic circulation and neglects the rate of absorption.

Bioequivalence: two proprietary preparation of a drug are said to be bioequivalent if they exhibit the same bioavailability when administered in equal doses.

FIRST-PASS (PRESYSTEMIC ['FIRST-PASS'] METABOLISM)

Some drugs are extracted so efficiently by the liver or gut wall that the amount reaching the systemic circulation is considerably less than the amount absorbed. This is known as presystemic (or first-pass) metabolism and reduces bioavailability, even when a drug is well absorbed.

Presystemic metabolism is important for many therapeutic drugs.

Hydrophobic substances can easily diffuse across the lipid bilayer of the cell membrane

Drug molecules usually exist both in free solution and in bound form; furthermore, drugs that are weak acids or bases will exist as an equilibrium mixture of the charged and uncharged forms, the position of the equilibrium depending on the pH. The equilibrium pattern of distribution between the various compartments will therefore depend on:

- permeability across tissue barriers
- binding within compartments
- pH partition
- fat : water partition.

The major compartments are:

– plasma (5% of body weight)
– interstitial fluid (16%)
– intracellular fluid (35%)
– transcellular fluid (2%)
– fat (20%).

To enter the transcellular compartments from the extracellular compartment, a drug must cross a cellular barrier, a particularly important example being the blood–brain barrier

The Blood Brain Barrier

The barrier consists of a continuous layer of endothelial cells joined by tight junctions and surrounded by pericytes. The brain is consequently inaccessible to many drugs whose lipid solubility is insufficient to allow penetration of the blood–brain barrier. However, inflammation can disrupt the integrity of the blood–brain barrier, allowing normally impermeable substances to enter the brain.

- Volume of distribution (*V*d) is defined as the volume that would contain the total body content of the drug at a concentration equal to that in the plasma.
- Lipid-soluble drugs reach all compartments and may accumulate in fat.
- For drugs that accumulate outside the plasma compartment (e.g. in fat or by being bound to tissues), *V*d may exceed total body volume

Drug elimination is the irreversible loss of drug from the body. It occurs by two processes: *metabolism* and *excretion*. Metabolism consists of anabolism and catabolism, i.e. respectively the build-up and breakdown of substances by enzymatic conversion of one chemical entity to another within the body, whereas excretion consists of elimination from the body of drug or drug metabolites. The main excretory routes are:

- the kidneys
- the hepatobiliary system
- the lungs (important for volatile/gaseous anesthetics).

Most drugs leave the body in the urine, either unchanged or as polar metabolites. Some drugs are secreted into bile via the liver, but most of these are then reabsorbed from the intestine. Hydrophobic substances are not eliminated efficiently by the kidney. Consequently, most hydrophobic drugs are metabolized to more polar products, which are then excreted in urine. Drug metabolism occurs predominantly in the liver, especially by the cytochrome P450 (CYP) system. Some P450 enzymes are extra hepatic and play an important part in the biosynthesis of steroid hormones.

DRUG METABOLISM

Drug metabolism involves two kinds of reaction, known as phase 1 and phase 2, which often occur sequentially. In both phases, drug is inactivated and modified into hydrophilic metabolite and also allows the hydrophobic substance to be excreted by the kidney or in the bile.

PHASE 1 REACTIONS

the drug is transformed into a polar metabolite (mostly through oxidation by the cytochrome P450 system and this allows phase two take place.

PHASE 2 REACTIONS

Phase 2 reactions involves coupling the metabolite with glucuronic acid, acetyl group (metabolism of isonizid), sulfate, amino acid or glutathione.

DRUG AND METABOLITE EXCRETION

BILIARY EXCRETION AND ENTEROHEPATIC CIRCULATION

Liver cells transfer various substances, including drugs, from plasma to bile by means of transport systems similar to those of the renal tubule; these include organic cation transporters (OCTs), organic anion transporters (OATs) and P-glycoproteins (P-gp). Various hydrophobic drug conjugates (particularly glucuronides) are concentrated in bile and delivered to the intestine, where the glucuronide can be hydrolysed, regenerating active drug; free drug can then be reabsorbed and the cycle repeated, a process referred to as enterohepatic circulation. The result is a 'reservoir' of recirculating drug that can amount to about 20% of total drug in the body, prolonging drug action

2b. hydrophilic substance differ from hydrophobic in their excretion pattern. Hydrophobic substance pass through the blood into the liver where it is metabolized and conjugated before excretion can be possible while hydrophilic substance pass through the blood into the kidney.

RENAL EXCRETION OF DRUGSAND METABOLITES

RENAL CLEARANCE

Elimination of drugs by the kidneys is best quantified by the renal clearance. This is defined as the volume of plasma containing the amount of substance that is removed from the body by the kidneys in unit time. Drugs differ greatly in the rate at which they are excreted by the kidney. Three fundamental processes account for renal drug excretion:

1. Glomerular filtration
2. Active tubular secretion
3. Passive reabsorption (diffusion from the concentrated tubular fluid back across tubular epithelium).

GLOMERULAR FILTRATION

Glomerular capillaries allow drug molecules of molecular weight below about 20kDa to pass into the glomerular filtrate. Plasma albumin (molecular weight approximately 68kDa) is almost completely impermeable, but most drugs – with the exception of macromolecules cross the barrier freely. If a drug binds to plasma albumin, only free drug is filtered. If, a drug is approximately 98% bound to albumin, the concentration in the filtrate is only 2% of that in plasma, and clearance by filtration is correspondingly reduced.

TUBULAR SECRETION

Up to 20% of renal plasma flow is filtered through the glomerulus, leaving at least 80% of delivered drug to pass on to the peritubular capillaries of the proximal tubule. One of these, the OAT, transports acidic drugs in their negatively charged anionic form (as well as various endogenous acids, such as uric acid), while an OCT handles organic bases in their protonated cationic form. The OAT carrier can transport drug molecules against an electrochemical gradient, and can therefore reduce the plasma concentration nearly to zero, whereas OCT facilitates transport down an electrochemical gradient.

DIFFUSION ACROSS THE RENAL TUBULE

Water is reabsorbed as fluid traverses the tubule, the volume of urine emerging being only about 1% of that of the glomerular filtrate. Consequently, if the tubule is freely permeable to drug molecules, some 99% of the filtered drug will be reabsorbed passively down the resulting concentration gradient. Lipid-soluble drugs are therefore excreted poorly, whereas polar drugs of low tubular permeability remain in the lumen and become progressively concentrated as water is reabsorbed. Important group of drugs that are not inactivated by metabolism, the rate of renal elimination being the main factor that determines their duration of action. Least 80% of the drug delivered to the kidney is presented to the carrier, tubular secretion is potentially the most effective mechanism of renal drug elimination. Unlike glomerular filtration, carrier-mediated transport can achieve maximal drug clearance even when most of the drug is bound to plasma protein. Because filtration involves is osmotic movement of both water and solutes, it does not affect the free concentration of drug in the plasma. Thus the equilibrium between free and bound drug is not disturbed, and there is no tendency for bound drug to dissociate as blood traverses the glomerular capillary. The rate of clearance of a drug by filtration is therefore reduced directly in proportion to the fraction that is bound. In the case of active tubular secretion, this is not so because the carrier transports drug molecules unaccompanied by water. As free drug molecules are taken from the plasma, therefore, the free plasma concentration falls, causing dissociation of bound drug from plasma albumin. Secretion is only retarded slightly, even though the drug is mostly bound, because effectively 100% of the drug, both bound and free, is available to the carrier.

3a. Drugs and their antidote.

Name of drug	Antidote
1. Barbiturates	Charcoal
2. Penicillin	Epinephrine
3. Caffeine	Esmolol
4. Acetaminophen	Acetylcycteine
5. Cyanide poisoning	Methylene blue
6. Benzodiazepine	Flumazenil
7. Magnesium sulphate	Calcium gluconate
8. Morphine sulphate	Naloxone hydrochloride
9. Salicylates	Charcoal
10. Tricyclic depressant	Phyostigmine
11. Amphetamine	Propranolol
12. Arsenic	Dimercaprol
13. Fluorouracil	Leucovorine calcium
14. Quinidine	Sodium bicarbonate
15. Chloroqunine	Diazepam
16. Digitalis	Digibind
17. Coumadin	Vitamin k

18. Iron	Desferal
19. Mestinon	Atropine sulphate
20. Carbamate	Atropine

3b. in studying the clinical effect of poison, history from all available source should be taken before directed testing.

- History: this is done to identify the drug, time of exposure, type of exposure, amount, first aid treatment, allergies etc.
- In most cases, Laboratory testing provides limited help. Standard, readily available tests to identify common drugs of abuse often called tox screen are qualitative, not quantitative. These tests may provide false-positive or false-negative results, and they check for only a limited number of substances. Also, the presence of a drug of abuse does not necessarily indicate that the drug caused the patient's symptoms or signs (i.e., a patient who had recently taken an opioid may in fact be obtunded because of encephalitis rather than the drug).

Urine drug screening is used most often but has limited value and usually detects classes of drugs or metabolites rather than specific drugs. For example, an opioid urine immunoassay test does not detect fentanyl or methadone but does react with very small amounts of morphine or codeine analogues. The test used to identify cocaine detects a metabolite rather than cocaine itself.

For most substances, blood levels cannot be easily determined or do not help guide treatment. For a few substances (eg,acetaminophen, aspirin, carbon monoxide,digoxin, ethylene glycol, iron, lithium, methanol,phenobarbital, phenytoin, theophylline), blood levels may help guide treatment. Many authorities recommend measuring acetaminophen levels in all patients with mixed ingestions because acetaminophen ingestion is common, is often asymptomatic during the early stages, and can cause serious delayed toxicity that can be prevented by an antidote. For some substances, other blood tests (eg, PT [prothrombin time] for warfarin overdose, methemoglobin levels for certain substances) help guide treatment. For patients who have altered consciousness or abnormal vital signs or who have ingested certain substances, tests should include serum electrolytes, blood urea nitrogen (BUN), creatinine, serum osmolality, glucose, coagulation studies, arterial blood gases (ABGs), and liver function test(total protein, albumin, globulin, bilirubin). Other tests (eg, methemoglobin level, carbon monoxide level, brain CT) may be indicated for certain suspected poisons or in certain clinical situations.

For certain poisonings (eg, due to iron, lead, arsenic, other metals, or to packets of cocaine or other illicit drugs ingested by so-called body packers), plain abdominal x-rays may show the presence and location of ingested substances.

For poisonings with drugs that have cardiovascular effects or with an unknown substance, electroencephalography (ECG) and cardiac monitoring are indicated.

If blood levels of a substance or symptoms of toxicity increase after initially decreasing or persist for an unusually long time, a bezoar, a sustained-release preparation, or reexposure (ie, repeated covert exposure to a recreationally used drug) should be suspected.