INTRODUCTION TOXICOLOGY

Toxicology is the science of poisons. It entails the detection, quantitative estimation of poisons effects and mechanisms, absorption, distribution, tonical, kinetics, metabolism, antidotes (specific/non-specific).

Toxicology is the qualitative and especially the quantitative study of the injurious effects of the chemical and physical agents involving alterations of structure and response in living system s and includes application of findings of these studies to the evaluation of safety and prevention of injury to useful life form.

Toxicology can also be defined as that branch of pharmacology that deals with the undesirable effects of chemicals on living systems, from individual cells to complex ecosystem.

Scope

Its found in areas such as clinical medicine, legal medicino, occupational, medicine and hygiene, vet medicine, experimental pathology, new compound developmental and evaluation medicine.

Bonaventura ORFILIA (1787-1853) is recognized as father of toxicology from toxicology. He defined poison is any substance which when take into the body in a very small dose or applied in any kind of manner to a living body depraves health or entirely destroys life.

A poison can be almost anything. Paracelsus (1493-1511) wrote there's nothing that, not toxic the dose done make the a thing not poisonous

Wilham Withering said that poison small doses are the best medicines and useful medicines and useful medicines in large doses are poisons."

Does as well as portal of entry of poisons are factors influencing poisoning.

Toxins are proteinaceous susbstances produced from plant and animal origin as well as from micro-organisms

1) They are unstable
2) They are protein in nature
3) Produce antitoxins, against themselves when introduced into the body
4) Tolerance occurs

Classification of Toxins

- Phytotoxins - derived from plants
- Endotoxins - found within in bacteria
- Exotoxins - elalcorated by bacteria
- Mycotoxins - from fungi
- Zootoxins - from lower animals-snake, bee, scorpion

Venom is a zootoxin transmitted to man or animal by lower animals thru bite on stung.

Sources of Poisons

Plants animas, norganic 6 organic compounds can be grouped into 2 categories

Naturally occurring and Man made industrial contamination poisons.

- heavy metals
- Poisonous plant
- Venomous animals and insects.

Effects of toxicity

1) Direct effect: Toxicants or the has a direct action on the tissue e.g pouring of conc. H_2SO_4 on the skin brings about chemical injury.
2) Secondary effect: Malnutrition, may occur. Anaemia due to destruction of red cells, modification of hormones e.g Cyanide intake interacts with specific enzyme system causing tissue asphyxia.

Effect of poisons

1) can be Neurotoxin
2) can be teratogenic
3) can be carcinogenic
4) causes hypersensitivity reactions
5) causes metabolic alterations such as enzyme induction.

Mode of Action

1) High conc of a particular poison can cause direct damages non-specific actions cos of its conc that is high
2) Specific action
   - Trivalent Arsenic acid reacts with SH group in the tissue.
   - Cyanide interacts with cytochrome oxidase
   - Chromiam carcinogenic action cos it reacts with DNA

Factors influencing toxicity

- Toxicokinetics: absorption, distribution, metabolism, excretion
- Dose
- Physical and chemical nature of the poison and its interaction with other compounds.
- Mode and route of exposure
- Species
- Size, sex and ages of animal
- General state of health –malmourishment, hypoproteinemia
- Pressure and attitude
- Reserved functional capacity –specific organ being attacked.

There are 3 major portals thru which poisons get into the body viz: oral gut, respiratory tract/skin.

Storage serves in a protective way by delaying the action of the toxins by immobilizing the toxins into certain organs Iodine in thyroid glands DDT is stored in DD fat lead in bones.

The highest conc of any poison in the body does not necessarily exist in an organ/tissue upon which it exerts its maximum toxic effect e.g Lead in bones result in CNS disorders.

Nature of poison

Tetraethyl pyrophosphate, pyrekinin (plant product), Nicotine (Plant product), Difenphos (Synthetic).

Generally, living organisms produce the most toxic materials know. Compounds that have the same chemical nature will produce toxicity that resemble each other qualitatively i.e they may produce the same kind of symptoms but the intensity of toxicity.

Compounds also show variation in their inherent ability to cause toxics lead “u always cause chronic toxicity while Cyanide or organophosphate acute toxicity. Some compounds do not cause toxicity until when metabolized i.e metabolites are toxins e.g Parathion (an insectide) which is broker to Panaoxon a toxic compound. A process known as LETUAL SYNTHESIS.

Methanol intake results in production of formic acid and formaldehyde thereby resulting in blindness. To counter this effect, ethanol is used (has same reception site).

Interaction of Compounds

Antagonism – competitive or non competitive. 2 different types of poisons can cause antagonism

Additive interaction – 2 drugs will produce the sum of effects when used.

Make full clinical report for your PM finding and also for the specific poison involved. Send each specimen is separate glass container that is well saled and labeled. Clean container chemically with Chromic acid.

ANTIDOTAL THERAPY

2 Concepts exist on which procedures are based on

- Intercity of all chemicals in biological reaction is determined by the dose.
- The conc of a compound in any tissue ill depend on its ability to cross membrane, e.g toxicokinetics.

Aims of antolotal therapy

- Prevent further absorption or slow down rate of absorption.
- To increase the rate of termination of action of the poison at the effective site by increasing the rate of excretion.
- To criminate the threshold (2) which toxic effects are caused felt by administration of another compound that will oppose the action of the poison i.e antidote.
- Maintenance of vital body functions i.e reduce muscular activity reduce high fever, the CVS, CNS and renal functions.

3 classification of antidotal, therapy

a) General non-specific therapy

b) Specific therapy

c) Supportive therapy

a) Aim is to prevent further absorption of the poison and also increase rate of elimination/excretion e.g if skin is the portal of entry, wash copiously with H_2O, use not soap (detergent. If poison was ingested, remove traces of poison that loss around, try and prevent absorption by inducing vomittion. Gastric lavege can also be done when activated charcoal for absorption.
Purgatives can be administered if poison has gotten to intestine. Saline purgative is given Purgatives can be co-administered with absorption agent. If poison has been long increase rate of excretion by manipulating urine PH compounds (2) Salicyted if urine is alkalinized.

b) Peritoneal dialysis
Haemodialysis (artifical Kidney)
Haemoperfusion

c) Multiple dosing (pulse dosing) – intestinal dialysis
Ways of eliminating poisons from the body by administration of activated charcoal.

d) Ion trapping

Specific therapy

A specific compound counteracts the effect of the poison. Mechanism by which antidotes will act.

1) Rendering the poison inactive by formation of complex between the poison and antedote chelating agent form chelats e.g of chelators- British Antilewicides (dimecarprol) 2,3-demecaptopropanol. BAL in oil

- BAL is used in Rx of Gold, Arseamic et Mercury Poison
- $CaNa_2$ EDTA used in treating lead, blranium and Phitonium poisoning – Calcium Disodium Versenate ®
- Pralidoxime (protopam) – Rx of organophosphartes poisoning. It reactivates cholinesterase.
- Penicillamine (Cuprime ® , Depan ®) – Rx of copper, Lead Gold, demental mercury and Zinc.

Deferoxamin: Rx of Iron poisoning

Forms insoluble complex Fe which is easily eliminated

Protamine: Rx of heparin poisoning or over dose

2) Increases the rate of conversion of poison to a non-toxic product e.g
3) Blocking of metabolic formation of poison metabolites from non-toxic precursors.
Monoacetin: Rx of Fluonoacetate Poisoning
Acetylcystein (paracetamol) Rx of paracetamol poisoning
4) Increase the rate of excretion of the poison.

Chloride – bromide

Calcium salt – Radium Strontium

5) Competition

Between antidote and poisons compete for a specific neceptors e.g ii) Oxygen displaces Carbon monoxide from haemoglobin.

i) Neostignine: Rx of curare poisoning

ii) Vit K: Coumarin anticoagulants

iii) Naloxone complete with opiod for opiodveceptors

iv) Flumazenil
Yolumoine
Tolazolize
} Xylazine overdose

6. Blocking of receptors responsible for toxic sings e.g Antropine-organophosphates/ poisoning cholinesterase inhibitors.

7. Restoration of normal function by the antidote

B- advenergic docking agent e.g Propanoloti wed in

Rx of digitalis poisoning

Folinic acid- folic acid antagonists

Supportive Therapy

Administration is based on clinical signs e.g in increased temperature should be lowed.

Toxicology of Pesticides

Pesticides can be classified as

- Insecticides e.g Acarcides
- Fungicides
- Herbicides

INSECTICIDES

Most cases of poisoning is due to insecticide overdosing or repeated exposure to insecticides. They are used in control to ectoparasites. They are effective against ectoparasites and endoparasites. They are also effective against burrowing larves such as Gastrophilus. Insecticides

might also be successively used in Rx of mites. When used in animals, it is administered parenterally, or topically (pour on, dipping dusting of powder, spraying) or by injection. Most insecticides contain keratolytic agent which facilitates the absorption of insecticides topically.

For an ideal insecticides, such an insecticides must be able to kill all stages of insect. It should have rapid action. The action should be potent against insects. Insecticides should be biodegradable e.g Pyrethrum (plant insecticide). Most organochlorides are not biodegradable and so have residual effects. Insects shouldn't develop resistance to the insecticides. The use of the insecticides should be done with every precaution (i) minimize human exposure and (ii) minimize poisoning in livestock. 1) Use of gloves, respirators, change clothing regularly (2) Don't exceed recommended dosages (3) Maximum precautions should be used to prevent driffs damage to adjoining field (pastures or ponds, streams or other premises in which the Rx is not essential).

Insecticides can be classified into

1) organochloride
2) Organophospates
3) Carbamates
4) Pyrethrics/Plant insecticides

Organochlorides insecticides: There are 2 groups

1) DDT Dichlorodiphenyl Chlonoethane
2) BHC Benzene Hexachloride

Most are not biodegradable and cos of the residual effects on human and environ:. Their use have been drastically curtailed. Only 3 members are approved for use in livestock around the world viz Lindane, Methoxychlar, Texaphone. Lindane and Toxaphene belongs to the BHC group while thoxychlor belongs to DDT.

Methoxychlor is one of the saxfest chlorinated hydrocarbon insecticides. Young dairy cows tolerate up to about 260mg/kg of Methoxychlor and its been found that 500mg/kg body weight is mildly toxic to cattle.

Notwithstanding many countries, it's not used for animals producing milk for consumption. Toxaphene is safe but toxic when applied in excessive quantities.

Lindane is BHC. It contains about 99% BHC. Other hydrochlorides that been used in the past include Aldrine, Dieldrin, Endrin (most toxic, 1st produced). Aldrin has been bound in many countries but the use in termite control.

Chlordane is another BHC compound that is been used in the past. It's poison is usually thru accidents e.g accidental poison thru Rx plants.

Strobane

Organochlorides are very lipid soluble and it produces residual effects and chromic toxicity. Their use have been reduces they are well absorbed and stored in fats and may exist with no apparent symptoms.

The symptoms of organochloride insectides include CNS stimulation which are mainly neuromuscular e.g for DDT group, not presents with muscle trenor which progresses into convulsion/ chronic or tonix) which progresses to the stage of paralysis death, cats are more susceptible to the DDT group. It is also been shown that for DDT group, amaciation and lactation increase the susceptololity of animals to poison.

For BHC group, there could be stimulation or depression of CNS xterized by muscle tremor, excaggerated response to muscle stimuli, salivation. There may be convulsion come and death. (ii) Pm, there are no xteristic lesions observed but there may be congestion of vaxious organs such as liver, lungs at kidney.

Diagnosis

Chemical analysis of appropriate samples tissues, serum, urine, fat.

Rx are purely symptomatic. No known specific antidote for organochlorode poisoning. When there is CNS stimulation CNS depressant is given, small young animals are given Barbiturates Calculum Berogluconat, large animals are given Chloralhydrate.

Excess insecticides can be removed by washing with water. Activated chancoal to prevent absorption from GIT.

Organophosphate insecticides e.g

- Diazinon (cattle) – Dichloruos (cattle, horses and pigs)
- Parathion (control of mosquitoes and other insects affecting crops)
- Coumaphos (cattle, horses and pigs) small animals
- Ronnel (Fenchlorphos) et small animals
- Fenthion – phasmet – Tetrachlorvinphos

They have very low margin of safety. The dose is usually very stuff. The signs of organophosphate poisoning are usually the signs of cholinergic over-stimulation i.e of nicotinic, muscarinic and central cholineigic receptors. Hypersalivation, myosis, frequent urination, diarrhea, colic, dyspnea (As a result of bronchial secretions and bronchocostriction).

Ifnicotic receptoms are over-stimulated, muscle fasciculation and weakness result. When central receptors are over stimulated; nervousness ataxia (wobbling gait) apprehension, seizures; severe depression, conclusion in dogs and cats.

Accesscholinesterase level in the blood and brain for Dx . Do chemical analysis of pesticide in blood and tissue. No specific lesions are @PM.

P_x

3 categories of drugs used are:-

- Muscarinic blocking agents e.g Atropine sulphate. It blocks the peripheral and central effects of the organophosphates.

- cholinesterate reactivators: They are usually Aldoxides e.g 2 Pyridine aldoxire methchloride (2-PAM), Pralidoxing chloride.
- Emetics, Purgatitive or Absorbents
  For symptomatic R_x. Wash the animal with H2O and detergent . Don't use emetics when animals is depressed.

Carbamates

Are derlvatives of carbamic acids (H2N, COOH) most cabamates are dimesthyl or dimethyl – or dimethyl derivates of carbamic acid. The most common/commonest is called Carbaryl = 1 naphthl N-methyl carbamate Serin ® They are not very good as Insecticides cause they have a low rate of penetration thru the skin. They have high insecticide effect and low toxicity.

Mechanism of action

It inhibits actyl cholinesterase by carbamylation. Symptoms of toxicity are also cholinergic i.e overstimulation of cholinergic receptor.

Lacrimation, salivation, convulsions, tremors, ataxia and death. Afropine sulphate as antidote.

Organic thiocynates used against ants and not in livestock.

There are 2 members

1) Thaniti (Isobomyl thiocyanocetate)
2) Lethare (Lauryl thiocynate)

They are toxic to aphids and soft bodies insects. They are usually used as contact poisons. They act of ganglia of insect and cause a rapid knockout. They aren't popular cos of their bad odour and cos of its initant effect on the mucous membrane. Symptoms of poisoning include restlessness, severe depression, dyspnea, ajanosis, tonic convulsion and death.

Plant insecticides

3 members of this group are

- pyrethroids – Pyrethrin
- Nicotinoids – Nicotine

- Rotenoids – Rotenone

Pyrethroids are extract from pyrethrum flowers. It is an effective and expensive insecticide and the distinquis feature is its rapid action causing paralysis and instant knockdown of the insect. In case of accidental poisoning there is depression hypersalvation, muscle tremors, ataxia, dysprea and at times anorexid

Rx

- Decontaminate by washing with mild detergent
- Use emotic
- Give atropine to control hypersalvation

Synthetic pyrethroids include permethrin, cypermethrin Decamethrin.

Nicotinoids are extract of the leaves of ground Tobacco. Nicotiana tobaccum. There are 3 alkaloids of tobacco leaves. Nicotune, Nornicetine and Anabasine Nicotine is particularly toxic to insects. Also overstimulation of the nicotinic cholinergic receptors. In nicotinic toxicity, the symptoms is usually central.

P_x

- Gastric larage- Artificial respiration
- In depression, stimulant are used
- Inover stimulation (convulsion, depressants are used.

Rotenoids are isolated from the plant called Derris which is a legume. Rotenone is a respiratory poisons. It affects the heart rate as well as 0_2 consumption and may lead to death.

Herbicides/Weedicides

Are chemicals used to kill plant pests a.k.a weed killers. Members of this group include: Arsenicals, Chlorates, Phenols, Several inorganic herbicides, compound such as Calcium, cyanamide, cupric sulphate, mercurious, chloride, potassium cyanate, Na k Chlorides, Sodium tetrabonate. Organic compounds such as:

- Phenoxiacetic acid derivatives
- Dinitrocompounds (Dinitrophenole derivatives)
- Substituted ures compounds
- Thiocarbamates
- Triazines
- Dipyridyls

A good herbicide has a good degree of selective action between weeds and crops

Phenoxyacetic acid derivative

These are plant hormones. They act as plant growth regulators rather than contact poisons. They alter the metabolism of the plants. The plants Rxed build up high level of NO_3 nitrates and cyanides leading to toxicity and death.

Weeds treated with are more palatable to animals than the untreated ones and animals consume them. The symptoms observed in animals include loss of appetite loss of weight, depression, muscular weakness, there be bloat in animals and may lead to death. Its also been shown that many are cardinogenic, teratogenic and may also cause reproductive damage in animals. There is no specific antidote for but Rx can be done symptomatically by and also give food supplements and vitamins.

Dinitrocompounds

Can be used not only as herbicides but also has mecticides. The 2,4 dinitrophenol and 2, 4, dinitro orthocresol are the most widely used. This group of herbicides act as contact poisons. Animals are usually exposed to them when the herbicides are spilled or contaminate vegetation and H_20. In ruminants, cumulative poisoning is possible.

Signs of toxicity include listlessness loss of appetite loss of activity, rapid respiration, sweating thirst, oligura, muscular weakness, yellowish green colour of the urine lumpacted by herbicided. No specific antidote for put

animal in clean environ use sedatives give animals glucose saline cos of observable dedydration and test, give O_2 therapy.

Dipyridyls

Diquat, paraquat. These are dessicant herbicidea. They cause defoliation of the plants. They act as contant poisons. Accidental poisoning either thru vegetation/drinking H_2O will lead to restlessness, loss of appetite, oliguria. i.e Kidney and CNS are affected Rx is symptomatically.

Substituted Urea compounds

Members include Diuron, Fenuron, Linuron. They act as plant growth regulator.

Triazines

Members include Atrazine, Cyanazine, Propazine. Toxic effects are localized to CNS and kidney.

Thiocanbamates

e.g Barban, Chlopropan. Signs include depression, anonexia, (CNS). There may also be diarrhea. No specific antidote Rx symptomatically. Chemical analysis of the affected material can be done. Other measures

- Delay absorption by using emetic drugs
- Gastric lavage- purgatives – supportive therapy

Fungicides

These are chemicals used to prevent fungai infections. They vary from low to high toxicity and are used to prevent foliage, fruits seeds against fungal infection. They are toxic to plants and livestock.

Hazards to livestock arises from feeding with treated fungicides are toxic

Petrodeum ethers, formaldehyde, carbon tetradilonides

Categaries of Fungicide

Organomencurial compounds

Phenyl mercuric chloride	-	May be used alone or in
Phenyl mercuric acetate	-	combination with Aldrin

Ethyl mercuric chloride - or Dieldrin

Casue irritation of the skin and respiratory tract, damage to the kidney, CNS, May cause permanent disability.

Carbamate fungicides

Thiuran (thiuram disulphide)

Fetba (Metallic disthiocarbamates)

Zineb (Ethylene bis dithnocarbamates)

Maneb

Signs of toxicity – anaorexia, depression, dianhoea and chronic effects may also manifest of thyroid glands i.e hyperplasia.

Miscellaneous

- Captan: an organic non-morcurials fungicides low toxicity in animals

  Sign Laboured respiration, anaemia, depression and death.
- Dinitro orthocresel: Can be used as herbicides, fungicides, insecticides, and wood preservative
- Pentachlorophene: Used as herbicide, bactericide, fungicide, molluscides insecticide .

Toxicity varies from mild, moderate to high formal

Mild toxicity- muscular weakness, anorexia and lethargy

Moderate toxicity: acalerated respiration, hypoglycemia, glycosuria sweaturg, imitation of the skin, eyes, nose, and throat. There could be dehydration

High toxicity (Lethal dosage) Cardiac and muscular collapse leading to cardiae failure and death.

Rodenticides

They are chemicals used to poison rats

They are toxic to domestic livestock. Banned chemicals used it their preparation include Barium, Arsenic, Thallium, Phosphoric, Zinc

phosphide, strychnine and some of them are very toxic. New preparations include:

- Alpha naphthyl thiourea (ANTU)
- Flouroacetate
- Flauroacetamide
- Warfarin and related anticoagulant

Alpha naphthyl thiourea.

Is a derivative of thiourea and is one of the most useful rodenticide. It causes increase in the permeability of lung capillaries resulting in oedema. When ingested, the rats are unable to vomit or expel it. Studies have revealed that brown rats are more susceptible. Ruminants and domestic poultry are resistant. Signs of modenticide poisoning difficult breathing, coughing, increased heart rate, hypethemia and diarrhea.

Flouroacetate and Fluoroacetamide

Toxic to able species of animals horses/goat dogs and cats, pigs, monkey, guinea pigs and rat. The toxic effect include ventricular amhythmias; myocardic astric depression, ventricular fibrillation, Animal dies, of cardia form abnormality.

Strychnine

CNS stimulate and susceptible animals develop stiffness of the neck, convulsions and death. Dogs and cat are susceptible to strychnine poison and they become susceptible when they consume batls intended for rats. Its been shown that cattle's are resistant to oral dose of strychnine. Where there's been strychnine poisoning in dogs and cats, potassium permanganate have been administered and its effect is to oxidize. Strychnine

Tannic acid can also be given

Gastric lavage or forced diuresis

Warfaring and related anticoagulant

These are coumarin derivatives and are natural products

They interfere with prothrombin production in the liver

Warfarin is toxic to all mammals and birds especially dogs and cats. Typical toxic symptoms include haemorrhage and bloody diarrhea

Animal Toxins

Many animals produce toxic secretions for defence or food capture. Based on their toxins, animals can be classified into 2 groups

- Venomous animals - produce venoms
- Poisonous animals - produce poisons
- Birds don't produce - toxic secretions

Venomous animals possess a gland (venomea gland) a group of highly secretory cells, a duct (venom duct) a structure for venom injection or delivery could be in form of teeth, fang, jaw, spine or sting. These apparatuses are known as the venom apparatus venom gland did and injecting.

Poisons animals don't have been venom appanatus. All poisoning caused by them is thru ingestion. All venomous animals are poisonais but not all poisonous are venomous poisonous animals- toads, shell fishes,

Vanomous animals- rattle snake, black widow spider.

Arthropod's toxins

Arthropods are joint footed animals

Bee venom

Produced by arthropods like bee, wasp, yellow pocket, hornest. Several animals are susceptible to this toxins- man, dog, guinea pig, mouse and frog. The toxic effects include local irritation and haemdysis.

Scorpion Toxin

Vanomous anthropods. Venoms produced cause musclar stimulations and haemorrhage. They also produce intense pains associated with the production of 5-hydroxyl tryptamine. Specific scorpion antiserum may be administered as an antidote.

Spider Toxin

A very strong toxin and the venom is about 15 times as toxic as rattle snake poison especially that of black widow spider. Signs include extreme pain leading to oedema the site of bite. Affected animals show weakness, loss of appetite, anorexia, and slowly becomes paralyzed. If available, specific antovenom may be given. Some animals have natural immunity against spider toxin. In many cases, the previous bite make the animal immure to subsequent ones.

Amphibian toxins

Toad Venon/Poison

Certain toads produce a poisonous secretion which are contained and elaborated in a pair of well defined skin glands behind the eyes which actually secretes the poison. They are known as parotid glands correlated to salivary glands). These secretions is a complex mixture of various cardioactive sterols bufogenin, bufotelin, bufotoxin, bufotenine, Serotonin. Dogs and cats which attack and bite toads quickly show symptoms which will be followed by prostration conclusion and death within 15 minutes. Atropinen may be used as an antidote.

Frog Verom

Combian frogs. The venom contains Batrachotoxin A and B. This secretion of frog venom is a most potent cardiotoxic and recrotoxic against Toxin produces paralysis convulsion and death within minutes.

Animals Toxins

Poisonous Snakes

Can be grouped into 2 classes

Elapine	Viperine
e.g cobras	Viperine
Mambas	moccassim
Corals	puffadder

Venoms are usually Neurotoxic.

Venoms are haemotoxic

Cobras

Black cobras (forest) Aegyption cobras in far North (Sokoto, Jigawa)
Black neck or spitting cobras common is savanna forest.

Mambas

Green mamba is predominantly found in the forest areas.

Vipers

About 17 species exist in Nigeria. Vipers have broad head thick body. When they bite, they cause severe local reactions followed by inflammation swelling and gangrenous lesions. Viper toxin is haemorrhagic i.e haemotoxic,. Front fanged snakes are poisonous while bark fanged ones are rarely poisonous.

Dogs are the most vulrerable to snake bites followed by cats, cattle and horses. Farm animals are likely to be bitten on lips or jows but because of their large size, the poison is les likely to be fatai.
Snake venoms are mixtures of different active constituent
Damage to endothelial of tissues

Phosphates: cause haemolysis as well as excessive bleeding cos fibrinogen is converted to fibrin and its broke down to fibrinogen is converted to fibrin and its broken down to fibrinolysm (no blood dot).
Local effects include:
Shoge cellentits, oedema, haemorhges, gangrene and ecchymosis.
The neurotoxins in Elapines have serious effect on CNS and most bits from them leads to a considerable release of histamine. The venom also contains hylauronidea which breaks down cement substances in tissue. After bite, the animal becomes nestless, excited followed by depression and quietness and incoordination if movement and then animals collapse.

Skill is usually cold, pupils are dilated and this stage, Diagnosis identify the presence of fang marks usually to the entire of a swollen and with blood oozing from there tissue reaction (2) point of bite depends on snake. Vipers reduce serious reactions which include sloughing of skin.

Rx

1) Use a tourniquet to reduce blood flow to the area to prevent spread
2) Incise the areas of bite and suck or excise the gland
3) Use a specific antivenom (antireun) if snake is identified or use a polyvalent serum, which is active against almost all snakes though more expensive. Initially give half of the dose locally and give the rest by i/v. The smaller the animals, the larger the dose of antivenin
4) Supportive Rx and antibiotics are useful. Gluccorticoids to reduce inflammatory reactions. Anthistamines (contraindicated in some animals). If there is respiratory distress, tracheostumy can be done. If verom is in eyes, physiological saline is used to wash.

Sea Animals

Spongos

Algae-like. They produce toxins that affect other sea animals like crabs and fishes.

Coelenterates: Hydroids jelly, fish, corals, sea anemones. They have stings (stunging units known as nematocysts). Toxic effect has been attributed to Hyprnotoxin. Thallasin. Attack man in that heritors. Symptoms of caeleterate poisoning including weakness, nausea, headache, pain in large muscle masses vertigo respiratory distress, increased respiration, collapse following cardiac arrest.

Echinoderms e.g starfish, seaorchins and cucumbers, starfish screte their toxins thru a glandular tissue. Sea archins have venom apparition.

Cuccmbers have specialized tulales where the main toxic component is produced.

Handing some spp of starfish produce dermatitis while some spp are toxic after ingestions. Toxins are described as Sapponin-like and have haemolytic proper. The action of the venom of sea orchins include respiratory distress, muscle paralysis convulsion and death. In sea molluses, sea arthropods and sea mammals. Venoms of are haemolytic, cardioactive and neuromuscular. Toxins of sea cucumbers are steroidai glycosides which posses haemolytic cytotoxins and neuromuscular effects.

- **Molluscs** e.g oysters, snails clams, muscle and octopuses. A snail spp know as Conus has the most venomous toxin Octopus toxins are present in their salivary glands and as shown to produce vasodilation, stimulation of certain muscle and also cardiac arrest.
- **Marine Fishes**: They contain poisons in their muscles, viscera, skin, glands and blood.

Poisonous fishes – produce Ciguatoxin is a poisonous principle from poisonous fishes living in warm water area. Common with many fishes used as food such as Bamacudas, Jacks, Moreyeels, Snappers. Symptoms with ciguatoxin include nausea, weakness, abdominal pain, vomiting diarrhea and incoordination and severe toxin will be fatai.

Another toxic principle is Tetrodotoxin (regarded as most toxic substance in the world today). Found in poisonous fishes such as puffers, ocea sunfishers, porcupine fishes, sea amphibians.

Venomas fishes such as stingrays, scorpion fishes, zebra fishes, stone, fishes, we evers, stargrazers, certain shard rat fishes, catfishes, surgeon fishes

Venoms produced by some of these fishes cause muscular weakness, hypotension, paralysis, depressed respiration, depressed heart rate which may lead to death.

PLANT TOXICOLOGY

Plant Poisoning

Phytotoxicology

1. Bacteria 2. Algae 3. Bryophyta (mosses, liverworts)
4. Pteridopyyta (ferns and club mosses)
5. Fungi (moluds and mushrooms)
6. Speamatophyta Gymnosperm
   Angiosperm (Monocots and dicots)

Plant poisoning occurs when an animals consumers plant which is poisonous or it is externally applied it. Poisonous plants are those which result in health and some may eventually cause animal's death I'll health caused by plants may individual-lergies such as hay fever of asthma.

2) Contact dermatitis
3) Abnormalities in blood function
4) CNS defect or internal tissue damage
5) Teratogenesis or cytotoxic effects which results in mutations or cancer.

Parts of the plants which are poisonous can be the leaves and not the fruits or all the parts of the plants may be poisonous.

Causes of Plant Poisoning

1) **Seasonal variation:** Some plants may be normally eaten under certain conditions of the season, rainfall or humidity and may suddenly become poisonous e.g Cynodon plectostahus, Sorghum vulgare (millets) may contain various levels of cyanide due to the season. In semi arid and arid environs, the pastures are most dangerous during the dry season cos poisoning becomes acute.

2) Poison could be accidental cos this happens when the poisonous plants grow close to the normal pasture. Also, poisoning may occur during hay preparation if poisonous plants, by accident are include in the grass that is cut poison. Occurs cos the animals are unable to use their selective eating habit.
3) Stanation may cause plant poisoning: During periods of starvation, plants which are normally not grazed are eaten by the starving animals. Sometimes, the animals may continue to eat the plant which has poisoned it.
4) Transhumans may be cause of poisoning when trade cattle trekking from one point to another during the dry season and are tempted to eat the poisonous plant e.g. Ergthrophleum suaredeus : During this period, they are less able to discriminate and during the dry season, animals may be attracted to some plants cos of the bright flowery nature e.g poison occurs with *Tribulus temestris* as a result of these changes.
5) Indirect plant poisoning occurs when fungus grow on some plants e.g it occurs with fungae which grows on cereal grains e.g Ergot poisoing due to Clarviceps purpurea. Animals could also be poisoned by poisonous mushrooms or toadstools.
6) **Change in locality**: Often, animals born in a location or which gros in a locality becomes tolerant to some poisonous plants whereas newly introduced animals will die cos they are not able to tolerate the active principle. Animals which are familiar with the effect a poisonous plant will avoid while strange animals.
7) **Soil type**: Plants which grow on some soil type absorb certain poisonous elements and become poisonous more toxic. Pasture plants which grow on soils reach in Cu and Se can accumulate these heavy metals. An imbalance of the soil nutrients such as P, S and M. Molybdenum in relation to N2 will influence the poisoning by N2 accumulating plants which are under those conditions are

unable to transform nitrate to NH3 and other N2 containing compound of the plants. This results in nitrate poisoning. The nature of the digestive system also influences poisoning cos ruminants with their complex stomach are able to break down the ingested poisonous plants but can also synthesize poisonous substances from plant constituents. The health status of the animals including latent infection, weight, age and species may also the determine the course of plant poisoning. Ruminants are less susceptible that horses and pigs are more susceptible with humans being equally susceptible as the pigs.

Chemical composition of Poisonous Plants

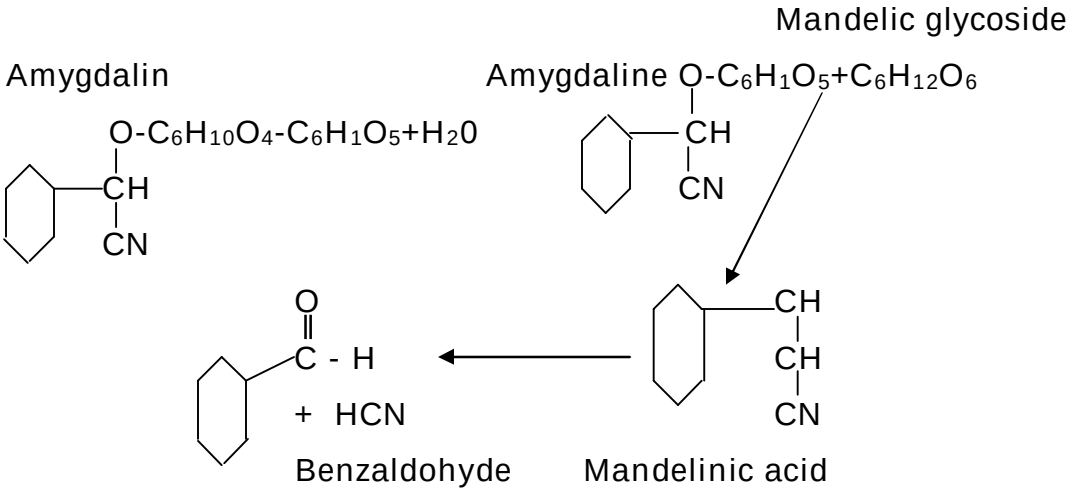
Major constituents found in plants include:

- Organic compound e.g alkaloid, diterpenes, cardiac and cynogenic/cynogenetic glycosides nitro containing compounds, oxalates, resins and certain proteins and or amino acids. Some plants may also accumulate inorganic compounds which may have serious effects on the animal.
- Alkabids are heterogenous compounds which are basic organic Nitrogenous compounds plant origin. They are active metabolic rather than end products of metabolism.

  Alkaloids could be of 2 types

  - heterocychc Nitorgen
  - Non-heterocychc Nitrogen
  - Plant which contain such alkaloids include Atropa belladonna atropine which consists of Solainaceae family.
  - Reserpine of Apocynacea family which is obtained from Ranwolfia sepentina
  - Strychnine of the Longanaceae family which is obtained from Strychnus-nux-vanica.

- Glycosides: On hydrolysis, produce useful sugars; which are also known as glycones and 1 or more compounds known as aglycones. Glucose is the most commonly occurring sugar Toxicity or other major activity may be due to the aglycone moiety of the (1) cynogenic glycosides which often yield Hydrogon cyanide as I product of hydrolysis. The most widely distributed cynogenia glycoside is Amygolalin. On hydrolysis a 2- step process occurs yielding 2 molecules of glucose tree HCN is one of the vidently toxic end result product of hydrolysis.



The severity from HCN poisoning in plants depends on how much free HCN and or cynogenic glycosides exist in the plant. Cyanide inhibits the action of cytochroms oxidass (terminal respiratory catalyst linking atmosphere 0_2 with metabolic respiration: HCN poisoning is asphyxiation the cellular level.

(2) Anthraquinone glycosides: On hydrdysis, they yield the aglycone anthroquinene which has a purgature effect e.g Cassia senna release the anthraquinone senna which is of the family Fabaceae and the plant Aloe barbadensis release alce which belongs to family Liliaceae.

(3) Cardioactive glycosides: are xterized by specific action of the heart muscle e.g family Apocynaeae e.g Nerium oleander strophatus.

4) Saponin glycosides: On hydrolyosis yields aglycone sapogenin which could be a steroled or a triterpene. The saponin glycosides form colloidal dispersion in H_2O. They foam when shaken in H_2O and usually have a bitter irritating taste. They irritate the mucous membrane and can destroy RBC by haemolusis. They are considered for the most toxic especially by cold blooded animals. Many of them are used for fish poisons e.g are obtained from the family Dioscoreaceae (yam). Dosicorease.

5) Coumarn glycosides are not common e.g Plant family Fabaceae e.g Melitotis spp.

6) Oxalato acid is the only organic acid of plants poisonous to animals under natural conditions. They more occur in plants as soluble K or Na oxalate or the insoluble Ca oxalate e.g Oxadidaceae with Oxalis sp.

7) Resins are amorphous products of a complex chemical nature. They are insoluble in H2O and do not contain N2 at all. Resins are also hard transparent or translucent. They soften when heated and finally met. They occur in complexes as in gum

- (gum resin)
- oil (oleoresin)
- sugar (glycoresin) e.g

Family Melianceae e.g Melia azadirachta.

PHYTOTOXINS

Are protein molecule of high toxicity. They are mostly antigenic,

Family Euphorbiaceae Ricinus communis nicin

Inorganic Compounds

Plants may absorbs and acculmulate NO_3 compounds Se, Mb and other elements that add high level to the animal. Nitrates after digestion to nitrites which are by fa more toxin than NO_3 especially in ruminants.

Algae

Fresh H_2O Microcystis aeruginosa and fresh H_2O Anaebaena spp (both blue-green algae) are the common algal blooms which are responsible for most death in livestock, pets, wild animals and birds and even man. When such group of animals consume H_2O in which such bloom grow. Toxicity resulting from such blooms may result from some fast death factors produced by blue-green algae from products of decomposition and from toxins produced by bacteria which are often associated with the bloom. Poisoning does not often occur unless dense bloom of toxic organisms is formed. Shell fish clam, crabs and other moluscs and invertebrate may contain dangerous level of the toxic agents of algae e.g the toxicity associated with shell fish is due to Gonyaulax tamerensis and G. carterella which are dinoflagellatos which produce the poisonous agent tetraodotoxin (N_2 substance).

Fungi

The poisonous agents obtained from this group can be divisible into both

i) Mycotoxin (with molubolites)

ii) Mushrooms (with poisons)

Mycotoxin

Are by products of metabolism and often remain long in food long after the fungus which produced them has died. Toxins can be produced in food which doesn't look visibly mouldy. In addition, many Mycotoxins remain toxic after the food has been cooked or processed.

Mushrooms

Basidiomycetes

Amanita phalloides and its close relatives are responsible for about 90% of the fatalist.

Ferns (Polypoidaceae)

e.g Pteridium equilinum a.k.a Bracken fern. Contains the enzyme. Thiaminase which metabolize thiamine and this results in Vit B,

deficiency. Serious poisoning occurs in ruminants and horses. Brackenfern also has mutagenic and carcinogenic factors which can be passed thru the milk of cows. This serves as a potential heath hazard in places where cattle which feeds on Bracken has their milk used for human consumption. The carcinogenic factors in known as Shikimic acid

Spermatophyta (Seed-producing plants).

Most diverse in terms of plant poisoning and almost all families appear to be toxic some stage of their development. It's not all the parts of the plants that may be poisonous. There are different families viz:

Asclepiadiceae
Euphorbiaceae } contains latex and are generally dangerous ingestants
Apocynanaceae

Fabaceae contains tannins, toxic glycosides and alkaloids Solanaceae has tropane alkaloids.

Plant families

Family thymelaceae

Lasosiphon Krausianus (Trunnbi by Hausa)

A small erect herb with yellow heads of flowers and a thickened root and it has a rhizome and the flower heads are located on a long peduncle. The calyx too is silky with longer whitish hair towards the base. The toxic principles are coumanin glycosides. Symptoms of poison include diarrhea, dyspnsea and ruminal stasis Abdominal pains and phetosensitization in calves. PM lesions include necrosis of the liver and gastroenteritis. Haemorhages, congestion and oedema of the brain, therefore, lymphopaenia.

Family Zygophylaceae

Tribulus terrestrus (Tsaido by Hause)

It is a prostrate plant and has yellow flowers and with small sharpy spined fruits or burs. This can injure the skin of animals or bare foot.

The main stem is woody and densely covered with short soft hairs. The leaflets are about 3-13cm long on the leaves which are about 12-15cm. The fruits are about 1cm. Poisoning cahsed by Tribulus temestrus is known as yellow thick head or Tribuclosis in some part of Africa. Wilting tends to increase the levees of poisonous components. Poisoning is often due to photosensitivity reaction which results from the inhibition of the excretion of the by product of chlorophyll known as Phylloerythrin. This inhibition to due to damage to the liver by the toxic factor. Symptoms of poisoning include anaemia, ananexia and lesions can be found in the kidney with epidermal necrosis of the limb and pundent dermatitis.

Family Apocynaceae

Strophantus hispidus

A shrub with hairy whip-like branches which in time grows into a climber. The flowers are yellow and purple spotted in the throat. They have long tails on the corolla. The fruits are in form of follicles about 30-40cm long with a beak at the end. It is comonly used for arrow.

Poisoning the flowers and

Other parts are commonly

Mixed to make the arrow poison with the seeds being very essential ingredients. The toxic factor known as Strophantine K which is a glycoside. It acts by stimulation of vagus nerve which:- slaws the heart and prolongs diastole. It also produces cardiac amythmias including tachycardia, pronourced bodycardia and an altermating weak and strong cardiac systoles (2) PM, the lungs of the animals are engorged and there's marked distention of the atrium which is filled with blood. The ventricles are contracted and empty. Strophantine K is similar to Digitoxin.

Family Euphorbiaceas

Ricinus communis

It is known as a castor oil plant or Palma Christi. It is a shrub up to about 3m high with seeds which look like engorged tick with smooth mottled appearance. The leaves are large palmate with 5 points which are semated. The flowers are small and yellow. The seeds may be eaten when treated by soaking but when entreated, it is very poisonous. The residue which remains after extraction of Castor oil from the seed contain the poison. Ricin which is a toxalbumin and which is antigenic. It differs from snake and bacterial poisons cos it can be absorbed from the GIT. All parts of the plants are potentially poisonous and repeated consumption causes immunity and immunized animals can tolerate up to 800 time, the normal lethal those of Ricin. Animals spp varies in their susceptibility to poisoning by Ricin. Horses are most susceptide, sheep, cattle and pigs are intermediate, ducks, and poultry are least.

Symptoms of poisoning include tumultuous heartbeats, with sweating and titanic spasms. Animals show diarrhea which may be bloody. Affected horses show dullness and in coordinated gaits.

PM lesions include patch gastroentesitis, sometimes punctform haemorrhages. The mesenteric glands are swollen and aedematous. The liver, kidney and spleen may be swollen with aedematous fluid.
Rx invlies the administration of the antitoxin.antisera if avaikable or symptomatic Rx.

Mannihot esculenta

A shrub about 180-300cm high or more. It has digitate leaves which may be pale bluish green. The pink and purple flowers which are bell-shaped known as campanulate. It is often grown as Ornamental but livestock often get poisoned. Generally, the pounded root are used as fish poison or also for ordeal or arrow poison. It also act as a cardiac poison; acting similarly to digitalis but it is complicated with an effect on CNS. The nerve mechanism of the heart muscle.

Family Papillionaceae

Tephrosia vogeilli

An erect shrub about 180-300cm high and it is covered with a dense yellowish or short soft hours. The flowers are red poison causing paralysis of the CNS. Leading to respiratory and cardiac failure. The toxic principle is known as Tephresin and it has been used against various insects. The leaves and the seeds also consist of the toxic principle diguelin which acts as a insecticide. The pulverized leaves or concretion of the leaves are used as contact insecticides.

Family Loganiaceae

Struchnus spinosa

Strychnus nux vomica

A small tree with stiff horizontal branchlets. The flowers are white, short compound cymes. The fruits are hard shelled and yellow, a little large than one. The pulp of the fruit is acidic and may be edible. The seeds are highly poisonous acting directly on the spircord with a xteristic opisthothonus cos the extensive muscle are stronger than the flexon muscle. Symptom include nerousness, restlessness to which the animal may temporally recover or may be stimulated into similar actions again.

Jatropha multifida

a.k.a J curcus: It is a small spreading tree about 4.5cm high with spear-shaped (lancedated) leaves. The flowers are inconspicuous. The fruits are flesh with 3 seeds. The seeds contain the toxalbumin Curcin.

Clinical signs appear few minutes-hours after ingestion and consist of diarrhea, dyspnoea, dehydration and loss of condition. Jetropha spp can also contain high levels of cyanogenic glycosides and prussic/HCN acid poisoning occur in ruminants which browse the leaves.

Family Fabaceae

Abrus precatorious

a.k.a love bean, luck bean or Minnie minnies. It is a wooden climber with compound leaves about 60-80 millimeters long; each having 11 hours of broad oblong leaftes. They have dusters of hairy pods about 30mm long 30mm long with decorative scarlet seeds. Less than 1 seed thoroughly chewed is fatal to human. The toxic principle is the antigenic substances Abrin which is a lectin of 2 polypeptide chains joined by disciphide bonds. Horses are fatally poisoned. Ruminants are more resistant probably cos Abin is disturbed in the rumen. Clinical signs are similar to those of Ricin. Pm lesions include severe gastroenteritis. Free blood in the digestive tract. Haemorrhages of various organs. Illerations of the abomasal mucosa, nephrosis and degenerative changes in the liver.

Family Solanaceae

1. Atropine group Atropa belladonna/deadly night shade
2. Solanin group Solanumsp, Datura Sp
3. Nicotone

Roots are vey poisonous if not properly prepared. It contains HCN which can be found in highest quantity in the young activity growing plants. Death normally occurs within few seconds and there may be convulsion paralysis, stupor and cessation of respiration before that of heartbeat.

PM lesions show congestion of blood vessels and the blood is bright red and is often unclotted. There is congestion and haemorrhages of the lung, reddening and congestion of the mucous membrane of the stomach. HCN is rapidly absorbed from the GIT if not in excess quantity and soluble-sulfur transferase rhodonase.

$$CN + S_2O_2 \xrightarrow[S_2 \text{ transferases}]{\text{Mitochondria}} CNS + SO^2_4$$

The thiocyanate also has effect on thyroid gland. HCN cause anoxia of the CNS by inactivating oxidase. Cyanide ions react readily with the ferric ion of cytochrome oxidase. The complex, is stable and when Fe is kept in this trivalent state, election transport chain stops. This causes cellular hypoxia and cytotoxic anoxia. Haemoglobin cannot release its O_2 to the electron transport change.

Euphorbia Kamerunica

a.k.a Caustic weed or milk weed. It is a shrubs up to about 1.5m high with a distinct trunk. They are xterize by the latex which is a milky exudates which core from the foliage when it is broken. The latex is irritant to the skin especially on the mouth when eaten by grazing animals. It contains cyanogenic glycosides:

Others similar to this spp include: E. tirucalli E. pulcherima

Datura stramonium

An erect branched annual with white flowers and sping fruits about 4cm indiameter. The leaves are palmate. The 2 or D. stramorium and D.metel are known as Thorn apple. The seeds are poisonous but contains less poisons than the leaves and root. The toxic principle is a glycealkaloid known as Scopdamine. Symptoms of poisoning are dilation of the pupils and blindness. Also causes dry mouthed pulse and respiratory rates, nerousness. Delirium and trembling followed by panalysis.

There is drop in temp from convulsion relaxation of the sphincter and death from asphyxia.

Solanum torvum

Also a shrub about 60-90cm high. The flowers are white

Others under Solanum spp include S. uncanum S. nigrum. All contain the glycoalkaberd. Solanin which resembles Sapponin in action but all produce atropire like symptoms like Datura Spp.

Family Cycadaceae

Encephalartus barteri

Has leaves up to 180cm long and they are pinrate. The toxic principles are glycosides Macrozanin and Cycasin and poisoning results in necrotic hepatitis and degenerative changes in the kidney and heart of calves and goats which is highly poisonous. The flowers are 1st green but soon change to red and the petal cur back. The leaf tips are prolonged into tendrils which attach to support and had the plants up. The toxic principle is the alkabid Colchicine with action similar to that of squil.

Family Mimosasae

Leucana leucocephala

A tree or a shrubs with bipinnate leaves and the fruits are pods 15cm long. They are used as Ordeal poisoning. Symptoms include anorexia, ed heart sounds and respiratory embarrassment. The active components include Erythrophleine and Casseine.

Cassis Sieberrana

C. simea

C. occidentalis

C. alata

They all contain the orthraquinone glycosides. The leaves of C.siebarana are pinnate. Their seeds can be roasted in place of coffee but they are lethal fatal to calves producing anonexia, weakness, ataxia, necumbency and death. PM lesions include wldespread degeneration of skeletal muscle. Diminished egg yield and mortality in poultry.

Family Dichapetalaceae

Dichapetalum madagascasiconse

A shrub or tree and the young leaves are more poisonous and they are used as rat poison. Their poison substance is a fluoroacetate and poisoning is xterized by a latent period of 24hrs before clinical signs

appear. This is the period for the plant to be digested and absorption of the fluoroacetate into the blood and from there, into the cells.

Signs include CNS effect or cardiac in cases of the carnivore or the ruminant. It is respiratory in cattle which produce lethal doses and symptoms begin after drinking of H2O or exercise. These include anxiety, hyperaesthesia, depression of salivation, respiratory distress, ataxia, animals may show a particular stane, muscle trenor, tachecardia. Some animals show tenesmus, stringy faeces, they bellow and urinate frequently. Fluoroacetate produces its symptoms of poisoning by inhibiting acenitrase which is important in the conversion of citric acid to isocitrate and thus in accumulation of citrates in tissue metab.

Family Sapindaceae

Paullinia pinnata

A small shrub and contain the poisonous principle Saponins, Timbein and Timbell. They have similar actions to Aconitine.

Family Leguminosae

Crotalaria retusa

Contains the pyrolizidine alkaloid. Symptoms of poisoning include anonexia, wasting, irritability and xteristic yawning. Muscular spasms lead to a phase of mad and aimless galloping which gradually leads to walking stage from which the other name of walkabout disease is derived where the animal may walk about for hours with slow staggering gait and the head held low. There is no cure for Crotalaria poisoning. Rx may prolong life but seldom results in recovery. The alkaloids responsible for these poisons include Crispatine, Monoaotaline and Fulvine.

CYANIDE POISONING

Sources of Cyanide Poisoning

- Fertilizers
- Effluent of gold, mines

- Plants: There are 2 mines

* Free hydrocyanic acid * Cyanogenetic glycosides

Absorption of the cyanide are mainly thru GIT and Lung.

Pathogenesis

Cyanide produced acute anoxia of the body tissues by inactivating the cytochrome oxidase enzyme system necessary for tissue respiration. As a result cyanide is called tissue asphyxiant. Death occur in acute cases within a few seconds; I'll cos of the asphyxiation. (2) CNS level.

Symptoms

In case of hydrocyanic acid and cyanides, death occur within a few seconds. There may be convulsions, paralysis, stupor, sensation of respiration before that of heartbeat.

With the cyanogenetic plants, onset of symptoms depend on the amount of glycoside ingested and the rate of liberation of cyanide from it (i.e glycosides needs to be hydrolyzed in the GIT before the HCN acid can be liberated).

It is possible for an amount of cyanide exceeding the minimum lethal dose to give rise to delay symptoms or even no symptom (2) all if ots absorption is sufficiently prolonged by slow hydrdysis of the glycosides. Death without symptoms may occur sometimes after cyanogenetic folder has been consumed. Otherwise, there may be evidence of excitement profuse salivation, convulsions of varying degree and duration, jerky movements of eyeball and respiratory distress with death ensuing from 15-60mins after the onset of symptoms.

Pathology

Congestion of blood vessels, the blood remain unclotted and often of a bright red colour which is pathognomonic. Congestion and haemorrhage of the lungs and reddening and congestion of the membrane of the

stomach. When plant has been responsible for death gastroenteritis may be observed.

Dx

Symptoms and lesions are not sufficient xtristics for accurate dx to be made. It is then essential to revert to chemical analysis of rumen or stomach content and of liver and or muscle.

Rx

Rx is aimed (2) fixing the highly lethal cyanide ion in a harmless form and converted to thiocyanate which is readily excretes by the kidney. The 1st stage is done by administration of Na nitrite i/v which converts haemoglobin to methaemoglobin. Cyanide then combines with methoglobin to form the non-toxic cyandnethaemeglobin. Cyanide readily Cyanide readily combines with circulating Hb thereby making it unavailable for O_2 carrying function.

Pathogenesis also

2nd stage: Na thiosulphate is then administered (not immediately) to act as a sulfur donor for the conversion of cyanide moiety of cyanomethaenoglobin to thiocyanate under the action Rhodenase.

VPC 302

INTRODUCTORY VETERINARY PHARMACOLOGY

PHARMACOLOGY

Pharmacology is derived from the 2 words

Pharmakon:- drugs, medicine and **Logia**: study

Pharmacology is the study of the actions of chemicals on biological materials.

The knowledge about medicine was developed by Egyptians Babylonians and Indians. Treatment of various diseases have connections with magical origins and this includes the use of incantations with various crude elements such as lizards, blood and an old book boiled in oil. The things of a hanged man, excreta and organs of various domestic animals.

Hippocrates 460-377BC was known as father of medicine and was reputed to have freed medicine from mysticism and philosophy making it more applied to rational therapy. He made little use of drug and dependent on fresh air, good food, purgatives, and enemas, blood letting, message and hydrotherapy. Hippocrates freed medicine from all inadequacies observed in crude practice. He associated disease with an imbalance of the body humor rather than demons, gods etc. He's also remembered for medical ethics.

DEFINITIONS AND TERMINOLOGIES IN PHARMACOLOGY

Toxicology

Is the study of poison and poisoning. It is considered as a division of pharmacology but it separates from pharmacology when we're concerned with overdoses and the misuse of drugs which results in toxic effects.

Pharmacy

Is concerned with the preparation and dispensing of drugs.

Posology: Study of the dosage of drugs

Metrology: has to do with the study of weights and measure as it applied to preparation and administration of drugs.

Chemotherapy: study of drugs which are capable of destroying invading organisms without destroying the host. The concept was 1st observed by Paul Erlirch. It has to do with antibiotics, anthelminthics, disinfectants, antiseptics etc.

Pharmacognosis: deal with the properties and identification of crude drugs or the study of crude drugs of vegetable and animal origin.

Therapeutics: the act of treating diseases.

Pharmacotherapeutics: the use of drugs in the treatment of diseases.

Drug: a chemical substrate which exerts a biological effect or broadly, *it is a chemical substrate which alter the responses of biological systems.* In the medicinal sense, it is a chemical or an agent which is used to treat, cure, prevent and in the diagnosis of diseases.

Potentiation: occurs when the combination of 2 drugs gives a therapeutic or pharmacological effect which is greater than the expected sum of the individual drugs when they are given alone? When the action is less, it is Antagonism effect?

Intolerance: occurs when the incidence of side effect to a drug is so great that the administration of the drug has to be discontinued, the patient is then said to show intolerance. This is an area of pharmacogenetics.

Pharmacodynamics define the ways by which drugs works or act i.e study of the effects and action of chemicals on biological systems and how these system handle the chemical.

Tolerance: is reduced/lessoned response to the action of a drug so that a larger dose than normal must be administered to give the characteristic effect.

Side Effects: are effects produced by a drug other than those which are desired which may cause some level of discomfort to the patient e.g Morphine is used as an analgesic and its use causes constipation. Atropine used to reduce muscarinic response in animals, causes blurred vision.

Idiosyncracy: an abnormal unexpected response to a drug following a normal dose of the drug. The response is a general effect of the compound.

Hypersensitivity: an allergic anaphylactic reaction which follow the use of some drug. The initial sensitizing reaction takes places when the drug is 1st given. Subsequent doses cause hypersensitivity reaction.

Habituation: A compulsive desire to continue taking a drug i.e physiological dependence on a drug in human.

Dependence: need for an individual to continue taking a drug. He/she cannot live normally without taking the drugs. When the drug is stopped, withdrawal symptoms occur. Occur in human and animal practice.

Addiction: A special form of chronic poisoning. Addicts show tolerance, habituation and dependence.

Species Tolerance: Is the ability of some animals to tolerate drugs which are toxic to most other animals.

Cross Tolerance: tolerance which is acquired by exposure to related drugs. Occur most especially in the use of antibiotics.

Biochemophology: relationship between the chemical structure and the ***Pharmacological activity***. Also known structure-activity relationship.

Bioassay: the determination of the potency or the concentration of a compound by its effect on animals. Isolated tissues, microorganism as compared with the standard.

Antagonism: reduction of the effect of one drug by another drug. Types to be studied include chemical, physiological and pharmacological (competitive and non-competitive) antagonisms.

SOURCES OF DRUGS

Drugs can be obtained from 4 major sources:

- Animal sources where vitamins, antisera and hormones can be obtained. Vitamins can be obtained from cod liver oil, hormones from extracts from thyroid gland and extracts from posterior pituitary used for the treatment of diabetes insipidus. Insulin can also be obtained from animal sources. Antisera such as anti rabies and DHLPP (anti distemper virus) vaccines.
- Plant Sources: Drugs can be obtained from the leaves, flower, fruits, their bark, the root, the wood or lignum bulbs, corms, rhizomes and seeds. The active agents from plants could be alkaloids such a atropine, glycosides such as digitalis, CHOs with sugars and pectins, fats and oils e.g castor oil. They may be saponins, tannins, waxes, oleoresin.
- Mineral sources e.g of minerals used as drug include potassium nitrate used as a diuretic, magnesium oxide used as an antacid, $MgSO_4$ as purgative.
- Synthetic sources make up the major sources of drugs in modern day therapy of disease. The 1^{st} synthetic drugs were volatile anaesthetics and this was followed by phenolic antiseptics.

DRUG NOMENCLATURE

This has to do with the naming and classification of drugs and therapeutic agents, can be divided into 2 main classes; prescription and

non-prescription drugs. Prescription drugs are those which are dispensed by law only by practisioners such as veteraninas, physicians and dentists.

Non-prescription drugs are those which can be sold over the counter e.g some analgesics such as aspirin.

Drugs can generically be classified by

1. Chemical relationship e.g sulphonamides, steroids, glycosides, barbiturates
2. Pharmacological relationship e.g sedatives, purgatives, analgestics, anaesthetics e.t.c.

In drug nomenclature, drugs have 3 different names

The chemical/first name which gives a description of the chemical constituent of the drug and shows the arrangement of atoms and atomic groups.

7-chbro- 2-methylamino -5-phenyl-3-H, 1,4, benzodiazepire-4-oxide a drug used for treatment of anxiety.

(2-Ohethyl) -2-CH3-5-nitromidazole used in treatment of protozoan parasite.

Non proprietary/approved/generic names are often given to the drug when they are found to have potential therapeutic usefulness. From above, is chlordiazepoxide and is metronidazole.

Proprietary/trade name is a registered trademark given by the company that manufactures that drug. For Librium, tropium, is flagyl.

STANDARDIZATION OF DRUGS

It is (n) an attempt to have a uniform composition and names of drugs. This is done thru the use of

- Pharmacopoiens or codex which is a medicamentarium which shows the list of all drugs. It consists of all works, monographs of therapeutic agents and this group normally show standard for their strength and purity and also contains the direction for making preparations of the drug.

There are various types of national pharmacopoieas and these are referred to as abbreviations. Some of the commonly encountered ones are BP-British Pharmacopoieas, USP- United State Pharmacopoieas Standardization of drugs is also achieved thru the use of

- Formulary which is a book which contains the various formulas for compounding the various medicinal preparation.
- National formulary is an official compendium (compilation) by the American Pharmaceutical Association with the main aim of proving standards and specifications which can be used to therapeutic agents.

ROUTES OF DRUG ADMINISTRATION

This represents the avenue or method by which drugs are introduced int the body. The routes used administration of drug will depend on whether the drug is intended for a systemic action i.e if the drug has to go thru the bloodstream to all parts of the body or if it intended for a local action (action is restricted to a small area). Drugs which have a local action do not need to be absorbed. However, drugs intended for systemic action have to be absorbed (i.e non Intravascular)

The 2 major routes for drug administration are

1) Enteral : are drugs administered through the mouth and so pass thru the GIT.
2) Parenteral: represents all the routes other than the oral route.

i. Inhalation. When drugs pass thru the respiratory tract using gases, vaporized liquids and finely distributed solids.
ii. Insufflation: use of snuff. Not common in vet practice
iii. Intracutaneous route: when drugs have to be injected into the skin.
iv. Diahermat: when a drug has to be placed on the skin. Also known as hypod

v. Subcutaneous/hypodermic: when drug is injected under the dry skin (s/c). required when large volumes of drug/solution is to be injected.
vi. Intraneural: injection a drug into a nerve trunk
vii. Intramuscular (i/m): injection of drug into the muscle
viii. Intraperitoreal: injection of drugs into the peritoneum
ix. Intrapleural: injection of drugs into the lungs
x. Intracisternal: injection of drugs into the cerebrospinal space
xi. Intraocular: (Injection of drugs directly into the blood could be by intravenous (i/v) or intra arterial.
xii. Intramammary: injection of drugs into the mammary gland.
xiii. Intravascular: by instillation, dropping of drugs into the eye.

MOLECULAR PHARMACOLOGY

Site of Action: Represents the part of the body, the organ or tissue or the cell where a drug or compound exerts its pharmacological action. With respect to the host, chemotherapeutic agents and antibiotics have an indirect action by destroying the invading organism without having a direct effect on the host. When the animal is provided with some deficient product such as bloo, fluid, electrolyte, hormones, this is known as replacement therapy.

Generally, drugs act cellularly, extracellularly and introcellularly.

- Cellular site type of action: when drugs act directly on the cell e.g drugs which alter cell membrane permeability such as thiazide diuretic and it tends to decrease Na absorption at the tubular site or local anaesthetics which alter neuronal permeability for Na and K.
- Extracellular site of action: drugs act outside the cell by combining with extracellular components e.g the neutralization of gastric acid by antacid such as $NaHCO_3$, $NaHCO_3$ + HCL = $NaCL+H_20$ + $C0_2$. Heparin prevents clothing by combining with

thrombin which is required for the blood clothing process. The action of heparin in preventing coagulation of blood is thru the attraction of opposite forces with the electron negative heparin combining with electropositive group of proteins to form new compound. These proteins within the blood are important for blood coagulation. The specific antidote Ca disodium EDTA is used to threat head poisoning at the extracelluar level.

- Intracellular site of action: drugs may act within the cell by combing with intracellular components e.g antibiotics like tetracycline, chloramphenecol act by preventing bacterial protein synthesis within the cell. (pharmacodynamic(s) deal with the site of drug action.

MECHANISM OF DRUG ACTION

Drugs are known to produce their action by combing with functional macromolecular component of the organism. This tends to alter some cellular components which initiates series of biochemical and physiological changes which is a characteristic response to the drug. This concept was 1st observed by Paul Erlirch and John Langeley who had independent observation. Paul Erlich observed agent and the toxic effect of a Varity of synthetic organic substances. This was stated in his thesis that bodies are inactive unless they are affixed. John Langeley noted the ability of curare a South African arrow poison to inhibit the effect of nicotine induced actions of the skeletal muscle when as the tissue remain responsive to the direct electrical stimulation.

RECEPTOR THEORY

The macromolecular site of the organism with which drugs interact is known as the RECEPTOR and the complex which is formed as a result of this interaction is known as the drug-receptor complex. This theory/concept is known as Receptor theory. The theory observes that

drugs combine reversibly/reversibly with the receptor and the macromolecular is the excised to undergo a configuration change. This change alone or by eliciting a chain of reaction of configurationally changes then manifest as a response/action. This effect could be muscle contraction increase in secretion, change in membrane permeability inhibition of an enzyme, or change in metabolism.

To form a drug-receptor complex, sufficient drug molecule in the vicinity of the cell or receptor.

Drugs which combine with a receptor to produce a response is known as an AGONIST. An against has

1) affinity for the receptor
2) intrinsic activity by producing a response.

The ability of a drug to produce an effect after fixing to a receptor is also known as EFFICACY.

- Some drugs may form a complex with the receptor and yet do not elicit a response. Such drugs are known as ANTAGONIST. They have affinity but do not have intrinsic activity.
- Some drugs may form a drug receptor complex and produce a small response. These are known a PARTIAL AGONIST. They have affinity with a minor intrinsic activity. In some cases, the drug may have affinity and do not produce antagonism, the receptors are then called SILENT RECEPTORS, e.g combination of some drugs with plasma protein does not produce response.

RECEPTION OCCUPATION AND RATE THEORIES

The response which is obtained as a result of drug-receptor complex formation are associated with 2 theories (i) Receptor occupation theory (ii) Rate theory.

The receptor occupation theory observes that the level of response which is produced from the drug-receptor complex is due to the number of receptors which are occupied by the drugs. This means that the level of the response will increase with increasing concentration of the drug.
The rate theory observes that response is not dependent on the number of receptors occupied but on the rate at which the complexes are formed i.e stimulus provided by an against/drug is proportional to the rate of combination between the drug molecules and the receptors. This means that each association between a drug molecule and a receptor produces a quantum of stimulation/response.

DOSAGE FORMS

This presents the preparations of the drug for administration in dose form to be given to the patient. Types are

1) Tablets consist of an active drug combined with a binder and the expicient/solvent and then compressed into shapes.
2) Pills are mixtures of drugs and sticky binder rolled into a uniform cylinder and then cut to form avoid or spherical shapes which are then provided with a glazing sugar coating.
3) Capsules are containers of mixtures of gelation and glycerine containing powder/liquid drug.
4) Boluses are large compressed tablets rectangular in shape
5) Mixtures are aqueous solutions/suspensions intended for oral administration.
6) Syrups are solutions of drugs in 85% sucrose
7) Elixins are clear sweetened hydro-alcoholic solution intended for oral use
8) Emulsions are oily substances dispersed in an aqueous medium with acacia, lecithin and CH3 cellulose which are added to stabilize the dispenson or it is a system with 2 immiscible liquids in which one is dispensed in a form of small

globules. The one in form of globules represents the internal phase and the other, external phase.

9) Tinctures are extractive preparations with alcohol or H20 types are alcoholic, ammoniated, ethereal, hydro-alcoholic, glycerinated tinctures.
10) Injections are sterile solution/suspensions in an aqueous or sometimes oil vehicle.
11) Vials injectable preparations that have to be reconstituted for injections.
12) Implants hand sterile pellets which are often inserted under the skin where they dissolve slowly T.
13) Liniments/braces are liquid/semisolid preparation applied to the skin with inuction/rubbing.
14) Lotions: solutions or suspensions of soothing substances applied to the skin without friction e.g calamine lotion.
15) Ointments: semisolid greasy preparations in which the drug is dispersed in a suitable base such as petrolatum or polyethylene glycol
16) Creams; drugs in water-oil emulsion
17) Aerosols are drugs in suitable solvents and packaged under pressure with propellants such as fluorinated hydrocarbon or Nitrogen.
18) Dusting powders are mixture of drugs in powder form for application to external surfaces. It may be applied for adsorbent (cornstarch) or for its lubricant defect (talcum).

PHARMACOKINETIC PRINCIPLES

Pharmacokinetic is an attempt to quantitatively account for the where-about of a drug after administration into the body. This involves, absorption distribution, elimination processes which control the drug molecule.

Drug absorption is the movement of the solute into the blood stream from the site of administration through biological barriers. Drugs which pass thru the GIT, lungs and skin must 1st have to pass thru epithelial barriers before they get into the interstitium. Drugs which are administered subcutaneously or intramuscularly do not pass thru these barriers. Drugs which go thru all the routes have to go thru the capillary barrier to get into the systemic circulation except when administered intracveinously.

Absorption through the GIT

Drug administration tgru the GIT include the dosage forms e.g tablets, capsules, suspensions, powders, elixirs suppositories, syrups and tinctures.

Advantages of the Oral Routes

It is the safest and most convenient

Disadvantages of the Oral Routes

1) Irritation to the gastric mucosa causing nausea and vomiting
2) Destruction of some of the drugs by gastric acidity e.g penicillin as well as gastric juice
3) Precipitation and insolubility of some drugs in the digestive fluid e.g acidic drugs such as aspirin and phenobarbitone are non-ionized and are easily absorbed whereas basic drugs such as atropine are ionized and poorly absorbed.
4) Variable rates of absorption due to factors associated with gastric function e.g motility
5) The route is too slow for it to be an ideal for emergency cases.
6) It cannot be used on unconscious patients
7) Some drugs have unpleasant tastes and this would be rejected by the animal. These unpleasant tastes can be masked thru the use of some expicient.

Absorption through subcutaneous route

This route by passes the barrier of the epidermis cos the drug is placed under the dermis. The hindrances to the capillary composed of endothelial cells. Drug absorption in this route can be accelerated by combining the drug with the enzyme hyarunonidase which breaks down the cutaneous tissue or absorption could be decreased by the use of vasoconstrictor adrenaline or a local anesthetic which reduces blood flow to the area and reduces uptake. The rate of capillary flow determine the rate of blood entry into the systemic circulation. The more vascular the area, the more absorption takes place.

Advantages

1) The relatives ease in rapid absorption
2) Absorption can be retarded in the presence of any adverse effect when compared with i/v route.

Disadvantages

1) Some drugs are too irritating and painful to be injected subcutaneously and may even cause sterile abscess.
2) Infection occurs more readily than i/v route

Absorption through intramuscular route.

The i/m route allows for greater volume of solution to be injected slowly as well as rapidly thru the i/m route by altering the physical state of the drug so that while it is in the muscle, it goes into solutions in small fractions over a period of time. This is the case with some microcrystalline preparations of penicillin which is known as depot penicillin.

Absorption through the intravenous route

The absorption is required and the drug moves directly into the systemic circulation. The jugular vein is mostly used in vet. Practice. It's very useful in emergency situation. It ensures that all the drug is taken. This

means caution has to taken during administration by ensuring that correct dose is used. This must be given slowly cos overdose cannot be withdrawn nor absorption/distribution retarded; the pharmacological action of the drug can be varied. Irritating, hypertonic relatively acidic solutions can be administered large doses/volumes can also be administered.

Intrapentoneal route

Has large absorptive surface. It is a faster route than i/m route cos of thin membrane. The parenteral routes are often used cos of:

1) poor absorption enterally
2) to obtain rapid response
3) drugs are inactivated in the GIT and their passage thru portal circulation.
4) Parenteral route is also used in vomiting or unconscious patient
5) It ensures compliance with the drug regime

FACTORS WHICH AFFECT ABSORPTION OF DRUGS

Drug ⟶ Dissolution of drug ⟶ Absorption

1. PH depends on the PK_A i.e the ionization of the drugs which is influenced by the pH of the medium. At low pH, as occurs within the gastric content, the ionization of acidic drugs is depressed. Within the intestine, where the pH is high, acidic drugs are well ionized and :. Are less absorbed whereas basic drugs are better absorbed.
2. Area of the absorbing surface: The mucosa of the small intestine is well adapted for absorption due to the presence of microvillus and high blood flow to the area.
3. Concentration of the dissolved drug: This is often high when there is less food within the GIT, but it low when the stomach is filled.
4. GIT secretions: Some drugs which are acid laile are easily destroyed in the stomach e.g some penicillin drugs and esters of

some drugs such as procaine. Some of these drugs however may be activated during absorption.

Chlorazepate ⟶ Nordiazepan

5. Influence of enzymes: Some protedytic digestive enzymes destroy polypeptide drugs such as insulin, oxytocin
6. Some drugs are metabolized by bacterial action and this affects GIT absorption.
7. Some drugs are metabolized during absorption cause the intestional mucosa has some sulphate conjugating enzymes which activate some drugs during the process of absorption e.g Chlorpromazine, Oestroges, isoprenaline.
8. Clearance after absorption: The greater the removal of a drug from the site of absorption the greater is the cone gradient the faster the rate of absorption.
9. Transite time: Slow intestinal movement favous high absorption.
10. GIT motolity: The propulsive movement of the GIT plays an important role in disintegration and dissolution of solid drug formulation.
11. Disorder of GIT affects absorption
12. Drug interaction within GIT affects absorption
13. Salts of acid or basic drugs are usually more soluble then the parent compound. This is why acidic drugs are prepared as salts of Na or other cations and basic drugs are prepared as the hydrochloride or acidic salt
14. Size of the drug particle determines the rate of dissolution. The smaller the particle size, the greater the rate of dissolution cos the proportion of the surface area exposed to the solvent compared with the volume of the particle increase with decreasing particle size. This is why some drugs are administered in their microcrystalline preparations e.g sulfadiazine. Microcrystalline solution ensures total absorption of drugs.

DRUG PASSAGE ACROSS BIOLOGICAL MEMBRANCES

The anatomic structure which influences or act as a barrier to the movement of compound is known as semi-permeable, it allows some drugs to pass are entirely excluded from passage.

MECHANISM OF DRUG ABSORPTION

Drugs can be absorbed by

1) Passive diffusion most drugs are absorbed from the GIT by lipid diffusion of non-ionized molecules. The molecules diffuse across a concentration gradient into the aqeous phase thru a double layerad lipoprotein membrane. Such drugs are said to have high lipid water partition coefficient lipid solubility, level of ionization, molecular size and the concentration gradient which is the driving force.
2) Filtration: Drugs which are not lipid soluble or ionized are absorbed by flowing through pores whose function is to allow passage of hydrophilic ions due to bydrostatic/osmetic differences across the membrane. The sizes of the pores differ with different body membranes.
3) Facilitated diffusion: A simple diffusion but a carrier is used and:. the rate of absorption greater across the membrane. The process is susceptible to blockage by metabolic inhibitors. It is selective and saturable. A⟶A+B⟶AB⟶ A + B. Most rugs may be absorbed by this mechanism. The transport is across a concentration gradient.
4) Active transport: This is the transport of drug molecule against conc, gradient with the use of energy. It is selective, saturable and can be blocked.
5) Pinocytosis: engulfment of large molecules by cells as a way of absorption.

DRUG DISTRIBUTION

The process whereby absorbed drugs which have gained access into the circulatory system are taken to parts of the body. The distribution of drugs is governed by the affinities they have for various constituents of the tissue including H20 solubility, lipid solubility, binding to extracellular membranes and intracellular up take.

Factors affecting drug distribution

1) Protein binding such proteins include globulin and albumin. Drug binding acts as a stronger site for the drug which is in equilibrium with free unbound drug in circulation and at the site of action. Toxicity of highly bound drugs tends to increase in cases of hypoproteinemia.
2) Binding to non-protein site include cellular and non-cellular structures e.g Lead is taken up in bones, lipid soluble compounds such as volatile anaesthetics compounds and organochlorine insecticides are sequestered in the fatty tissue of the body.
3) Physico-chemical nature of the drug: Drug distribution is affected by factors such as pH differences between the plasma and extracellular fluid. The pKA and the lipid solubility of the drug, the presence of binding sites and active transport mechanisms.
4) Presence of specialized barrier such barriers include (i) blood brain barrier between the blood and the extracellular space of the brain. capillary endothelium and astrocytic sheath (ii) blood CSF barrier (endothelium of blood vessels and epithelium of choroids plexus. (iii) placenta barriers (maternal vascular endothelium and the epithelial membrane of the foetal villus and the capillary endothelium of the foetus). These barriers control to a greater extent, the amount of drugs getting into

these systems. Normally the non-ionize lipid soluble drugs are readily absorbed.

5) Dilution and drug distribution: Most drugs are dissolved in body water after absorption since different drugs have different level of dilution. The level of drug distribution equally differ:. Drugs such as antipyrine which are distributed thru-out the total body water is used to estimate the total body H_20. The volume of extracellular H_20 can be determined by Inulin and NaI Plasma volume can be determined by I albumin.

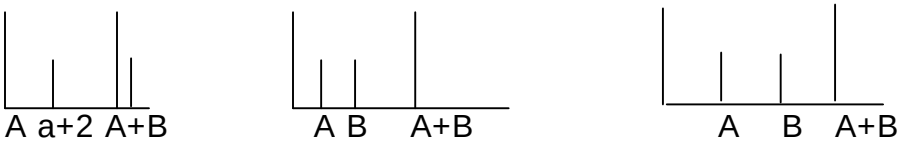
DRUG REDESTRIBUTION

The way by which drug action effect is terminated. It represents the transport of drug from their try source of action to where they have no pharmacology action; this occurs after the process of distribution e.g the movement of the general anaesthetic drug thiopentone from it's 1 site of action (brain) to the fat depot and muscle is redistribution. This redistribution of thiopentone is known to be responsible for the short acting action of the drug.

Secondly, in organic, lead following absorption is concentrated with the RBC, visceral organs with highest conc. Within the liver and kidney leads is then redistributed to the bone where the highest conc is attained.

DRUG INTERACTIONS

Occur when drugs are administered simultaneously. This include Antagonism is the reduction of the effect of I drug by the other. The drug which produces the response is known as the agonist and the I reducing its response is known as the antagonist.



Antagonism **Addition** **Synergism**

Addition: 2 drugs which act by similar mechanism to produce an effect equal to the anticipated combined effect of both of each of the drug.

Summation: 2 drugs, irrespective of the mechanism of action elicit a response equal to the anticipated effect of each of the 2 drugs.

Synergism: 2 drugs producing an effect greater than the sum of the individual effect of the 2 compound. It is also known as a potentiating effect. Usually the 2 drugs act by different mechanism at different sites.

ANTAGONISM

Could be physiological chemical or pharmacological

- Physiological Anatgonism: An antagonism is physiological if the 2 drugs produce apposite effect e.g histamine produces contraction on the guinea pig ileum, this is antagonized by adrenaline which relaxes the tissue (which causes relaxation of the tissue)* with both drugs acting on different receptors.
- ***Chemical antagonism***: Involves the reaction between the drugs e.g chelation of lead by Ca EDTA; this is used in treatment of lead poisoning.
- ***Pharmacological antagonism***: Occurs when both drugs excites the same types of receptors. However, it is only one of the drugs which produces the response or it is a against with intrinsic activity could be competitive or non-competitive. The degree of antagonism produced depends on the concentration of the antagonist and its affinities constant.

Competitive antagonism occurs when increasing the dose of the maximum response can be achieved with the agonist alone or in the presence of the antagonist. The antagonist combines reversibly with the same binding site as the agonist.

Non-competitive antagonism: If increasing the dose of the agonist does not change the antagonism remarkably, this is non-competitive. The antagonist combines irreversibly with the bi receptor site of the agonist.

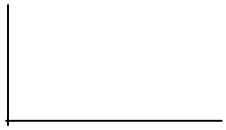
EVALUATION OF DRUG SAFETY

The ideal drug will produce its therapeutic effect without having a side effect. However, there is no ideal drug and drugs may have 1 or 2 side effects. This means for any drug, there'll be some dose that'll produce a toxic effect. The safety of the drug depends on the degree of separation between the dose producing the desirable effect and the dose which elicits the side effect.

PARAMETERS FOR EVALUATION OF DRUG SAFETY

1) Effective Dose 50 (EDso) represents the dose which will produce a response which is 50% of the maximum possible.

2) Lethal, Dose 50 (LD50) is the dose of the drug or poison which 'll kill half of the test animal. This could be a measure of toxicity of the drug cos the higher the LDso, the lesser that toxicity or the safer the drug.



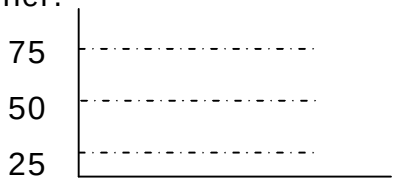
3) Therapeutic Index (TI) is the ratio of LDso to EDso i.e TI

   $= \frac{\text{LDso}}{\text{EDso}}$. The higher the TI, the safer the drug.

   However, TI of most drugs is usually greater than I cos the LDso is greater than the EDso. A drug with a high TI is said to have a wide safety margin.

   2 drugs having the same TI may not necessarily have the same safety.

4) Therapeutic Ratio (TR) is the ratio of LD24 to ED's of a drug. It serves as a better evaluation of the drug than TI e.g 2 drugs may have same. TR but their TR ratio may reveal one to be safer than the other.



5) Certain safety factor gives an idea of relative safety A C & F greater than I indicates that the dose effective in 99% of the population is less than that which will be lethal to 1% of the population.

CSF – LD 1

ED 99

6) Standard Safety Margin ha. $\frac{LD - ED_{99}}{ED_{99}} \times 100$ in percent

Non-Receptor Mediator Action

It is observed that a number of drugs may differ in their chemical structures but still have the same pharmacological action e.g the different types of general anaesthetic drugs have different structures yet they depress the CNS. The implication of this might be that these drugs are not acting thru receptor interaction or structural specificity. These actions are associated with physicohemical properties of the drugs. Other drugs in this group include osmotic diuretics, saline carthartic/purgative, antiseptics, antacids, urinary aciolifiers and alkalizers.

There are usually effective ways of obtaining their actions and this is by high concentrations of the drug. The general anaesthetic agents have different types of chemical structures and are all known to act on cells in a non-specific manner. They act on the cell membrane of neuron due to their physicochemical nature causing events which

results in anaesthetic. General anacethetic are highly lipid soluble and this form the basis for the hydrophobic anaesthetics form clathrate type microcrystals with the water within the brain. The microcrystals then increase electrical resistance and this impreds prevents the function of the brain from acting and this results in depression.

It is also assumed that anaesthetics form hydrophobic bonds with a polar patches of protoplasmic proteins and this alters their configuration and physiological action Osmotic diuretics such as Mannitol act indirectly by inhibiting the re-absorption of Na at the proximal tabule. Saline purgatives such as Na_2SO_4 or $MgSO_4$ act by retaining H_20 in the GIT. It is the increased intraluminal volume which causes motility and diarrhea. Antacids such as Al hydroxide, $NaHCo_3$ also act by reacting with excess acid within the GIT. Urinary acidifiers such as NH_4CL and ascorbate salts and urinary alkalizers such as $NaHCO_3$ associate their action with their chemical nature.

DRUG ELIMINATION

It involves the processes of drug metabolism and excretion.

PRINCIPLE OF DRUG METABOLISM

Drug metabolism is also known as drug biotrainsformation or drug detoxification. The process involves the attenuation/loss of pharmacological activity of the drug resulting from enzymatically controlled changes within the body. This results in the loss/reduction in activity/toxicity of the compound. Sometimes, there is increase in the activity of the drug and the metabolite is more active than the parent compound; this is known as Lethal synthesis. Metabolism makes the compound less lipid soluble, more polar and Hydrophilic. The major sites of drug metabolism is in the liver where the microsomal enzymes within the hepatocytes are important.

Other sites include the kidney, lung intestinal mucosa, plasma and nervous tissue. The number of microsomal enzymes are influenced by factors such as drug, hormones and the sex of animals. Stress temperature, nutritional status and the pathological state of the animal; this is known as enzyme induction and could result in increased enzyme activity or reduced activity.

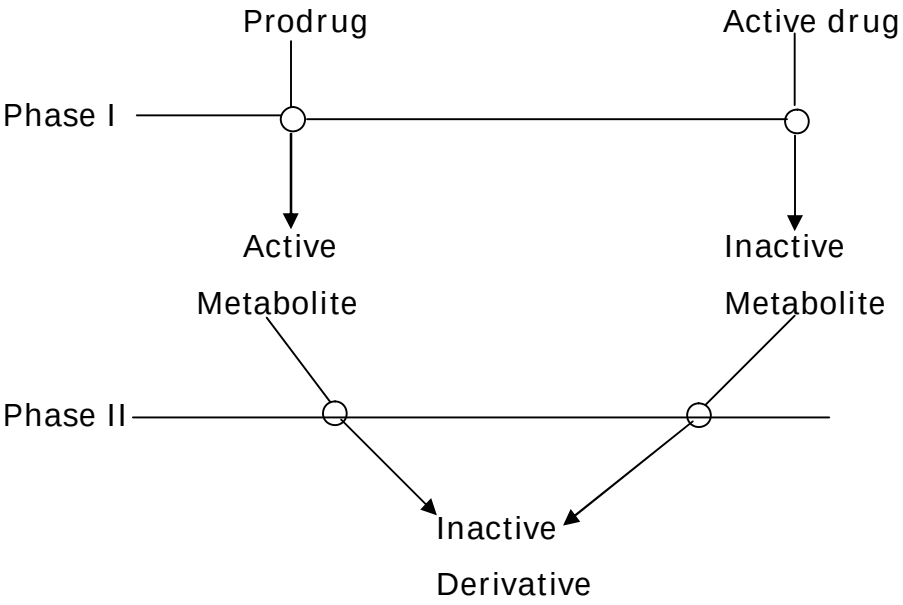
The qualitative and quantitative differences in enzyme result in species differences in drug toxicity.

Types of metabolic transformations

Involves phase I and II metabolic reactions

Phase I: Non synthetic phase and involves a change in drug molecule and it includes oxidation, reduction and hydrolysis reaction. It may result in activation change or inactivation of the drug.

Phase II: synthetic phase and involves the formation of conjugates with drugs and the metabolites from the phase I reactions. The conjugate is formed with endogenous substances such as CHO3 and amino acids



OXIDATION REACTIONS

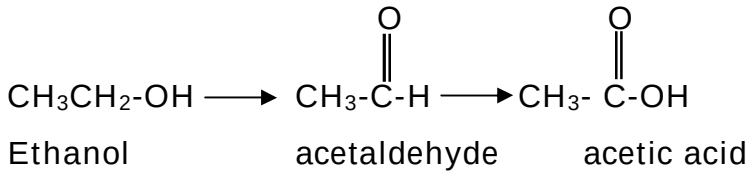
Results in proton enriched products and there are 2 types

- Microsomal oxidation reactions
- Non-microsomal oxidation reactions.

Microsomal oxidation reactions is also known as mixed function oxidase reaction and takes place mainly in the liver. These reactions include

1) Oxidation of alkyl chains. It involves alkyl compounds alkyl side chains of aromatic compound with carbonyl, carboxyl, aldehyde or amino groups. This include

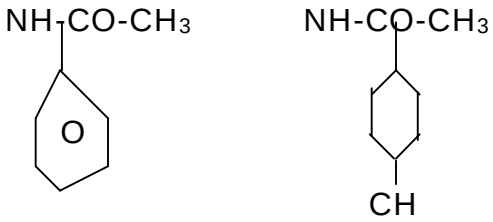
   (a) ethanol breakdown to acetylaldehyde then to acetic acid



   (b) amine compounds undergo deamination such as 5-OH tryptamine or serotonine 5-OH acetic acid

2) Oxidation of aromatic ring

   a) acetanilide ⟶ acetaminophen



3) Oxidative dealkylation could be on an O_2 or N2

   O – dealkylation codeine ⟶ morphine

   Phenacetin ⟶ acetaminophen

   N- dealkylation mephobarbital ⟶ Phenobarbital

4) N-oxidation

   Aniline ⟶ nitrobenzene

5) Sulphoxidation

   Thioethers are oxidized to their corresponding sulphoxides such as oxidation of

Chlorpromazine ⟶ chlorpromazine sulfoxide

Non-microsomal oxidation reactions are catalyzed by enzymes within the mitochondria cytoplasmic plasma or other organelles.

REDUCTION REACTION

Involves the conversion of aldehydes to 1o alcochols

e.g chlorohydrate trichloroethanol

cyclic ketone alcohol

Reduction reaction normally take place with disulphide bonds or azo bonds or nitro N02 group

Progesterone ⟶ pregnandiol

Protonsil ⟶ sulfanilamide

Dehalogenation reactions e.g removal of Cl, I and Br by H are examples of reduction reaction.

REDUCTION REACTION

Breakdown of esters e.g esters of choline, amide bonds, hydrazides, glycoside

* Atropine ⟶ tropine + tropic acid
* Cocaine is hydrolysed to benzoic acid and ergonine methyl ester
* Procaine ⟶ P-amino benzoic acid + diethylamino – ethanol
* Acetylcholine ⟶ Chloine + acetic acid

PHASE II-SYNTHETIC REACTION

Is usually the last step in detoxification reaction and it always almost result in the loss of biological activity of the drug. It may be preceded by 1 or more of the phase I reactions. It's also known as the conjugation reaction and it involves chemical combination of the compound of the metabolite with a molecule provided by the body.

The conjugating agent is usually a CHO, amino acid, or compounds derived from them. The conjugation takes place when the metabolite has an appropriate group or center and these include –SH,-OH, COOH etc

and amino group. Compounds which have none of this acquire it from the non-synthetic reactions. Conjugated metabolites are invariably less lipid soluble than their parent compound. Conjugation reaction include

1) Glucuronide conjugation is the most frequently occurring conjugation and it is the conjugation of glucuronide by UDP-glucuronic acid within the hepatocytes . Glucuronidation results in a compound which can easily be secreated in the urine and bile because they are highly water soluble. They've broken down within the intestine by bacteria and may result in the enterohepatic circulation of the drug. Glucuronide formation is low in cats.
2) Sulphate ethereal/SO4 conjugation is the transfer of S04 group from the compound phosphate-adenosyl-l- phosphor SO4 by sulphokinase to aliphatic/aromatic hydroxyl containing compounds as well as amines e.g ethereal SO4 formed with H2 groups of phenol and catechol, isoprenaline, chloramphenicol, serotonin and other steroids.
3) Acetylation: L-amino acids, alkyl and aryl amines are combined with organic acids to form amides. In this way, amines such as sulphonilamide or acids such as benzoic acid and phenyl acetic acid are metabolized. The endogeous acid is usually acetic acid. The amine is glycine which ccurs in many species or ghitamine, which occurs mainly in primates. Ornithine or glycine occurs in birds. Dogs have little or no ability to aceylate amino groups e,g acylation sulfonamides + alcetic acid salicylic acid + acetic acid, phenyl acetic acid + glycine (b) salicyluric acid (c) phenaceturic acid

   a) sulfonaceturic acid (b) Benzoic + ornithine → benzoly ornitine

   e) Indoleacetic aicd + glutamine indoacetic → acidglutamine

   the enzymes which catalyze these reactions are in the mitochondria of the liver and the kidney.

4) Alkylation is the transfer of an alkyl group mainly a methyl/ethyl group occurring thru an active group methionine known as S-adenosyl methionine e.g

Nicotinamide ⟶ N-methyl nicotinamide

Histamine ⟶ N-methyl histamine

FACTORS AFFECTING DRUG METABOLISM

i) Species differences e.g Phenylbutazone, procaine or barbiturate have differences in spp. Metabolism

ii) Genetic differences

iii) Age of the animal drug metal is usually feeble in the foctus and newborn cos the microsomal drug metabolizing enzymes and the conjugating enzymes are not fully formed. In the aged animal, therez loss of activity.

iv) Sex: differences in metab is under the influence of hormones

v) Nutrition: Starvation/malnutrition affects the way drugs are metabolized i.e depress drug metab.

vi) Pathological conditions: Damage to the liver reduces drug metab cos it is the major site of drug metab.

THE FIRST PASS EFFECT

Drugs which are absorbed from the intestine into the portal circulation are exposed to drug metab before they get into systemic circulation. When large proportion of the drug is metabolized, as a result of this, it is said to be subject to the 1st pass effect e.g (i) Lidocaine (ii) diazepam (iii) phenbatazone (iv) Griseofulvin (v) Propanol.

DRUG EXCRETION

Involves glomerular fithration carrier-mediated excretion within the proximal convoluted tubule and passive resorption by diffusion in the distal portion of the nephron. Substances eliminated in the kidney are

H_2O soluble and only drugs which are protein bound or excessively large molecule sized are retained in the plasma.

The amount of drug which enter the tubular lumen by filtration is dependent on binding to plasma proteins and glomecular filtration rate. The drug concentration increases as the H2O resorption from GF which is a concentration gradient favouring drug resorption is established along nephion. The urine can be manipulated in order to achieve increased/decrease blood excretion. The normal pH for normal carnivones e.g dogs and cats is acidic 5.5-7 whereas it is basic for cattle, horses and sheep generally herbivores. Urine pH is dependent on diet. Animal protein or grains with high protein leads to an acid urine. Grasses eating could result in alkaline urine. The manipulation of the urine is used in the treatment of poisoning with some weak acid drug e.g Phenobarbital, Na2CO3 is then used to produce an alkaline urine to hasten elimination acidic drug is eliminated in the urine following secretion depends on the degree of ionization within the tubular urin.

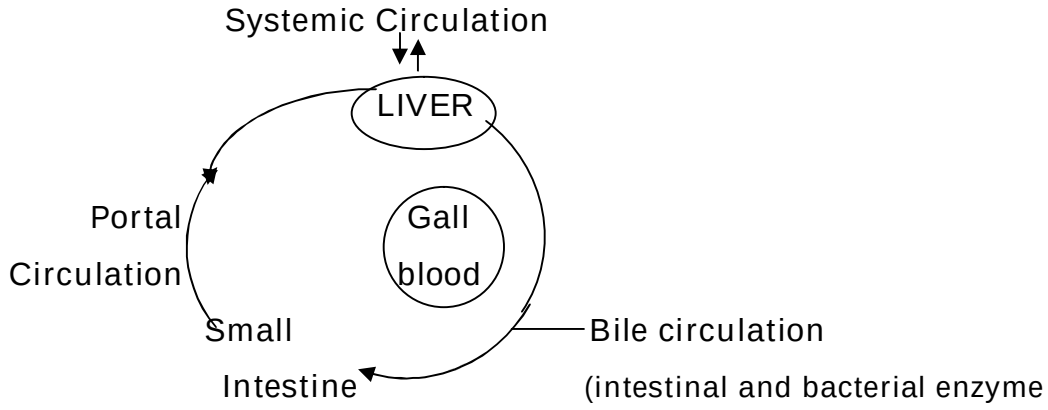
Some drugs are excreted unchanged in the urine e.g antibiotios (penicillins, cephallosporins, aminoglycoside oxytetracycline).

b) non-depolarizing (competitive) neuromuscular blockers-d-tubocuraine, gallamine

c) diuretics (except ethacrynic acid and digoxin)

In dogs, alkanilization of the urine increase the excretion of salicylate (aspirin), sulfisoxazole, phenobarbitone or acidification of the urine in dog increases the excretion of the drug amphetamine. The induction of alkaline diuretic may combat intoxication by lipid soluble weak organic acids.

ENTEROHEPATIC CIRCULATION



COMPARATIVE ASPECT OF DRUG ABSORPTION IN ANIMALS

Based on the food/diet they eat, domestic animals can be classified into carnivore (dogs, cats, herbivores, pigs) (goat and sheep) omnivores. The pH gradient between GIT fluid and the plasma of these animals is very important in

i) The rate of drug absorption and the consequent degree of distribution

ii) Excretion of weak organic electrolytes parantrally administered into the GIT.

The rate of gastric emptying is also an important physiologic factor in determining drug absorption. The digestive physiological features of the ruminants which allows fermentation to take place in their forestomach and in which semi-solid fermentation product is maintained at a narrow pH range of 5.5-6.5. This is made possible with the buffers which is secreted with the alkaline saliva pH 8.0-8.4 and it's also due to the large ruminal fluid which is about 60L in cattle, 4-4.5L in sheep and goat. This means a drug can only attain minimal /low level concentration in this

organ. This has the effect of decreasing the rate but not the extent of absorption.

The non-ionized lipid soluble drugs from organic acids are well absorbed from the rumen. The microfloral within the rumen has the effect of metabolizing some drugs. Chronic administration of antimicrobial has the effect of killing all the microfloral and thereby disturbing digestion.

Lipid soluble organic bases, when parentrally administered may diffuse from systemic circulation and be trapped within the rumen by the process of ionization depending on their pKa values. The horse is a continuous feeder with a small stomach which is seldom empty. The microbial digestion of polysaccharides in the colon of the horses is an essential digestive process.

PHARMACGENETICS

Deals with the study of genenetic modification of drug response. It's observed that therez variability in response to drugs. This is under genetic control and inherited characteristics are controlled by 1 gene or pairs or many gone multifactorial inheritance. Characteristics controlled by many genes show continuous traits e.g height is a continuous trait. When a trait is controlled by a single gene, it is discontinuous and the animals may show the traits or may not show it.

The function of a gene is to control synthesis by mRNA which is responsible for production specific proteins. This means that genetic control of pharmacological responses will be in the control of the synthesis of specific proteins. The 2 main structural proteins which are important in drug action are the drug receptors and the drug metabolizing enzymes in a population, a situation known as polymorphism may exist. Polymorphism is a situation in which 2 or more discontinuous forms of a species occur within the same population. This

situation exists in the metabolism of the drugs known as **ISONIAZID.** This drug is metabolized by acetylation and it has been observed to occur by 2 distint population slow and rapid metabolizers. This means that the group which metabolizes the drug fast have the necessary enzymes for acetylation whereas the slow metabolizers do not. The xteristic is controlled by a single pair of genes with those showing rapid metabolism being dominant and slow metabolizers having a recessive gene. This is a case of polymorphism in drug metabolism. This means that all drugs which are metabolized by acetylation will show similar characteristics.

Some groups of rabbits are resistant to the toxic effect of the enzyme atropine cos they have enzymes for its metabolism. The enzyme known as atropinesterase in the liver. The enzyme is gene iontrolled. Other animals which don't have atropinestrases suffer toxicity from atropine.

H_2O_2 is used as an antiseptic. However, it is also produced in the tissues by the process ofoxidation and it is rapidly converted to 0_2 and H_2O by the enzyme catalase. Catalase is under the control of a single gene. An animal that does not have catalase suffers from acsitution known as acatalase i.e tissues 'll be subjected to all kinds of radical damage.

The use of Carbon tetrachloride (GCl_4) in sheep as a fasciolicide requires test dosing as a result of abnormal reactions to the drug among sheep population.

Sometimes, the control of drug response is also sex linked. This means that it could be the X or Y chromosome which carriers the gene controlling the response e.g primaquine is known to cause extensive haemolytic defect in some individuals cos they lack the enzyme glucose-6-P-dehydrogenase which is required for cell membrane integrity of the RBC. This cells of then succumb to the lytic effect of primaquine. This inherited lack of this enzyme is on the X-chronosome and cos females have 2 x chromosomes and since only 1 of them carries this characteristics of does not manifest itself as dearly as it does in male

where a single x chromosome can give a clear cut deficiency. This G-6-PD deficient patient also react to other haemolytic agents such as the drugs acetailid, phenacelin, sulfonamide and some fava-beans.

Other factors which may also be considered under pharmacogenetics are the issue of whether a drug can influence genetic materials in terms of producing irritations. Some chemical have been used to produce subspecies of some plants by chromosomal mutation. Such chemicals as colchicines urethane which is a cytotoxic drug and is used in the treatment of cancer. Substances which have been used for experimental mutation include barbiturate, sulfolamides, phendic compound, acridines, steroid, hormones, caffeine, nicotine and vitamins. Therapeutic levels of these drugs however may not produce mutation.

Cancer cell production within the body may result from the metanogenic ability cancernogens. All concernogic agents have immunosur pressor activity i.e they can depress the production of immune bodies.

IDIOSYNCRACY

Is a congenital quantitatively/qualitatively unusual reaction to drug e.g the drug produce depression in most animals but in some patients, it may produce excitement.

A situation in which a simple dose of a drug produces an unexpected response/autoward response idiosyncracy.

DRUG ALLERGY

Is an attered response to a drug as a result of exposure to a previous sensitizing dosage. It is an immunological mechanism. It may result in immediate reactions such anphylaxis, urticara and angroneurotic reactions. It could also result in drug fever asthma or a delayed appearance of manifestation following an initial sensizing dose.

QUANTITATIVE ASPECT OF DRUG ACTION

Provides the basis for the evaluation and comparison of drug safety. Effectiveness and for rational application of the drug for its therapeutic effect.... The selection of a route of administration is an important factor in determining

i) rate of absorption of the drug

ii) latent period before the effect of the drug is seen

iii) the maximal attainable drug concentration and the rate of clearance and consequently, the maximal obtainable effect for the selected dose and the duration of action.

QUANTITATIVE ASPECT OF DRUG RECEPTOR REACTION

The product of reaction between a drug and its receptor results in a stimulus which leads to the events leading to the effect which is associated with the drug.

Drug + Receptor $\rightleftharpoons$ D-R complex $\rightleftharpoons$ Effect

Drug + Receptor $\rightleftharpoons$ Response

D + x

If 100% receptor is available

Then D + 100-Y $\underset{K2}{\overset{K_1}{\rightleftharpoons}}$ Y Drug + free receptor Response

$$D = \frac{K_2}{K_1} \quad \frac{Y}{100-Y}$$

If $Ke = K_1/K_2$

Then $D = \frac{Y}{K_e(100-Y)}$

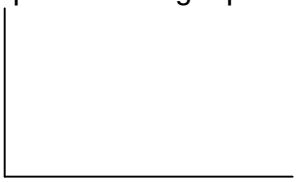
where D- concentration of drug

Y- % of the total receptor Occupied by the drug

K1 and K2 – Association and disassociation constant.

This equation obeys the law of mass action just like enzyme substrate reactions. At equilibrium when the rate of combination equals rate of

dissociation then this equation become valid. This is a mathematical expression of the relationship between the dose and effect. It can be represented graphically by the dose response or dose effect curves.



This is observed when the response of a drug varies in concentration of the drug

The increasing response which is obtained with in an arithmetic increase in the conc. Of the drug is known as a graded response e,g the use of histamine on a guinea pig ileum preparation shows this phenomenom. A plot of the arithmetic increase in dose on the abscissa against response on the ordinate gives a hypenbolic curve.

However, a plot of logarithin of dose against the response of the maximum gives a sigmoid curve. This is known as the log dose response curve.

hyperbolic curve, the dose in concentration is the independent variable and by conversion is plotted on the horizontal scale.

Its value is not determined by any other variable and can be chosen and varied at will. The dependent variable which is the response is plotted on the vertical plane. On the sigmoid curve, the steepress/slope of the linear part determines/indicates the extent by which the dose must be increased to obtain an increased in response i.e the steeper, the smaller the dose increment to obtain the same response increase. Curves which are produced by different concentrations of the same drug are parallel. Drugs which produce the same response by acting on the same receptor will also give simlar sigmoid curve e.g the local anaesthetics lidocaine, cocaine, procaine act by similar mechanism and their effect can be determined using pin pricks on wheals which are produced by the drugs.

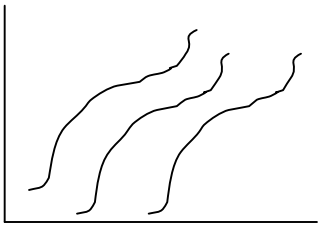
The concentrations are also equivalent to the reciprocal of their affinities of the drug for its receptor. Cocaine has the highest affinity, procaine follows it and lidocaine.

The sigmoid curve permits the presentation of more detailed data in the low dose range as well as the wide range of doses in a single graph. The centre of symmetry which is nearly linear allows for the measurement of ED50. The linear middle segment also lends itself to mathematical analysis more readily than do curves. They are convenient devices for comparing the mechanism by which 2 or more drugs produce the same end effects.

POTENCY

Is a property determined by pharmacokinetic behaviour and the ability of the drug to occupy and activated receptors. it is determined by the dose needed to produce a particular response of a given intensity and it varies inversely with the magnitude of the dose required to produce the effect. The intensity is determined by the inherent ability of the drug to combine with its receptor and by the concentration of the drug at the site.

Potency is a comparative expression of the activity rather than an absolute expression. Deposition of the drug dose effect curve on the dose-oxis reflect then relative potency e.g



With these curves, hydromorphine is more potent than morphine, morphine more potent than codeine regardless of the response level at which they're considered. The different shaped and the maximum height of the curve for aspirin do not allow a comparison with the narcotic analgestics in terms of potency. This shows that aspirin acts by a different mechanism of action. Differences in potencies between the drugs as a result of differences in their relative affinities for the some

group of receptors on the differences proportion of the dose reaching the receptor site or both factors have effect on potency.

AUTONOMIC NERVOUS SYSTEM

Read Physiology of ANSA He repentant decide to teach as NS coordinate the function of the whole body system

Coordinates activities of the body ANS- innervates smooth miodes

CHOLINERGIC DRUGS

Receptor is or a complex protein structure on body cells or tissue or sometimes inside organelles of cells which biological change. There is no action without chemical/receptor.

Cholinergic drug is a compound which mimics acetyl choline and will bind to a cholinergic receptor. Cholinomimetic drug mimics acetyl choline and can be used interchangeably with cholinergic drugs.

i) Choline esters include Carbachol Metachodine, Bethanechol. They are produced by the esterification if between choline and acetic acid under the influence of acetyl transferans choline + Acetic Acid. ACH is formed in the synaptic vesicle from where it is stored and released upon stimulation. Choline esters are formed this way synthetically esterase.

ii) Naturally occurring cholinomimetic alkaloid e.g Aroceline, Muscarine (naturally occurring in plants)

iii) Cholinesterase Inhibitors: 2 types Reversible e.g Physostigmine, Neostigmine, irreversible e.g coumphos, Melathion, Parathion, Dichlorvas-Organaphosphate.

iv) Nicotric agonist e.g Lobeline

ANTICHOLINERGIC DRUGS

Are drugs that antagonize acetyl choline at the receptor they achiee this by displacing acetyl choline fro the receptor. This displacement or antagonism could be competitive or non-competitive. Examples of anticholinegic drugs are atropine, hyoscine, scopolamine.

Pharmacological effects atropine oppose those of acetyl choline. Subjected to atterations.

CLINICAL USE

Carbacohl is mostly available in clinical application unlike acetylcholine which is highly and rapidly destroyed bycholinesterase. Colic treatment. Used in treating myesting gravis: a condition whereby there is an eutoimmune disorder resulting in ponalysis of skeletal muscles.

ADRENERGIC RECEPTORS/DRUGS

α and B adrenergic receptor β_1, β_2, β_3, β_4

α_1 presynaptic inhibitory receptor on the membrane of prosynaptic neurone Adrenaline release from vasclelsynaptic is stopped by its contact with the advenergic receptors (including presynaptic receptors

β_1 is seen only in the heart. Its stimulation resulted heart rate

β_2 is seen in non vascular smooth muscles e.g ureter, bladder wale bronchus its stimulation causes bronchodilation. In GIT decrease motility relaxation.

α_2 s found in vascular and non-vascular tissues e.g blood vessels and intestines

α_1 is found in all systems cos nerves supply all

β_2 is assumed to be on inhibitory but may not be true always.

$\alpha_2$is stimulatory causes vasoconstriction in blood vessel. In other tissues, it stimulates theme of increased metabolic rate in the liver.

α_2 is also found in bronches and can cause vasoconstriction Adrenaline is released by adrenal medulla Noradrenaline by neuronast

- Monoamibo oxidase-MAO found in neurons oxialize no repinephrine
- Catheco-methyl transferase-COM in the blood – oxidize adrenalic C.O-cardiac output.

Amphetamine : is a CNS stimulant Reduced fatigability:- Allows the heart to function excessively without being stress leads to abuse cos of babituation. Euphoria results when used and this is followed by depression. Depression takes over after a while.

Metaraminol, methoxamine and Phenylephrine are vasoconstrictor, α-adrenergic stimulants

Ephedrine inasal anticongestant

Dopamine – cardiac reinforecement

ANTIADRENERGIC

α – antiadrenergic

1) Haloalkylamines – Phenoxbenzamine

2) Tolazoline and phentolamine – good anti hypertensive drugs

3) Prazosine

β - blockers

Propanodol affects β_2 and βx

Acebutabol	}	Cardioselective – β_1 – Proctolol
Atenolol	}	blockers
Sotalol		β_1 and β_2
Labetolol		α and β

They are used as antihypertensive drugs

GANGLION AGONIST

Nicotinic cholinergic receptors are present on the autonomic zinglion lobeline may also be P. A ganglion can eithr be in para or sympathetic deline stimulates both the parasympathetic and sympathetic lobeline is a cholinergic drug and acts on nicotinic and not muscarinic receptors it acts like acetyl choline.

Lobeline is not a drug of any therapeutic effect it is used in detrmining defets in autonomic transmission in the Ganlion has nicotinic receptors.

GANGLION BLOCKERS

Hexamenthonium blocks all transmission along autonomic pathway: has no therapeutic effect.

NEUROMUSCULAR BLOCKERS

MEP

Motor and plate – organization of pre and post synaptic membranes by the thickening. MEP has nicotinic receptors muscle Neunomusaila blockers act on the axon MEP MEP and blocks

H. Muscle becomes paralyzed, atonic, flaccid, non-turgig. NMB are lily used during convulsion and are used prior to surgery i.e premedicant

There are 2 divisions NMB:

Depolarising and Non-depolarising

e.g Succinyl choline e.g D-Iubicurarine

A polarized membrane is synthetic of original

Tonea oxcited or patent plant extract that were used b4 the advent

+ve of the synthetic ones

-ve e.g Curane effect i.e has a paralytic effect

+ve

A sustained state depolarization results in tetany/convulsion

Succinyl choline occupies receptos and blocks acetyl choline action though it has a bit of cholinergic action.

Non- depolarizing causes no contraction, it blocks without undergoing depolarization.

Organophosphate toxicity – Blocks are used as remedy.

Cholinergic receptors Muscarinic

Nicotinic

Acetylcholine is the neurotransmitter substance at p-sympal neueffector jxns, autonomic ganglia, the adrenal medulla, somatic myoneural jxns and probably certain CNS regions Nicotone found in autonomic ganglia, adrenal medullary chromaffin cells and also neuromuscular jnx of somatic NS. Inhibition acetylich by nicotine does not take place at the para sy neurieefector jnx in heart muscle and secretor glands.

PHARMACOLOGICAL EFFECTS OF CHOLINERGIC TRANSMISSION

ORGAN	EFFECTS
Heart	Slows
Iris	Constriction (miosis)
Gliary muscle	Contract
Blood vessels	Dilatation
Exocrin glands	Secretion
Stomach and gut	Increased tone and motility
	Relaxation of sphincter
Gall bladder	Contraction
Urinary bladder	Contraction of detrusor m
	Relaxation of sphincter
Bronchi	Constriction
CNS	Transmission, modulation
Sympathetic and Parasympathetic	
Ganglia	Neuronal firing
Adrenal medulla	Adrenaline release
Motor end plate	Muscle contraction

SYNTHESIS OF ACETYLCHOLINE

Acetylcholine is produced by esterification of acetic acid and choline under the influence of acetyl transferase. The product i.e acetylcholine is catalyzed by cholinesterase into acetic acid and choline. The synthesis of

acetyl choline takes place in the neuron and is stored in neuronal vesicles in the form of granules at the terminal portion of the neuron.

CHOLINERGIC RECEPTORS

Acetylcholine acts on 2 population of receptors in the autonomic NS. One of which is activated by natural alkaloid muscarine and the other by nicotine. Hence, the terms muscarinic and nicotinic. There are other subdivisions of these main group.

CLASSES OF CHOLEINERGIC DRUGS

Choline ester

Metacholine, Bethanecol and Carbachol are product of etherification between choline and acetic acid. The different cholinergic esters are products of different manipulation of the structure and moletie of and on a parent compound.

Naturally occurring cholinomimetic alkaloids

Muscarine derived from	*Amanita muscaria*
Pilocarpine	*Pilocarpus jabonandi*
Arecholine	Arecae catecho

Cholinesterase inhibitors

Cholinesterase attracts acetyl choline to an anionic site at which ionic bond is established. Choline is then cleaved from the acetyl residue finally. The acetylated enzyme is rapidly hydrolysed, acetic acid liberated and the active enzyme is reformed.

Cholinesterase inhibitors fall into 2 groups:

Reversible and Irreversible

_ **Reversible inhibitors** have been used as drugs and differ from acetylcholine in their slower rate of dissociation from the enzyme. Reversible inhibilors include Physostigmine/Eserine, Neastygmine and they both bind to the anionic and esteratic operative sites of

cholinesterase and they are slowly hydrolysed. In the binding, they are compete with acetyl choline for the enzyme for which they are false substrates. These then lead to accumulation of acetyl choline and the attendant effect.

- **Irreversible inhibitors**: The ability to bind to cholinesterase covalently is shared by all organophosphate irreversible inhibitors. These highly lipid soluble agents do not resemble. ACH structurally and most bind only to the esterase site. The resultant phosphorylated enzyme is stable and the return of cholinesterase activity e.g Coumaphos, Dyflos, Parathion, Malathion Irreversible inhibitors are mostly used as pesticides.

Cholinesterase Reactivators

Are agents which promote the dissociation of phosphorylated cholinesterase enzyme. The 1st being P-2-AM, 2-Pan or Pralidoxime. They have the activity to break the phosphonylated enzyme. The usefulness of enzyme reactivation is limited to a short period. Because the enzyme phosphate complex becomes resistant when further group is removed by hydrodysis. Maximum antidotal benefits require both the use of atropine (1mg/kg body weight) and 2-pan (between 10-40kg) body weight).

Nicotinic, agonist

Lobeline and Nicotine

CLINICAL USES

Cholinergic drugs are indicated in Vet. Medicine in Ophthamology and digestive disturbances. ACH is too transient in effect to be valuable and choline itself is off two low in order of potency. A part from these endogeneous substances, cholinomimetics are either naturally occurring alkaloids or synthetic analogue of ACn

- ***Paralytic*** ileus and atony of urinary bladder Neostygmine is most generally satisfactory of the drugs. Tis used as a relief of abdominal distension for a variety of medical and surgical causes.

- ***Glaucoma:*** A disease complex xterized chiefly by an increase in intraocular tension which can be traced to an increase accumulation of fluid in the eye chamber. If the tension is persistent and sufficientlky high, it can lead to irreversible blindness. 3 origins of glaucoma are 1^{o}, 2^{o} and congenital. Cholinergic are of great value for both 1^{o} and 2^{o} but not congenital. Cholinergic drugs produce a fall in intraocular tension by lowering the resistance to outflows of aqueous humour.(This is achieved by effect on the volume of various intraocular vascular bed. i.e dilatation) and on the rate of secretion of aqeous humour into the posterior chamber.

- ***Myaesthina gravis:*** Weakness and rapid fatigaldility of skeletal muscle. Neostygmine increase the response of myaesthenic into repetitive nerve impulses probably 1^{o}:ly by preservation of endogeneous ACn and 2ily by its direct cholinomimetic action.

ANTICHOLINERGIC DRUGS

Musarinic blockage or antimuscarinic is used to describe the action of drugs which competitively antagonize the action of ACn at its muscarinic receptor e.g Atropine, Hyoscine, Homatroprine Eucatropine, Benzetimide, Effects oppose those of cholinergic drugs.

CLINICAL USES

It is used as premedicant in anaesthesia, as relaxation of smooth in the bronchi, digestive and urinary tracts are mydriatics and as antidotes in parasympato-cholinomimetic overdose and organophosphate poisoning.

PHARMACOLOGY OF ADRENERGIC TRANSMISSION

ORGAN	α- EFFECT	β-EFFECT
Eye	Radial.m. contraction	Ciliary's m. relaxation
Vasculature	Vasoconstriction	Vasodilatation
Gut		
Wall	Relaxation	Relaxation
Sphincter	Contraction	-
Bladder Wall	-	Relaxation
Bladder sphincter	Contraction	-
Uterus	Contraction	Relaxation
Bronchi	Constriction	Dilatation
Heart	-	Acceleration
Heart Force	Augmentation	Augmentation
Sweat glands	Sweating	-
Salivary glands	Salivation	-
Pancreas	Inhibition of insulin Release	Release of insulin
Depot fat	-	Lipolysis
Brown fat	-	Thermogenesis
Hepatocytes	-	Glycogendysis

NOTE: The metabolic effects of adrenaline is carried out by B3 receptors

SYNTHESIS OF ADRENALINE AND NORADRENALINE

Tyrosine Dopa Dopamine Adrenaline

Neurotransmitters are stored in granules with the help of a protein called chromogrania and it is stored in form of granules at the neuronal end of adrenergic fibres.

Norodrenaline is entirely neuronal and adrenaline is released by neurone on transmission of impulses while adrenaline is released into the blood by adrenal medulla. Monoamine oxidase catalyzes noradronaline in the neurone, while catechomethl transferase catabolizes catecholamines in the blood (extraneurone).

Adrenergic receptors are mainly α and β

α is usually excitatory except the gut wall and

β inhibitory except the heart rate and force.

β_2 mediates relaxation of smooth m. in bronchi, vasculature and uterus and β_1 is found in the heart and intestine. α_2 adrenergic receptors surpresses further release of neurohormones when activated by adrenaline. α_1 is found in smooth of blood vessesls are highly dynamic infunction and they all have specific functions e.g α-1a, 1b, etc.

CLINICALLY USEFUL SYMPATOMIMETIC DRUGS

Ephedrine: Used as sympatimimetic CNS stimular. It has both α and β agonist activity. Hence, it is used as anbronchodilators, vasoconstrictors and heart stimulant CNS stimulant amphetamine is an indirect α and β agonist. It has a long lasting CNS stimulant. This is much exploited to avert fatigue to treat depression and to surpress appetite. It is now strictly controlled cos of their euphoriant habit forming properties and the depression that follows their withdrawal.

Vasocontrictors- Metharaminol, phenyl ephrine

Methoxamine are powerful α- adrenoceptor agonist 1.

Brochodilators- Isoprinaline, Salbutamol, Genbuterol.

There are many β_2 agonist and they induce bronchodilation to relieve asthma in man. Card Cardiac reinforcement agents. Dopamine, Dobutamine. They increase cardiac output but have little or no effect on heart rate.

Anti-adrenergic drugs

ANTIADRENERGIC DRUGS

A more precise control of sympathetic function is not offered by these drugs which compete with nor adrenaline and these antagonists referred to as adrendytic can be competitive.

α-blockers

- Haloalkylamines e.g Phenoxyl benzamine, Dibenamine. It is used in man to relieve severe vasoconstriction to normalize blood pressure prior to surgery and to correct anaesthetic induced amythmia.
- Imidazoline group derivatives: Tolazoline and Phentolamine are competive α-blockers. Hearts rate is increased as with other α-blockers. A fall in blood pressure thus occur.
- Prazosine: It has the usual smooth m relaxant, α-blocking mediated action but its interesting cos its induced hypotension is not accompanied by tachycardia. In this, it appears to be acting selectively at vascular α_1 receptors and so does not block the presynaptic α_2 receptors which hurt, stops nor adrenaline release.

β – blockers

Pronethalol (obsolete): Cause abdominal adhesions

Propanolol, Sotalol, Oxprenolol. They are referred to as non-selective. β -blockers. Used in prevention of Angina pectoris. It may also protect the heart from sympathetic drive. Thus, the heart cannot respond to stress or exercise and the subject can still live within its somewhat isohaemic limits. They block β_1 and β_2 receptors. In addition to its haemodynamic

effects, it also induces bronchoconstrict especially in airway disease patient and inhibits metabolic action of adrenaline.

Practolol is 1st β_1 specific cardioselective blocker. Also absolete
Acebutold, metoprolol and Atenolo cardioselective blockers used in managing Angina, hypotension and cardiac amythmia. They lack interference with blood pressure haemostasis GIT and sexual function.

Labetolol blocks both α and β receptors. It combines vasodilation with cardiac output in the control of hypertension which is tantamount to administering α and β-blockers simulataneously. However, failure of ejaculation, postural hypotension and nasal congestion are noted side effects.

GANGLION STIMULANTS

Have no essential therapeutic uses. They are only of considerable interest for experimental tools for probing the complexity of ganglionic transmission.

Nicotine is derived from Nicotiana tabocum leaves.

Lobeline is derived from loberlia inflate Pharmacological effects of these agonists are complex and unpredictable due to its action a varity of neuroeffector junctions. These actions are sometimes counteracting on same organ or tissue but the effect that is seen is mostly the dominant type.

GANGLION BLOCKERS

Hexamentonium, Tetraethyl ammonium and Mecamylamine

Pharmacological effects

The alteration of physiological processes attending ganglionic blockagea can be anticipated with reasonable accuracy which is seen along the main division of the autonomic nervous system e.g blockage of

sympathetic ganglia results in interruption of adrenergic control of arterioles and results in vasoconstriction, improved peripheral blood flow of some vascular beds and a fall in blood prossure. In addition generalized ganglonic blockade may result in atony of the bladder GIT etc.

NEUROMUSCULAR DRUGS

Several drugs employed clinically have a their major action, the interruption of transmission of the nerve impulse at the skeletal neuromuscular junction. On the basis of the 1o mechanism by which they produce these effects, they are classified either as competitive non-depolarizing or depolarizing.

Non-depolarising neuromuscular drugs: The cellular locus and mechanism of action of D-Tubocurarine and Dimethyl tubocurarine and Gallmine is explained by the combination of the drug with cholinoceptive sites at the post junctional membrane and thereby blocks the transmitter action acetylcholine. Thus, leading to flaccidity or paralysis of the muscle.

Depolarising agents: Succinyl choline and Decamethonium. Prior to causing paralysis, the depolarizing agent evoke transient muscular fasciculation observed especially over the chest and abdomen. Relaxation occurs within 1 minute after a single intravenous dose of 10-30mg of succinyl choline.

CLINICAL USES

Main therapeutic uses of neuromuscular agents is as an adjuvants in surgical anaestisia to obtain relaxation of skeletal m. particularly of the abdominal wall so that operative manipulation required to provide muscular relaxation, a much higher level of anaestisia suffices. Its used has also been tried for symptomatic control of muscular spasm in acute

convulsive states such as tetanus, status epilepticus and other convulsions.

LOCAL ANAESTHETICS

They are drugs capable of producing local analgesia by depressing the peripheral nervous system. Local analgesia or anaesthesia can be produced by injection or application to the mucous membrane of local anaesthetics. Local analgesia can be produced by applying the drug locally in very low conc.

Local analgesics are referred to as Na+ blockers. Others drugs like neurotoxin, certain antoconvulsants such as phentoin and drugs used in cardiac amythmia. Local anaesthetic paralyse sensory or motor nerve endings when used in low conc.

- By producing tissue anaemia e.g by bandage, local analgesia can be produced.
- Application of pressure on nerve trunks
- By using cold substances
- CO_2 spray or ethylchloride spray

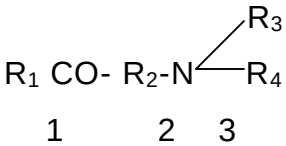
The above mentioned examples do not have a lasting effect on the tissue and:. surgery cannot be done.

An ideal local anaesthetics should not be irritating to the mucous membrane or cause any permanent damage to the nerve structure. It must be efficacious whether administered topically, locally or paventerally, its effect must last the desired time of action, it must be low in toxicity, it must be H_2O soluble, stable in solution and capable of being subjected to sterilization.

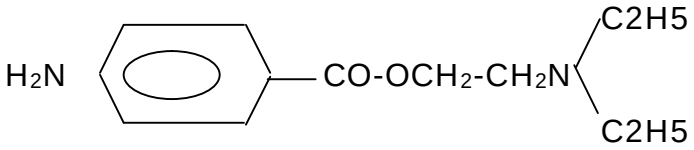
The local anaesthetic structure how 3 parts

- Aromatic part: Often referred to as the acidic or lipophylic part

- Connecting group which corrects the aromatic part to the amino alcohol residue. It is either an ester or amide
- The amino alcohol residue is hydrophilic or basic



PROCAINS



The connecting group is the portion susceptible to hydrolysis. Esteric anaesthetics are broken down by plasma esterase's whereas amide anesthetics are broken down in the liver (this makes them more stable and duration of action is longer). All local anaesthetic agents are weak bases with PKa value of 8-9. This basic nature is important in assisting them penetrate nerve cheaths and axon membranes and brings out their effect. Local analgestic agents do not act on the external part of the membrane.

Changes in any part of the molecule may alter the anaesthetic potency and toxicity of the drug. The length of the intermediate group determines the anaesthetic potency i.e the greater the length the greater the potency. Mechanism of action of local anaesthetic agents.

They block the initiation and propagation og action potential by preventing the voltage dependent increases in Na conduction. This is done in 2 world

1. They act by specifically plugging Na channels.
2. By acting non-specifically on membranes by virtue of their surface activities.

This action is strongly pH dependent and it is increased at alkaline pH. The blockage of nerve conduction is a reversible process. The use of local anaesthetic agent is followed by complete recovery of in nerve function with no evidence of structural damage to nerve fibres or cells. The main site of action is the cell membrane of a nerve. Apart from blockage of Na, they affect the membrane of permeability of K. Local anaesthetic agents complete with Ca at some site that conrol the permeability of membrane.
The site of action of local anaesthetics is located on the inner side of the membrane. Thus local anaesthetic applied to the external surface must 1st cross the membrane in the uncharged form before they can exert a blocking action.

Duration of action of local anaesthetic agent

Is proportional to the time during which its in contact with the nervous tissue. Cocaine is the 1st anaesthetic agent to be used but its not in use again. Cocaine is capable of constricting blood vessels and consequently prevents its own absorption the duration of action is longer than in others. Other local anaesthetic cause vasodilation of blood vessels. The addition of epinephrine to local anaesthetic solution prolongs and intensifies their actions. Epinephrine diminishes local blood flow, slows the rate of absorption of local anaesthetic and prolong its local effect. Adrenaline is used in a concentration of 1 in 200,000.

Apart from acting of the peripheral NS, the CNS, the autonomic ganglia, cardic vascular system, the muoneural junction and the muscle fibres are also affected.

CNS – stimulation ensues Overdose produces restlessness, tremor and convulsion and this stimulation may be followed by depression and death may result from respiratory depression. In man, cocaine is addictive and has a powerful effect on the cerebral cortex.

Cardiovascular system- they have Quinidine like action on the heart (myocardium) and capable of reducing the excitability and force of contraction of the heart. Prolongs refractory period and cause slow conduction. All local anaesthetics produce vasodilation except Lidocaine and Cocaine and is by direct action on the anteriole.

Fate and Metabolism of local anaesthetic agents

All local anaesthesic agents are broken down in the liver and the plasma to non toxic products. The enzymes involved are plasma esterases or cholinesterases and also liver esterases. The metabolities are eliminated in the urine.

COCAINE

Leaves of Erythroxylon coca (Peru,Bolivia) Initially used to relief hunger, thirst and fatigues on the farm. Its an esteric local anaesthetic agent.

Pharmacological action

- To block nerve conduction upon local application
- CNS stimulation-most striking tomic effect.

This is xterized by increased mental power, ed capacity for muscular work- Tolerances and addiction can result from the continued used.

Cocaine potentiates the action of adrenaline producing vasoconstriction. Locally used on the eye to produce anaesthesia. In high doses, cydoplegia and corneal ulcerations. Cocaine can be administered topically systermically. If given orally is ineffective cos it is hydrdyzed in the GIT. It is detoxified in the liver and excreted uncharged in the urine.

Cocaine poisoning can ensue if 20mg is administer and 1.2g can lead to death of the individual. It is availably in hydrochloride form. Employed clinically for eye anaesthesia and for nose and throat work. It is used far less these days and subjected to all sorts of legal restriction and is under the DDA.

PROCAINE

Synthetic substite for cocaine, its an ester of para-amino benzoic acid PABA. It is hydrolyzed in the body to produce PABA and diethyl amino alcohol. PABA is antagonistic to sulphonamides. (1st antibacterial agents). Procaine and other local anaesthetics derivatives should not be used where sulphonamide therapy is being employed. Cos procaine and many other local anaesthetics are hydrolysed in the body to produce PABA which inhibits the action of sulphonamides.

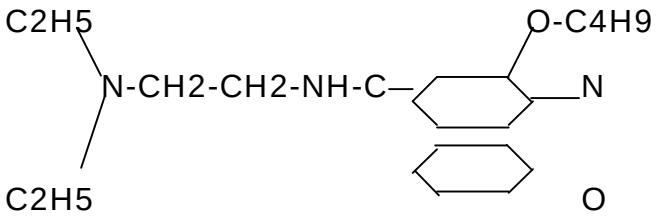
Procaine is readily absorbed following parental circulation. To retard absorption, vasoconstriction drugs are employed. Following absorption it is hydrolysed by procaine esterase foundi in both liver and plasma.

Procaine – PABA – Glysine _ Glucaronide

Cocaine is 4x as toxic as procaine and procaine is ineffective for surface anaesthisia but can be used for infiltration epidermal and subarachnoid analgesia. Procaine is also used as salts of other drugs to prolong their action e.g Procaine penicillin or procaine heparin.

CINCHOCAINE

Tis an amide anagelsic group



It's the most potent, most toxic and longest acting local anaesthetic used today outside cocaine. It is 15 times as potent as procaine and the anaesthetic action last 3 times as procaine. Its good for subarachnoid and epidural analgesia but procaine is about 45-50 minutes. It is inappropriate for infiltration and regional block and mucous membrane.

LIDOCAINE/LIGNOCAINE/XYLOCAINE

Tiz a very potent local anaesthetic. Used for both topical and injection anaesthesia. Non-irritation and highly stable. Suitable for infiltration anaesthesia, regional block and mucosal anaesthesis. Tiz effective when used as a vasoconstrictor in the case, the rate of absorption and toxicity is increased and the duration of action shortened. Duration of action is about 90 minutes. This is the anaesthetic of choice.

AMETHOCAINE / TETRACAINE

An amide local anaesthetic agent. 10 times more toxic and more active than procaine after intraverous injection. Used for topical anaelgisia of the eye. Also used for mucous membrane anaesthesia of ENT. Also good for epidural anaesthesia, infiltration and regional block and subarachnoid anaesthesia.

Duration of anaesthesia is between 90-120 minutes and cos it is rapidly absorbed from mucous membrane, it should never be applied to inflamed, traumatized by highly vascular surfaces.

Tetraccune

or

Amide local anaesthetic agent ⟶ Amethocaine and cinchocain

Estric local anaesthetic agent ⟶ Cocaine, Procaine