

VPC 302 – ROUTES OF ADMINISTRATION OF DRUG

INSTRUCTIONAL OBJECTIVES

At the end of the period of instruction, the student should be able to;

- a) List various routes of administration of drug.
- b) Select or make a choice of route of a drug depending on clinical condition of patient.
- c) Vividly describe advantages and disadvantages of various routes of drug administration.

Introduction:

To administer a drug is to make the drug accessible to the patient's body where the effect is desired. The drug therefore, is desired by the therapist to elicit or manifests an effect where it is desired. For this to occur, the drug must come in contact with the tissues of organs and cells of tissues by one way or the other, the way the drug comes in contact or is made accessible to the tissue fluids tissues, cells, extracellular and intracellular fluids is the route of administration of drug.

Choice of Route of Administration

- 1) This is based on the way the drug is preferred for administration i.e. based on the drug dosage forms. Drugs are administered in various dosage forms: as solid – e.g. oxtetracycline capsule.

Paracetamol tablet

Dimenhydrinate pill.

as solution - codeine syrup

as suspension – insulin, penicillin procaine.

Aerosol - beclomethesone

Volatile liquid - halothane or nitrous oxide

as ointments, lotions, pastes etc.

- 2) Based on the nature of the drug, oil based, organic. Polar, non polar solvent etc.
- 3) The desired bioavailability of the therapist.
- 4) Desired onset of action - how fast the therapist wants to see the manifest effect of the drug. This is important, especially in life threatening conditions or circumstances that require immediate onset of action are shock, circulatory collapse, the nature of the disease and its location of the disease.

5) Duration of action – If a duration is required to be long; the drug is administered 2-4 times daily. This could be done in a depot form as a patch on the skin, another example is treating anaplasmosis, the aqueous oxytetracycline is administered 2-3 days by intramuscular, subcutaneous or intravenous injection. The long acting oxytetracycline, which is designated for slow absorption over 4-5 days.

LOCATION OF DESIRED EFFECTS OF THE DRUG

Routes of drug administration:

The routes of drug administration for systemic effect may be divided into two major groups: Oral (enteral) and parenteral (systemic). When the gastrointestinal tract is by-passed by injection or introduction into the lungs (inhalation). When the drug is effect is desired locally it is administered topically, that is on the skin.

ORAL OR ENTERAL ADMINISTRATION OF DRUG

Oral ingestion is the most ancient method of drug administration, another organ where the substance or drug to be administered is placed is the rectum. Intravectally

The drug could be placed in the mouth, under the tongue, that is (sublingual).

The drug could be administered directly into the stomach using intragastric tube.

Advantages:

- Safe
- Sterility is not required
- Danger of acute drug reaction is minimal

Disadvantages:

- Ingestion of drug could cause gastric irritation.
- Nausea
- Vomiting (in animals like dog, pig)
- Complexes formed with ingesta could prevent the drug absorption
- The drug could be destroyed by low gastric pH or by the digestive and live enzymes before entry into the circulation.

PARENTERAL ADMINISTRATION

Parenterally “par” means beyond “enteral” means intestinal. This is the route of administration of drug without crossing the intestinal mucosa. This is possible when the drug is directly into the blood or tissue fluid using

needle and syringe. It is important to note that the man that led to the introduction of the hypodermic needle and syringe is Alexander Wood.

The most important and most frequently used parenteral routes are I.V. (intravenous route), intramuscular route and SC (subcutaneous route) respectively.

Other less frequent routes are:

- Tissue infiltration
- Intra articular
- Intradermal
- Epidural
- Subarachnoid
- Intra-arterial
- Intrathecal
- Intrathoracic
- Intracardiac
- Intramedullary
- Intratesticular
- Intralesional
- Subconjunctival
- Intramammary

Advantages of Parenteral route of drug administration

1. Bioavailability is faster and more predictable.
2. Gastric irritation and vomiting are provoked.
3. Parenteral routes could be used in unconscious, uncooperative and vomiting patient.
4. There are no chances of interference by food or digestive enzymes.
5. Liver enzymes are by-passed.
6. It essential sometimes in the absorption of the active form of the drug.

Disadvantages

- It is generally more risky
- The preparation must be sterile
- The technique is intensive and painful.
- Drug administered by all routes except intra-arterial might still be eliminated by first pass elimination in liver prior to distribution to the rest of the body.

INTRAVENOUS ROUTE:

The drug is injected slowly, sometimes it could be infused rapidly as bodies.

This method provides accurate, reliable dosage of drug directly into the circulation.

It means that the bioavailability of drug is 100% when administered intravenously.

Advantages:

- This route is often used in drug administration in life threatening situations.
- The drug would have rapid onset of action.
- Irritating and non-isotonic solutions can be administered intravenously, since the intima of the vein are insensitive.

Disadvantages:

- The drugs administered by this method have short duration of action.
- Thrombophlebitis of veins
- Necrosis of adjoining tissue.
- Severe adverse effect especially when organs such as liver, heart, brain are involved in toxicity.

INTRAMUSCULAR

The drug is injected deep in the belly of a large skeletal muscle. The muscles that are usually used are detoid, triceps, Gluteus,. Maximus, rectus, femurs depending on the specie of animal.

The muscle is less richly supplied with sensory nerves, hence injecting a drug 1m is less painful.

Advantages:

1. It is convenient route in administering drugs in animals that are difficult to restrain.
2. It is used in administering aqueous or oleaginous suspensions or solutions.
3. Muscles are highly vascularized thus, the drug could be absorbed haematogenously or through the lymphatic fluid.

Disadvantages

1. Intermuscular injection into fascia might lead to erratic absorption of the drug.
2. There is a possibility of improper deposition of drug preparation in nerves, fats, blood vessels or between muscle bundles in connective sheaths.

SUBCUTANEOUS

The drug is deposited in the loose subcutaneous tissue that is richly supplied with nerves but less vascular. The rate of absorption is slower than the intramuscular route.

Advantages:

- It is a good route of administration especially in skin infections.
- It is relatively safer than I.M. and I.V.
- Absorption is slower thus, it is a good route of a prolonged effect is to be achieved.

Disadvantages:

- If the drug is irritating it might cause the sloughing off of the skin epithelial tissue.

Other forms of subcutaneous route include;

- pellet implantation and dermoject.

Pellet implantation – The drug dosage form of the drug is in solid pellet and is implanted subcutaneously using a trochar and cannula under the skin.

Dermoject: In this method, needle is not used, rather a high velocity jet of drug solution is projected from a microfine orifice of gun-like implement. The solution passes through the superficial layer of the skin and gets deposited in the subcutaneously. This method is used in Mass inoculation.

INTRA-ARTERIAL ROUTE

Drugs and diagnostic agents are administered via this route. The diagnostic media e.g. (Contrast media in angiography) is injected directly into the artery. This is also of great use in treatment of limb malignancies.

Advantages:

- The first pass and cleansing effects are by-passed.
- Bioavailability is 100%.
- It is of great clinical value in administering anticancer drugs for example, in limb malignancies, the drug is administered into the brachial artery or femoral artery.

Disadvantages:

- Intra arterial injection requires great and expertise
- If the drug is of adverse effect there might be great danger.

INTRAPERITONEAL

The peritoneum possess a cavity that offers a large absorptive area for drugs. The peritoneum is highly vascularized. This route is used in laboratory animals administration and large animal practice for administration of large volumes of fluid. The injection is made via the sub-lumbarfossa.

Disadvantages:

- Irritating compounds may produce peritonitis or adhesion.

INTRATHECAL

This is a route of administration of drug in which the effects of the drug is desired in the C.N.S. The blood brain barrier and the blood-cerebrospinal fluid barrier often slow the entrance of drug into the C. N. S. The drug will be accessible to the meninges and cerebrospinal axis. The injection made in the lumbar area or in the cisterna magna.

These routes are primarily for diagnostic procedures (e.g. myel;ography), and treatment of meningoencephelitis. Local anaesthetics are sometimes administered intrathecally to produce region or spinal anaesthesia.

Intrademal: the drug is injected into the skin raising a bleb. This route is used in diagnosis of tuberculosis (tuberculin testing inc attle) and (allergen sensitivity testing).

Intra-articular: Intra-articular injection of anti-inflammatory preparation (e.g. steroids) may be justified in some forms of lameness due to acute inflammation or trauma e.g. (swollen bursa or tendon sheath)

Other routes of drug injection include intra-medullary, which is used for blood transfusion directly into the bone marrow. This is done in neonates when other is difficult.

Pulmonary Route (Inhalation)

Gases, volatile liquids, and aerosols (fine droplets in air). Some drugs such as ventoline are administered using a nebulizer or inhalers. Anaesthesia such as halothane, sevoflurane are vaporized and made to be atomized by a process atomization – This is delivered into the respiratory passages with the aid of anaesthetic machine or vapourizer. The vapourised anaesthesia is inhaled to cause anaesthesia and thus is eliciting its effect.

REFERENCES

VPC 402 – LECTURE NOTES ON: CHLORAMPHENICOL, MACROLIDES, LINCOSAMIDES AND SULPHONAMIDES

CHLORAMPHENICOL

History:

- First isolated in 1947
- First synthesized in 1949
- It is the first commercially synthesized antibiotic.

Source:

- It was first isolated from *Streptomyces venezuelae*
- Later synthesized artificially.

Chemistry:

- Chemically, it is derived from dichloroacetic acid containing anitrobemen moiety.
- It is a neutral stable compound.
- Plamitate salt is its form of salt and it is water0insoluble thus it is administered orally.
- While the *Sodium succinate* salt for parenteral use is water soluble.

Mode of action:

- Chloramphenicol binds with the 50 s ribosomal subunit to inhibit peptide bond formation and protein synthesis in the bacterial or disease causing organism.

Antimicrobial Spectrum

Chloramphenicol is a broad-spectrum bacteriostatic agents active against many gram-positive and gram-negative bacteria, *Rickettria*,

Mycoplasmas, and *Chylamydia*. It has an excellent therapeutic activity against *Salmonella*.

Resistance: The resistance bacteria inactivate chloramphenicol by *acetyltransferase* and other enzymes.

Pharmacokinetics:

- Following oral administration, chloramphenicol is rapidly absorbed especially in monogastrics.
- The peak plasma concentration is attained in dog about 30 minutes after an intramuscular injection.
- The drug becomes widely distributed in the tissues including those of the eye and eye.
- The circulatory chloramphenicol becomes bound to red blood cells and plasma proteins producing similar concentration inc ells as in plasma.
- The drug is widely metabolized in the liver by nitro-reduction and glucuronide conjugation. This metabolism is rapid in the horse.
- Elimination half-life is 1-1.5hours in the dog and horses and 4-5 hours in cats.
- The drug is eliminated entirely in-active in its metabolites in urine and faeces via the entero-hepatic shunt.

Why chloramphenicol is not administered orally in ruminants for the following reasons:

1. Nitro-reduction takes place in the rumen due to the rumenal flora.
2. The drug would be inactivated or would loose its therapeutic value.

Therapeutic Uses:

- Its use is restricted to life-threatening infections, such as systemic *salmonellosis* and respiratory disease in calves.
- The drug is used in humans in typhoid fever.
- 1% topically or 0.5% solution is used in the treatment of acquired *Dermatophilus* infection.
- Ovine foot rot.
- Mastitis in cattle
- In skin and eye infections.

Adverse Effects:

- The effect of chloramphenicol via its protein synthesis inhibition might be specific to the cells of bacteria thus, since the mitochondrial ribosomes of mammals or the host is similar to the bacteria, this might predispose to toxicity of bone marrow.
- There is a dose-related anaemia associated with the use of this drug especially in cats, chicks and dogs.
- In man, the drug is said to produce blood dyscrasia, a aplastic anaemia and super infection with overgrowth of *candida* or mucous membranes

Newer, safer derivatives of chloramphenicol derivatives are: *florfenicol*, *thiamphenicol*. The use of chloramphenicol in food animals is banned due to the fact that there is potential to predispose humans to residue-induced aplastic anaemia in humans.

DOSE:

Oral administration

Dog, fowl, calf, - 50mg/kg every 12 hours

Cat - 25mg/kg every 12 hours

Parenteral administration

Dog - 50mg/kg I.M, SC slow I.V. every 12 hours

Cat - 25mg/kg I.M. Sc. Or slow I.V. every 12 hours

Horse - 30-50mg/kg I.M. every 12 hours.

Ruminant - 10-25mg/kg I.M., every 12 hours

Pig - 10-25mg/kg I.M. daily

MACROLIDE ANTIBIOTICS

History: Erythromycin which is a prototype macrolide was isolated from *Streptomyces erythreus* in 1952.

Erythromycin was the first of these drugs to find clinical application both as the drug of first choice, and as alternatives to penicillin.

Chemistry: The Macrolides are a group of antibiotics with a macrocyclic lactone ring to which deoxysugars (desoamino and cladinose) are attached. Other examples include; oleandomycin, tylosin, carbomycin, spiramycin, tiamulin, tilmicin.

Newer ones: roxithromycin, and dithromycin.

Mode of action of the drug:

The mechanisms of action of the drug - it inhibits bacterial protein synthesis by binding to the 50s ribosome, preventing translocation of amino acids to the growing peptide.

Antimicrobial spectrum: It is effective against gram positive organisms such as staphylococci, mycoplasma, spirochaetes, and certain mycobacteria are sensitive to the group.

Resistance: Resistance to macrolides can develop rapidly, it may be chromosomal or plasmid – mediated and results from decreased drug binding by the 50s ribosome. This occurs as a result of resistance and Methylase enzymes which alters the ribosomal binding site for erythromycin.

Pharmacokinetics:

The erythromycin is destroyed by gastric acid, thus either enteric coated tablets or stable esterified salts (*stearate, tartrate, estolate or lactobionate*) are administered and allow oral absorption. The Newer ones (macrolides) are stable to gastric acids and are readily absorbed. The drug diffuses throughout the tissues of the organs except those of C.N.S.

The Macrolides accumulates in the macrophages. The Macrolides are concentrated in the lung tissue at levels sixty times higher than serum levels. Erythromycin is metabolized by the liver and excreted in bile. The remainder is excreted in active form in urine and bile.

Tylosin and tilmicosin are excreted in unchanged in bile and urine.

Azithromycin is primarily concentrated and excreted in active form in the bile. Minor amounts are eliminated in the milk of lactating animals.

Roxithromycin is long acting with a half-life of 12 hours and it is becoming an alternative to erythromycin for respiratory, genital tract, skin and soft tissue infections.

Tylosin – is effective against mycoplasma, and is a drug of choice in mycoplasmosis in poultry, in particular chronic respiratory disease in chickens, an infectious sinusitis in turkey, as well as respiratory infections in small animals and calves. The drug is used in pleuropneumonia in goats; it is used in vibronic dysentery exudative dermatitis (greasy pig disease) in swine. 100 and 500 gm per ton of feed to improve weight gain by feed conversion efficiency of swine, cattle, and chickens.

Spiramycin: has been added to drinking water for the mass treatment and prevention of mycoplasmosis in chickens and turkey. It is used in treatment of mastitis due to penicillin – resistant staphylococci. In dry –cow mastitis spiramycin – neomycin combinations have been used effectively.

Students should read on :

- Clarithromycin
- Azithromycin
- Tamulin.

ADVERSE EFFECTS:

Alteration of gastrointestinal flora following biliary excretion.

The effect of distortion of microbial flora is very common in horses and might cause diarrhea.

DOSE:

Veterinary Macrolide preparations are limited to base forms of erythromycin and tylosin for oral and parenteral use.

All Species: 10mg/kg I.M. daily

Dog: erythromycin 15mg/kg P.O. 3 times per day

Swine: tylosin 7mg/kg, in feed; 0.2-0.5gm per litre of water

Poultry: tylosin 0.5gm/litre of drinking water, in turkeys; tylosin may be injected directly into the sinuses.

LINCOSAMIDES :

Lincomycin.

Source:- Lincomycin was isolated from streptomyces lincolnensis, and its semi-synthetic derivative, clindamycin

CHEMISTRY: They are derivatives of a sulphur containing octose with an amino acid- like side chain.

MODE OF ACTION: Same as erythromycin and chlorphenicol.

SPECTRUM OF ACTIVITY: They are effective against gram-positive cocci, anaerobes, Toxoplasma and mycoplasma species.

RESISTANCE: Takes place as a result of altered drug binding by bacterial ribosomes is the usual form of resistance. There is a cross resistance between Lincosamides and macrolides is common.

PHARMACOKINETICS:

Lincomycin is not completely absorbed following oral administration; but clindamycin is well absorbed orally, distribution is wide, with excellent penetration of bone and soft tissues, including tendon sheath. The

lincosamides accumulate in neutrophils and macrophages, but CNS levels are low unless the meninges are inflamed clindamycin is extensively protein – bound. Elimination is via hepatic oxidative metabolism primarily, with some excreted unchanged in the urine, bile and faeces . Elimination half-lives are 3-5 hours in dogs and cats.

THERAPEUTIC USES:

Lincomycin is has become obsolete clindamycin is used in dogs and cats for periodontal disease, osteomyelitis, dermatitis, and deeps of tissue infections and for treating toxoplasmosis. Lincomycin has been used in swine in the treatment of arthritis and pneumonia involving mycoplasma species. A combination of lincomycin and spectinomycin (an amino- cyclitol) is used in respiratory diseases of cattle due to mycoplasma and pasteurella.

DOSE:

Lincomycin or Clindamycin

Cow, Swin, Dogs, Cats : 10mg/kg 1m, twice a day

Lincomycin

Dog, Cats : 25mg/kg P.O every 12hour

15mg/kg P.O, every 8 hours

22 mg/kg 1m, Sc daily

Pig : Feed –mix: 110 – 220gm/ tones feed

Clindamycin

Dog : 5 – 10 mg/kg P.O every 12 hours

ADVERSE EFFECTS: Lincosamides are relatively safe in dogs and cats.

- Clindamycin may cause local irritation at injection site.

- Serious diarrhea with hemorrhage colitis may occur in horses after low doses. Clindamycin is very toxic in rabbits, guinea pig and hamsters.
- Fatal pseudomembranous colitis due to over growth of *Clostridium difficile* in the lower bowel, which elaborates necrotizing toxins.

SULPHANAMIDES:

HISTORY:-The sulphanamides originated from the dye prontosil which was shown in 1935 by Gerhard Domagk to be effective in VIVO against haemolytic streptococcal infection in mice. He was awarded the 1939 Nobel prize medicine for his discovery.

Also in 1935, four French scientists, Bovet Nitti, Trefovel and Trefouel demonstrated that the body converted prontosil to Sulphanilamide, which is the active part of the molecule since then the sulphanomide nucleus has been modified. The modifications are designed to achieve greater antibacterial potency, a wider spectrum of activity, greater solubility in urine and a longer duration of action.

In the 1970s, a synergistic combination of sulphamethoxazole with trimethoprim (Co-trimazole)

CHEMISTRY

The sulphanomades are derivatives of P-aminobenzene sulphonic acid and are structurally similar to P-aminobenzoic acid (PABA, an essential member of Vitamin B complex, and an intermediate in bacteria synthesis of folic acid).

- Sulphamides are insoluble in water
- Sodium salts of sulphanomides are soluble
- Sulpharnomides mixtures are used to reduce toxicity and increase solubility in water.
- It is important to note that only sulpharnomides that have free or potentially free P-amino group show antibacterial activity

MODE OF ACTION

Being impermeable to folic acid, many bacteria must rely on their ability to synthesise folate from PABA, Pteridine, and glutamate in contrast the mammalian in cells cannot synthesise folic acid and must obtain preformed folate as a vitamin in their diet. The sulphonamides are structurally similar to PABA, the sulphonamides competitively inhibit dihydropteroate synthetase, the enzyme that catalyses the incorporation of PABA. Into dihydrofolic acid. The folic acid is required for punre and D.N.A synthesis which without it bacteria growth is inhibited.

A Schematic biochemical reaction sulphonamides

ANTIBACTERIA SPECTUM: sulphonamides have a broad- spectrum of activity against both gram- positive and gram – negative bacteria, and some protozoa (coccidia, Neospora, Toxoplasma), rickettsiae e.tc

RESISTANCE: is common in animals isolated and usually exhibit cross-resistance to the whole group. Resistance occur gradually and may be due to plasmid transfer or random mutation resulting in decrease affinity of the bacterial dihydropterate synthetase for the sulphas., decrease uptake, or increased PABA synthesis by bacteria.

Sulphonamides Classes :

Long acting examples - sulphamethoxypyridazine

- sulphamethoxine
- sulphadoxine

Peak plasma levels are attained in 2-6hours.

Note: These are not well absorbed orally others that are insoluble are called the (enteric or gut-active) sulphonamides.

- Phthalylsulphathiazole
- Succinyl sulphathiazole
- Sulpha-bromethazine
- Sulphaquinoxaline

- Salsalazine
- Sulphacetamide

These are used orally and parenterally to treat variety of conditions, including local lesions such as foot rot or podo-dermatitis and systemic disease such as actinobacillosis, mastitis, metritis, colibacillosis, polyarthritis and respiratory infections.

Clinical Uses:

Sulphadimidine is favoured as it maintains effective blood levels for 24 hours following one intravenous injection.

Sulphadoxine is most advantages in goats because only a moderate dose is required every 24 hours.

Sulphonamides are used in urinary tract infections because only few are water soluble.

Sulphafurazole and *sulphisomidine*, it is important to note that sulphafurazole is also called (sulphisoxazole). These soluble sulphonamides are rapidly excreted in the urine in 24 hours in an unchanged form for these reason, they are used to treat urinary tract infections, particularly active against *proteus*, *coliforms*, and *Psuedomonasspecies*.

Sulphanamides are used in topical uses e.g. *Silver sulphadiazine* is used topically to avoid colonization by *Pseudomonas* species.

Today in Clinical Practice.

The development of other antimicrobial agents has reduced the importance of sulphonamide in Veterinary Practice. Sulphadimidine and sulphasalazine are the two that still retain their uses in urinary tract infections and chronic inflammatory bowel disease and colitis in dogs and cats.

CYANIDE POISONS

Poison :- Any solid, liquid or gas that, when introduced into or applied to the body can interfere with the processes of the cells of the organism by its own inherent chemical properties without acting mechanically regardless of temperature.

Xenobiotic :- Any substance, harmful or not, that is foreign to the body.

Sources of cyanide poisons / Etoxicants

- Plants
- Fumigants
- Soil sterilizer
- Fertilizer

And rodenticides (e.g calcium cyanamide) ingestion of plants that contain cyanogenic glycosides. These are examples by feed the fruiting.

- *Triglochin maritima* (: arrow grass)
- *Hoechstia lunata* (velvet grass)
- *Sorghum spp.* (common sorghum)
- *Zea mays* (corn)
- *Linum spp* (flax)
- *Sambucus canadensis*
- *Pyrus malus* apple

- *Eucalyptus spp* At home cause to small animals or in implicated in toxicity.
- *Manihot exculator*
- *Surghum bicilar*
- *Pheseolus lunatus* (lime bear)
- *Passiflora fetrda*

Mechanism of Release of Cyanide and Cause of Toxicity

The cyanogenic glycosides in plants yield free hydrocyanic acid. (HCN). The free hydrocyanic acid also known as prussic acid, when is hydrolysed by *hydroxynitrilelyase P- glycosidase* and when other plant cell structures is damaged e.g by freezing, chopping, chewing etc The microbial flora and fauna that are inhabitants of the rumen would cause further release, thus discharging the free cyanide.

The toxic of HCN is attributed to the high affinity towards metalloporphyrin this contains enzymes. The HCN reacts with (Fe^{3+}) of cytochrome oxidase results in *CN-cytochrone oxidase complex*. This impairs respiratory electron chain resulting in *cytotoxic anoxra* and death.

PREDISPOSING FACTORS TO CYANIDE POISONING

1. Soil factors or edaphic factors
2. Season: - cyanogenic glycosides decrease in drought – stricken plants.
More at rains or wet season when there are new shoot.
3. Herbicide Sprayer and Fertilizers: Increases the tendencies especially nitrates in phosphorus deficient soils. Cyanogene forage when sprayed with folier herbicides such as 2,4– D, this increases the prussic acid concentrations for several weeks after application.
4. Feeding on frozen plants may cause a high release of cyanogenic glycosides.
5. Part of the plant eaten - for example in *Pyrus malus* the poison is more in the leaves and seeds and is less in the fleshy fruit.
6. Species factor: - It is common in large animals such as cattle (ruminants) the monogastrics that are less likely to get poisoned.
Hereford cattle - is the breed that is reported to be less susceptible than other breeds.

7. The processing of the material: when stage is not dried / increase toxicity if plant materials contain 20 mg HCN /100 gram, in considered toxic.

FORM OF CYCROTONIDES TOXICITY

Clinical Findings

15 – 20 min to few hrs after the animal has consumed the forage.

- Excitement can be dilynolied
- Rapid respiratory state
- Dyspnoea
- Tachycardia
- Salivation
- Lacrimation (in excess)
- U – urination
- Vomiting (especially in pigs)
- Fasciculation in common and progreeses to generalized spasm
- Animal staggers, struggles and falls.
- Asphyxia cyanodes , the mucuos membrane bluish.

The whole syndrome does not exceed 30-45min if lives up to 2hrs after onset of clinical signs, survives except if cyanide continuous absorbed from the gastro intestinal tract.

Lezims

LEZINS

In acute and peracute cases, blood may be clear red initially but can be dark red if recuperating is delayed. Agured hemorrhages in the heart.

- Mucuous membrane :- gzanotic
- Gastro intestinal
- Rumen may be distended with gas in the odom of (bitter almondi)

Respiratory System

- Froth in trachea serosed surfaces of trachea mucosa and lungs may be crystaled or haemorrhagic.
- Liver:- Congestion with hemorrhages

C.N.S.

Multitude foci of degeneration or necrosis may be seen in the C.N.S. of dogs in chronically exposed to sublethal amount of cyanide.

Differential degrees

- Nitrate poisoning
- Organophosphorus poisons
- Sulphur poison

- Nitrate poison.

Diagnosis

- Appropriate history
- Clinical signs
- Postmortem finding
- Demonstration of cyanide poisoning the stomach rumen

Taking appropriate samples, these samples include:

- Suspected plant
- Rumen and stomach content
- Heparinized whole blood
- Liver and muscle

Samples should be taken preferably not more than 4 hours after death.

Method of storage of samples used for diagnoses:

Sealed in airtight container, refrigerated or frozen. In the absence of refrigeration, immersion of specimens in 1-3% mercury chloride.

Another way of diagnosis is by estimating the amount of cyanide in the food.

1. >220ppm cyanide on HCN is considered very dangerous.
2. 750ppm HCN is considered hazardous
3. 500-750ppm is doubtful

4. <500ppm is considered safe.
5. <100ppm is considered very safe.

Picrate Paper is used to test the plants materials in stomach/rumen.

TREATMENT

What is used are as follows:

- NaNO_3 – sodium nitrate
- Sodium thiosulphate
- Dimethyl amino thenol (DMAP) or Acdroxamine

Sodium Nitrate – (1 of 100ml of distilled water or isomic solution)

20mg/kg. It could be repeated for 2-4hours or as needed.

Sodium thiosulphate at $\geq 500\text{mg/kg}$ I.V. plus 30g/con to detoxify the rumen.

The basis of the use of NaNO_2 is I.V bring about vasodilatation and counteracts the CN indeed – vasospasm.

It combines with haemoglobin (Hb) and converts it to methaemoglobin (Fe^{3+}) competes with cyanide complexed cytochrome oxidase so preventing the combination of HCN in the cytochrome oxidase.

So, the sodium thiosulphate should be immediately given to detoxify the *cyanmethaemoglobin* so that the already discharged cyanide from this compound *cyanmethaemoglobin* react and combine with *thiosulphate* to

produce *Thiocynate*. Artificial respiration with oxygen 100% should also be given along with sodium nitrate and sodium thiosulphate.

The use of sodium thiosulphate will fix the HCN present in the rumen as free cyanide in the blood decreases, additional cyanide dissociate from cyamethaemoglobin.

NITRATE/NITRITE POISONING

Animals inhabitants –

Animals susceptible include: Ruminants, especially cattle, the reason is the microflora reduces the nitrates +.

Ammonia, young pigs are also vulnerable to this.

Note: Usually, questions are asked why it that nitrite is treated with nitrate, the nitrite is an intermediate product. But are 10 times more toxic than nitrates.

Forms of toxicity

Acute, sub-acute, or chronic form of toxicity.

Acute toxicity – Effects:

- The cellular basis is this – Nitrate converted to nitrite ion and combines with Hgb, iron is converted to Ferric state this form Methaemoglobin when there is 80% or >methaemoglobin.
- Secondary effect is Nitrate has vasocilatory effect and would interfere with Metabolic protein enzymes.

- It irritates the mucosal lining and causes abdominal pain and diarrhea.

The subcutaneous chronic effects:

- Lowered milk production
- Minor transitory goitrogenic effects.
- Abortion
- Fetotoxicity
- Increase susceptible to infection.

Chronic form controversial and lowered milk production does not occur in chronic form of the disease.

Source:

Fertilizers.

Preservatives, (prickling and bines)

Machination

Gun powder

As medicine in treatment of unacclimated animals might feed on plants containing this include:

- Zea mays
- Sunflower
- Sorghum
- Cereal grasses (oats, millet and rye)

Factors that affect Nitrate poisoning

1. Excess nitrate in plants is associated with damp weather condition and cool temperatures of 55°F(13°C).
2. In drought especially when plants are immature.
3. Decreased light, cloudy weather and shading associated with crowding conditions can cause increase in nitrates poisoning.
4. Edarphic factors : Lupa, soil thesis deficient in trace elements like *onolybolenum* and in macro elements like *sulphur* or *phosporus*.
5. Anythin that stunts growth increases nitrate accumulation in the lower parts of the plants.

6. Herbicides use (Phenoxy dermede herbicides)
7. Nitrates are accumulated in lower stalks but are lesser in leaves and upper stalk.

Clinical finding/Percentage Methemoglobin

- Rapid weak heart beat
- Subnormal body temperature
- Weakness
- Dyspnoea
- Tachypnea
- Boom or muddy cyanotic, mucous membrane.
- Frequent urination (Methemaglobinuria)

Signs of plant sources are:

- Pains abdominal discomfort, diarrhea salivation, vomiting

The Acute form occurs when 80% of haemoglobin is converted to Methemoglobin or Methemoglobin 58%, this would result to dyspnea.

The lung would later recover but later worsen to Interstitial Pulmonary emphysema; If conditions are favorable it may recover in 10-14 days but in adverse conditions the animal dies.

Lesions:

- Chocolate – brown colour, although dark red lividity may also be seen.
- Pin point haemorrhage in Serous surfaces.

Diagnosis:

1. The specimen most preferred is plasma for pre mortem specimen analysis of Plasma-protein-bound nitrate, because if the blood is clotted, nitrate could be lost in the clot if serum was collected.
2. Other specimens may be postmortem
3. Methemoglobin analysis (not reliable).

Interpretation: If the nitrate present in white blood cells other postmortem specimens is indicative of nitrate poisoning.

Post mortem specimens

Specimens to be taken are as follows:

- Ocular fluids
- Fetal pleural
- Thoracic fluids
- Fetal stomach content
- Maternal uterine fluid.

Method of storage and preservation

- Frozen in clean plastic or glass containers labeled before submission.
- Blood collected whole for methemoglobin analysis is not frozen.

4. Standard analytical methods at qualified laboratory.

5. Field test for nitrate (presumptive) dopsticies are used to determine nitrate values.

Differential diagnoses

* Cyanide * pesticides * toxic gas

* Urea * toxic gases * H₂S and carbon monoxide

Some infectious diseases could be confused and non infectious.

Non infectious diseases:

- hypocalcemia
- Hypo magnesemia
- Pulmonary endenomatoxins

Treatment of Nitrate poisoning

Low I.V. injection of methylene blue in distilled water or isotonic saline should be given of 22mg/kg or depending on severity of exposure. Lower dosage may be repeated in 20-30minutes. If the initial response is not satisfactory, higher dosage can be used.

Control: Animal may adapt to high nitrate content in feed, especially grazing summer animals such as sorghum Sudan hybrid.

- Multiple small feeding help animals adapt.
- Balanced diet and trace element and this prevents metabolic disorders and predisposed to this poisoning.
- High-nitrate forage may also be harvested and stored as ensilaged rather than dried hay or green shop, this reduces the nitrate content.

OXALATE POISONING

An oxalate poisoning is a salt of oxalic acid this include potassium oxalate and sodium oxalate.

Aetiology:

A. Plants (natural source)

1. *Amaranthus retroflexus*
2. *Psinacia alerales.*
3. *Beta vulgaris*
4. *Oxalis spp. O. corniculeta O. latifolia*
5. *Caladnium spp*
6. *Mexican breadfruit (Monstera spp)*
7. *Setaria spp.*

B. Metabolically synthesized - Formed during the metabolism of ascorbic acid, this forms the insoluble form of the salt or urolithic

C. Oxalic acid (ingestion).

FACTORS AFFECTING OXALATES POSIONING

Annulus spp. – Cat and dog are susceptible to insoluble form while large animals to soluble.

Animals left to move from one place to the other.

Unacclimated animals might prove and eat plants that are poisonous.

Extreme system of husbandry.

It is important to not that:

Oxalate

Soluble oxalates

insoluble oxalates

MgO_{x1} sodium oxalate and NH₄O

calcium oxalate

Insoluble form of calcium

Signs –

- Irritated oral mucosa stomatitis, that is Dysplogia

- Anorexia or animal go off feed. – It causes some nervous signs such as depression, convulsion may occur due to altered level of consciousness due to acidosis and cerebral damage.
- Stranguria; dysuria.

Soluble form of poisoning (Oxalate Mg, NH₄ Na)

- It causes hypocalcemia in ruminant as a result of acute poisoning
- Muscle weakness
- Recumbency
- In horses, it causes *Osteochondrodysplasia fibrosis* when the horses take oxalate rich forage or long-term ingestion of plant.

Lesions:

- Sloughing off the mucosa of oral cavity stomatitis, increased salivation.
- Precipitation of crystals in the kidney.
- Haemorrhages in central nervous system.
- Nerve bones especially in horses.
- *Histopathologically*

Cerebral nervous cell degeneration.

Haemorrhages

Neprosis, Nephritis

Urolith deposition.

The degeneration of the tubular cells lining thus results to the destruction of Mitochondria in the cells.

Diagnosis:

History

Clinical surveying

Taking samples

a) Plant or food of animal

b) Urine

c) Blood

These are analysed in the laboratory

P.M.

Histopathology

Treatment:

If the commercial form is ingested lime or calcium hydroxide solution should be given. This reacts with acid to produce insoluble form of calcium oxalate.

Use methol or eucalyptus oil to soothe the buccal cavity.