**QUESTION BANK ( VETERINARY PHARMACOLOGY)**

**PAPER NO. 20**

**Analgesic, anti inflammatory and antipyretic drugs.**

**I. NAME THE FOLLOWING:**

1.Other name for methyl salicylas --( oil of winter green)

2.One aryl acetic acid derivative used as anti inflammatory agent.-(Diclofenac sodium)

3.One COX and LOX inhibitor-( Tepoxalin))

4.Scientific name of Willow tree.-(*Salix alba*)

5.The enzyme acting on Arachidonic acid to produce PGI 2.-( Cyclooxygenase)

6.The glycoside obtained from willow bark having antipyretic action.-(Salicin)

7.The “house keeping enzyme in the body” .-(COX-1)

8.The active ingredient of brufen.-(Ibuprofen)

9.The active metabolite of Phenacetin.-(Acetaminophen)

10.The other name of acetaminophen.—(Paracetamol)

11.The active ingredient of Metacin.-(Paracetamol)

12.Two isoforms of cyclooxygenase .-(COX-1 and COX-2)

13.Two selective COX 2 inhibitor-(Deracoxib and firocoxib)

**II. FILL UP THE BLANKS WITH MOST APPROPRIATE WORDS.**

1.Antipyrin was banned as antipyretic because of its side effect…………………………..—(agranulocytosis)

2.Acidum acetyl salicylicum is otherwise known as …………………--(aspirin)

3.Acetaminophen is otherwise known as ……………………--(Paracetamol)

4.Aspirin was introduced in the year ……………….--( 1899)

5.Aspirin is otherwise known as acetyl ……………………………….( salicylic acid)

6.Anti inflammatory activity of NSAIDs correspond with the potency to inhibit mainly……….—(COX)

7.Because of its…………………… effect phenylbutazone is used as antirheumatic agent –(uricosuric)

8.COX-3 participate in the ………………………..process in canines.-(pyresis)

9.Deficiency of PGE 2 and PGI  2 reduce mucous and bicarbonate secretion in the stomach and enhance gastric …………………..secretion.-(acid)

10.DMSO application over the body give………odour to the breath.—( garlic )

11.ECAM-1 and ICAM-1 attract ………………………to the site of inflammation.-( leucocytes)

12.Ketoprofen is a .........................................derivative NSAIDs .—( propionic acid )

13.Lipoxygenase enzyme is located more in........................tissues.---( lungs, WBC, platelets and liver.)

14.Methyl salicylas is otherwise known as …………………….--(gaultharia oil/oil of wintergreen)

15.NSAIDs administered along with ……………………(PG analogue)antagonize their gastric toxicity.-(misprostol)

16.NSAID s inhibit gastro protective prostaglandins…………………………..—(E 2 and I 2)

17.NSAIDs stabilized the …………………………………….membrane of leucocytes to contribute their anti-inflammatory action.-(lysosomal)

18.NSAID s inhibits platelet aggregation and prolonged …………………….time.-( bleeding)

19.Orgotein is a copper and zinc containing protein isolated from bovine……………(organ)----(Liver)

20.Paracetamol is having .............................toxicity.-(hepato)

21.PGI 2 and TXA 2 are produced from arachidonic acid by the enzyme………………….—(Cyclo oxygenase)

22.Polysulfonated glycosamino glycan enhances the synovial membrane activity and increases the ……….........…of synovial fluid.—(Viscosity/lubricating property)

23.Prolonged use of salicylic acid cause metabolic ………………………..—( acidosis)

24.Phenacetin is banned because of its ……………………-(Nephropathy)

25.Phenyl butazone was introduced in the year ………………….--(1963)

26.Phenyl salicylate is otherwise known as …………………..—( salol)

27.Quinine is obtained from ..................................bark.-( cinchona)

28.Salol will break in to ……………and ……………………acid.-( phenol, salicylic)

29.Salol coated pills will protect the drugs from ………………..—( gastric acidity)

30.Salicin is a .......................present in ................................bark.-( glycoside, willow)

31.Salol will split in to ............................and.............................acid in the intestine.-( phenol , salicylic)

32.Salicylic acid can also be produced from oil of …………………………-(wintergreen)

33.Sodium salicylate is orally administered along with …………… as an antipyretic. -( sodium bicarbonate)

34.Sodium salicylate was introduced in the year ……………..for treatment.-(1975)

35.Soluble aspirin contain ……………………….and ……………………………in addition to aspirin.-( calcium carbonate and citric acid)

36.Stevens Johnson syndrome is one of the important side effect of …………………………..(Phenyl butazone)

37.The active ingredient of metacin is…………………………-(paracetamol)

38. The most important side effect of paracetamol is ………………..and……………….—(Hepatopathy , nephropathy)

39.The inducible form of cyclooxygenase enzyme is ………………….( COX -2)

40.The constitutional form of cycloxygenase enzyme is ………………….—(COX-1)

41.The activated endothelial cells express adhesion molecules …………………………and ………………….on their surface.-( ECAM-1 and ICAM-1),Extra cellular and intra cellular adhesion molecules)

42. The majority of the anti inflammatory effect of ketoprofen is due to …………enantiomer.-( S (+)

43.The R (-) enantiomer of ketoprofen impart …………………….effect.—(analgesic)

44.In normal condition prostaglandins ………and………confer cytoptotective effect.-(E2 and F 2)

45.In cats the only NSAID approved is …………………………..-(meloxicam)

46.In Horse flunixin preferentially inhibit COX-2 than COX-1, However, in …………………(species) it is just reverse.—(Dogs)

47.Meclofenamic acid is a derivative of …………………………………..acid.—(anthranilic)

48. …………………….is the most common and serious adverse effect of NSAIDs.—(G I ulceration)

**III. STATE TRUE OR FALSE**

1.Acetaminophen is unsafe in small animals.-(T)

2.Acetaminophen (paracetamol) is a coaltar analgesic –(T)

3.Acetaminophen does not inhibit COX.-(T)

4.Acetaminophen is normally conjugated with glucuronide for excretion.-(T)

5.Acetaminophen is more effective against inflammatory condition in the CNS.-(T)

6.Acetaminophen interfere with the endoperoxide intermediate of AA conversion.-(T)

7.Administration of sodium bicarbonate increases the urinary excretion of aspirin.-(T)

8.All NSAIDs can not cause adverse effect even in higher dose.-(F)

9.Aminopyrin will give blood red colour to urine and gave green colour in reflected light.-(T)

10.Aspirin irreversibly inhibit COX-1.-(T)

11.Aspirin toxicity mainly cause damage to kidney .-(T)

12.Bone marrow hypoplasia is seen in aspirin toxicity.-(T)

13.Cats have insufficient CP 450 and glucuronidation conjugation.-(T)

14.Carprofen inhibits COX-2 hundred times more than COX-1.-(T)

15.Caprofen is an AAA agent approved for use in dogs , its main toxic action is on cartilage synthesis.-(T)

16.COX-3 can be inhibited by acetaminophen.-(T)

17.COX-1 is called as house keeping enzyme.-(T)

18.COX-2is an inducible form because it is expressed at the site of injury and inflammation.-(T)

19.Celecoxib is a selective Cox-2 inhibitor.-(T)

20.Dimethyl sulfoxide (DMSO) is an anti inflammatory agent possessing antimicrobial and anti fungal action.-(T)

21.DMSO carry the dirt in the area of application in to circulation.-(T)

22.Flunixin meglumin is very powerful analgesic preferred in colic.-(T)

23.Gs coupled receptors mediate vasodilatation.-(T)

24.High pH increase the solubility of salicylic acid.-(T)

25.High pH increase the ionisation and reduce the diffusible form of salicylic acid.-(T)

26.Indomethacin is available as Idicin.-(T)

27.Ibuprofen is not approved for use in animals.-(T)

28.Ibuprofen have no action on superoxide ions or release of lysosomal enzymes.-(T)

29.Ibuprofen is less analgesic than aspirin.-(T)

30.Ibuprofen is a propionic acid derivative.—(T)

31.Ibuprofen is having more duration of action than Flurbiprofen .-(F)

32.It is not advisable to give aspirin one week prior to surgery.-(T)

33.Ibuprofen is not approved for use in animals.—(T)

34.Indomethacin is better than aspirin in rheumatic arthritis.-(T)

35.Ketorolac is a pyrrolo- pyrrole derivative anti inflammatory agent .-(T)

36.Keterolac is used in veterinary medicine to treat uveitis, bursitis , osteoarthritis and Spondylitis.-(T)

37.Ketoprofen is a racemic mixture of S(+) and R(-) enantiomers.-(T)

38.Meclofenamic acid is an anthranilic acid derivative NSAIDs .-(T)

39.Methyl salicylas is not soluble in alcohol.-(F)

40.Mephenamic acid is an anthranilic acid derivative.-(T)

41.Nimesulide is a selective Cox -2 inhibitor.-(T)

42.NSAID S have anti thrombotic effect for a very short period.-(F)

43.NSAIDs are also capable of immunomodulation.-(T)

44.NSAIDs enhance the cellular immunity by inhibiting PGE-2, a mediator which dampens the immune system.

45. NSAIDs blocks the pain sensitizing mechanism induced by bradykinin , TNF alpha and interleukins.-(T)

46.NSAID s retard labour.-(T)

47.NSAIDs induced inhibition of PGE 2 and PGI 2 biosynthesis may cause oedema, hyperkalemia and acute renal failure.-(T)

48.Orgotein exert anti inflammatory effect by suppressing the superoxide dismutase activity.-(T)

49. Orgotein stimulate chemotactic activity of polymorph and prevent disruption of lysosomes.-(T)

50.Oxyphenbutazone is a metabolite of phenylbutazone.-(T)

51.Paracetamol is a weak anti inflammatory agent -(T)

52.Piroxicam is more ulcerogenic than indomethacin.-(F)

53.Piroxicam has the ability to reduce the size of tumor.-(T)

54.Prostaglandin F 2 and E 2 stimulate synthesis of gastric mucous .-(T)

55.Phenyl butazone is more preferred as anti-inflammatory .-(T)

56.Phenyl butazone is having uricosuric effect.-(T)

57.Phenyl butazone is less toxic than aspirin.-(F)

58.Phenyl butazone induces microsomal enzymes.-(T)

59.Phenyl butazone displaces drugs from protein binding site.-(T)

60.Phenyl butazone is discouraged in food producing animals because of its prolonged excretion time.-(T)

61.Prostanoids PGE2 and PGI2 play a key role in the regulation of renal blood flow.-(T)

62.Polysulfated glycosaminoglycan is an anti arthritic compound.-(T)

63.Polysulfated glycosaminoglycan is extracted from the bovine trachea.-(T)

64.Protamine is a low molecular weight protein obtained from fishes.-(T)

65.Prostaglandin formation is mediated by either one or two isoforms of cyclooxygenase.-(T)

66.Salicylates are toxic in cats because of limited glucuronidation .-(T)

67.Salicylates acetylate cyclooxygenase enzyme and reduce P.G. synthesis .-(T)

68.Salicylates increases the utilization of glucose.-(T)

69.Salicylates causes a reduction in blood glucose level.-(T)

70.Salicylates have cholagogue and uricosuric action.—(T)

71.Some of the antiinfammatory agents like piroxicam inhibits both the generation of superoxide ions and the release of lysosomal enzymes.-(T)

72.Sulindac is an anti inflammatory drug and it is a prodrug.-(T)

73.The active ingredient of Brufen is Ibuprofen.-(T)

74.The active ingredient of voveran is diclofenac sodium.-(T)

75.The t1/2 of salicylic acid in cat is 30 hours .-(T)

76.The ulcerogenic effect of NSAID is mainly due to inhibition of PGE2 and PGI 2.-(T)

77.The temperature lowering action of NSAIDs influence normal body temperature.-(F)

78.The breath will have a garlicky or oyster like odor on application of DMSO on the skin.—(T)

79.The anticoagulant effect of aspirin is due to blockade of TXA-2 production.-(T)

80.Toxic dose of salicylates cause hyperglycemia.-(T)

81.Unlike narcotic analgesics NSAIDs do not produce tolerance or physical dependence.-(T)

**IV.CHOOSE THE CORRECT ANSWERS:**

1.DMSO possesses a) anti-inflammatory analgesic action b) anti microbial anti fungal action c) anticholinesterase action d) diuretic action e) all the above.—(e)

2.Heparin have the following activity a) antithromboplastic b) antiprothrombin c) antithrombin d) all the above.-(d)

3.Heparin is stored in a) mast cells b) granules of basophils c) intima of blood vessels d) all the above -(d)

4.Hyaluronic acid has the following effects in joints a) a cushioning effect b) a lubricating effect c) a scavenging effect d) all the above.-(d)

5.One of the following is a selective Cox2 inhibitor. a) Rofecoxib b) Piroxicam c) Leptazole d) Methyl phenidate.-( a)

6.One of the following drug is white pearly flakes in nature a) aspirin b) sodium salicylate c) phenyl salicylates d) none of the above,-( b)

7.Polysulfonated glycosaminoglycan (PSGAG) a) enhances synovial membrane activity and increase the viscosity of synovial fluid b) inhibit PGE2 biosynthesis c) inhibit leukocyte migration and elevated interleukin level d) elevation of hyaluronate level at the joints e) all the above.—(e)

8.The original source of methyl salicylas is a) plant b) earth c) synthetic d) animals .—(a)

9. The inflammatory mediators other than COX are a) leucotrenes b) Cytokins c) PAF d) selectins e) integrins f)all the above.—(f)

10.The metabolic acidosis due to aspirin is due to a) salicylic acid induced release of H+ b) uncoupling of oxidative phosphorylation ,may leads to build up of pyruvate and lactate c) an increase in fat metabolism , leading to ketoacidosis. d) a depression of renal function resulting in the accumulation of sulfuric and phosphoric acid. e) all the above.—(e)

11.The commonly seen adverse effects of NSAIDs in animal is a) vomition b) diarrhea c) G I ulceration d) hepato- renal toxicity e) all the above.—(e)

12.Ulcer production by NSAIDs is due to the inhibition of a) PG H 2 b) PGI 2 c) PGE 2 d) PGD 2.-(b)

**V. CHOOSE THE CORRECT ANSWER FROM THE GIVEN ONE AND GIVE YOUR REASONS :**

1.Which one of the following enzymes influences the t1/2 of aspirin in domestic animals? A) glutathione reductase B) Cyclo oxigenase C) N-acetyl transferase D) Glucuronide transferase E) Cytochrome P 450 oxidase

 The answer is D: Glucuronidation is the main biotransformation process for aspirin and dictates the plasma half life of the compound. Because of the ability to conjugate with glucuronic acid varies among species , the plasma t 1/2 of aspirin also varies . Aspirin irreversibly binds cyclooxygenase to inhibit the formation of prostaglandins. When glucuronidation capabilities are exhausted , salicylates form conjugate with glutathione. N-Acetyl transferase and cytochrome P 450 enzyme are not involved in the biotransformation of aspirin.

2. Bioavailability of carprofen can be increased by A) increasing urine pH. B) using enteric –coated tablets. C) administering sodium bicarbonate only. D) maintaining a low pH in the stomach.

 The answer is D: Carprofen is a weak acid that crosses biologic membranes most readily in an acidic environment and least in an alkaline environment. Increasing the pH of the urine or administering sodium bicarbonate decreases the bioavailability of aspirin because these measures induce an alkaline environment.

3. Most widely used analgesic in race horse is A) aspirin. B) phenyl butazone. C) naproxen D) xylazine E) meclofenamic acid.

 The answer is B: Phenyl butazone is widely used as an equine analgesic because it is effective against many types of lameness and of its low cost.

4. Which one of the following anti-inflammatory drugs acts through proteolytic enzyme inhibition to reverse the loss of cartilaginous mucopolysaccharides that occurs in arthritis? A) Carprofen B) Dimethyl sulfoxide C) Polysulfated glycosaminoglycan D) Phenylbutazone. E) Flunixin meglumin.

 The answer is C: Polysulfated glycosaminoglycan is chemically similar to the mucopolysaccharides of cartilage, therefore it can reverse the mechanisms that causes the loss of these mucopolysaccharides. DMSO exerts anti-inflammatory effects mainly by scavenging free radicals. Phenyl butazone and flunixin meglumine inhibits prostaglandin synthesis.

5. which of the following is the most frequently seen adverse effect of the prostaglandin inhibitors?. A) A granulocytosis B) Gastric ulcer C) Renal papillary necrosis D) Anemia E) Hepatitis.

 The answer is B: GI erosions and ulcer are the most frequently seen adverse effects of the prostaglandin inhibitors.

6. Meloxicam alleviates all of the following types of pain except. A) headache B) muscle pain C) joint pain D) colic.

 The answer is D: The inhibitors of prostaglandin synthesis do not relieve deep visceral pain, such as colic. They usually alleviate pain from the integument, including skeletal muscles and joints.

7. The antipyretic effect of an NSAID can result from all of the following except A)inhibition of prostaglandin synthesis in the central nervous system. B) dilation of the peripheral vasculature. C) sweating D) lowering body temperature in both normal and febrile animals.

 The answer is D: Prostaglandin synthesis inhibitors lowers the set point of thermoregulatory centre of hypothalamus in febrile animals ( but not normal) , causing vasodilation and panting.

8. which of the following NSAIDs is approved by FDA to be used in cats? A) Carprofen B) Etodolac C) Firocoxib D) Meloxicam E) Tepoxalin

 The answer is D:Meloxicam is approved for dogs and cats for the treatment of chronic pain and inflammation associated with osteoarthritis. None of the others are approved in cats.

9. Which of the following NSAIDs is the most selective in inhibiting COX-2 among the ones approved for use in dogs? A) Carprofen B) Etodolac C) Firocoxib D) Meloxicam E) Tepoxalin

 The answer is C: Firocoxib is one of the most selective COX-2 inhibitors used in veterinary medicine.

10. All the following concerning the pharmacological action of aspirin are true except: A) reversible inhibition of COX-1 B) Significant drug interaction with anticoagulants. C) GI ulceration and hemorrhage D) antiplatelet effects.

 The answer is A: Aspirin act through acetylation and irreversible inhibition of COX-1 active site. The COX -1 inhibitory effects may account for the increased frequency of GI ulceration and bleeding.

11. Which of the following NSAIDs exerts its actions through dual inhibition of cyclooxygenase (COX) and 5-lipooxygenase (5-LOX) A) Deracoxib B) Carprofen C) phenylbutazone D) Tepoxalin

 The answer is D: Tepoxalin,NSAID for the treatment of osteoarthritis , is categorized under dual inhibitors. Act by inhibiting both COX and 5-LOX pathways. Its inhibitory effects on both branches of the arachidonic acid metabolism pathway have been shown to produce fewer GI damage in dogs.

12. Which of the following NSAIDs is used for the alleviation of visceral pain associated with colic in horse? A) Flunixin meglumine B) phenyl butazone C) Aspirn D) Carprofen E)Meclofenamic acid

 The answer is A: NSAIDs alleviate pain that is of somatic and integument origin; although less effective in relieving visceral pain. Flunixin is an exception; it alleviate visceral pain related to colic in horse. In addition, it provide the longest duration of postoperative analgesia in comparison to carprofen and phenylbutazone in horse.

13. Which of the following is the correct statement concerning COX-2 inhibitors? A) they decreases platelet function B) they have greater analgesic activity than other NSAIDs. C) their anti inflammatory activity is better than that of other NSAIDs. D) they do not affect the kidney. E) they cause less gastric ulceration than other NSAIDs.

 The answer is E: COX-2 inhibitors cause less gastric damages than other NSAIDs; this is why it is widely used . they do not decrease platelet activity; do not have greater analgesic or anti inflammatory activity than other NSAIDs. Their nephrotoxic effect is not less than other NSAIDs.

14. Which of the following is an incorrect statement concerning the drug interactions of NSAID?

A) Concurrent use of a glucocorticoid is encouraged , since this practice will ensure better anti-inflammatory activity. B) Concurrent use of diazepam may increase the activity of both drugs. C) Concurrent use of Gentamicin can increase nephrotoxicity of NSAID. D) Concurrent use of two NSAIDs should be avoided.

 The answer is A: Concurrent use of glucocorticoid with an NSAID should be avoided, since this practice will increase the risk of GI ulceration. Since NSAIDs are bound to plasma protein any drug that are bound by albumin will cause drug interaction with NSAID many drugs affecting CNS including diazepam , fall into this category. Concurrent use of NSAIDs is discouraged since this practice will increase the free form of both drug in the plasma, increasing the pharmacological and toxicological effects of both drugs. Aminoglycoside antibiotics are potentially nephrotoxic, and thus concurrent use of an aminoglycoside with an NSAID will increase the risk of nephrotoxicity.

15. Which of the following is a correct statement regarding DMSO? A) It is more useful in the treatment of chronic inflammatory conditions than acute ones. B) It has potent antidiuretic effect. C) DMSO traps free radicals and inhibits prostaglandin synthesis, which may account for its anti-inflammatory effect. D) The adverse effects include CNS and respiratory disturbances, but not hepatic or nephro toxicity.

 The answer is C: DMSO traps free radical oxidants that evoke inflammatory process. this is why it is more useful in treating acute than chronic condition. DMSO has potent diuretic effect. the adverse effects of DMSO are many , which include CNS and respiratory disturbances as well as hepatotoxicity and nephrotoxicity.

**V. ANSWER THE FOLLOWING:**

1. Classify AAA with one example each :

 A. Analgesic, anti inflammatory and antipyretic.

 a. Salicylates- aspirin, salicylic acid, sod. salicylate, salol, methyl salicylas.

b. Pyrazolone derivative- phenyl butazone, oxyphenbutazone.

c. Indole derivative- indomethacin, sulindac.

d. Propionic acid derivative.Ibuprofen, naproxen, ketoprofen, fenoprofen

e. Anthranilic acid derivatives- mephenamic acid.

f. Aryl acetic acid derivatives- diclofenac , tolmetin.

g. Oxicam derivatives-piroxicam,tenoxicam.

h. Pyrolapyrrole derivative- ketorolac.

i. Sulfonanilide – nimesulide

j. Alkanones-nabumetone.

B. Analgesic but poor anti inflammatory:

 a. Paraaminophenol derivatives- phenacetin. b. pyrazolone derivatives-Metamizole.

c. Benzoxazocine derivative-nefopam.

2. Classify drugs which will reduce body temperature.

I.Centrally acting a) paraamino phenol derivative .- phenacetin. b) pyrazolone derivative-phenyl butazone

 c) salicylates.-sodium salicylate. d)Quinine derivative—cinchona . II.Diaphoretic III. Anti bacterials IV. Miscellaneous agents- cold water bath ,alcohol pads.

3.Classify NSAIDS with one example each:

 I. Non selective COX inhibitors

 A.Enolic acids- a)Oxicam-meloxicam, b) Pyrazolones-phenyl butazone

 B. Carboxylic acid- a)Nicotinic acid-Flunixin meglumine b) Fenamates-meclofenamic acid c) Salicylates-aspirin d) propionates- ibuprofen e) indole acetic acid-Etodolac

II.COX 2 selective inhibitors, coxibs, deracoxib

III. Dual inhibitors ( COX & 5 LOX) propanamide, tepoxalin.

4. Classify selective COX-2 inhibitors with one eg.each. a) Furazone derivative—rofecoxib b) Pyrazole derivatives—celecoxib c) Isoxazole derivatives.—valdecoxib d) Hetero aryl acetic acid derivative—lumiracoxib e) Mixed COX and 5LOX inhibitor—tepoxalin.

5.COX -1 is termed as” House keeping enzyme” why? It is constantly expressed in several tissues and is essential for maintenance of several homeostatic process including gastric mucosal, cytoprotection, renal function, vascular homeostasis, platelet aggregation etc. .hence it is called

6.How prostanoids are synthesized: Prostaglandins, prostacyclins and thromboxanes are collectively known as prostanoids and are synthesized from the same precursor arachidonic acid which is an important component of cell membrane and is released by the action of phospholipase A2 and other acyl hydrolases. This is regulated by hormones and other stimuli. Arachidonic acid undergoes cyclization and oxygenation to prostanoids via the cyclooxygenase (COX) pathway and to leukotrienes via the lipoxygenase (LOX) pathway . Majority of the NSAIDs elicit their potent anti-inflammatory , antipyretic and analgesic effect through differential inhibition of COX-1, and COX-2 and to a lesser extent LOX

 . How Aspirin induced hyperpyrexia: it is an adverse effect of aspirin, it is due to increase in oxygen consumption, leading to increased metabolic rate and increase in heat production due to uncoupling of oxidative phosphorylation.

7.How COX-1 inhibitor decrease blood cloting? They inhibit platelet aggregation ( they inhibit synthesis of thromboxane A2 ( TXA2) which are pro aggregatory) Since platelets can not synthesize new COX the inhibition is irreversible and prolonged bleeding results.

8. Tepoxalin as an anti inflammatory and analgesic agent have only fewer side effects on G I tract ,Why? It has only less side effect because of its inhibition of LOX along with COX. Inhibition of LOX may reduce leukotrienes synthesis , including LTB4 . LTB4 contribute to increased G I tract inflammation by increasing cytokine production, neutrophil longevity and release of proteases. The reduction in LTB4 will help to protect GI mucosa . Leukotrienes may also contribute to inflammatory response seen in osteoarthritis, their inhibition could reduce clinical signs seen with the disorders.

9.What are the mediators of inflammation and their role?

a. Lysosomal content from phagocytes: degradation of collagen , fibrin, cartilage, chemotactic factors, membrane degradation, vessel permeability.

b. Histamine from granulocytes: vasodilation, capillary permeability and pain.

c. Serotonin from platelets: vasodilation/ constriction, capillary permeability and pain

d. Eicosanoids, prostaglandins, leukotrienes and lipoxygenase from all cells: chemotaxis, vascular permeability

e. Platelet actvating factor from platelets: platelet activation and chemotaxis, oxygen radical production.

f. Oxygen radicals from damaged cells, leucocytes: destruction of a number of cellular constituents particularly lipid membrane.

g. Kinins from plasma: vasodilation, pain, capillary permeability.

h. Complement : lysis of cells, histamine release, release of lysosomal content, chemotaxis.

i. Fibrino peptide from plasma: chemotaxis and vascular permeability.

10.What are the mechanism involving in the anti inflammatory action of NSAIDs. a)suppress inflammatory mediators like COX, leucotrens, PAF, and cytokins. b) Attract leucocyte to the site of inflammation releasing ECAM-1 and ICAM-1 from activated endothelial cell c) inhibit molecules like selectin and integrins d) stabilizes the lysosomal membrane of leucocytes.

11. What are the adverse effect of NSAIDs? The adverse effects include G.I.disturbances, erosion and ulceration , prolonged bleeding( because of inhibition of PG E2 mediated HCO3 and mucous secretion ) epithelisation , impair platelet activity due to impaired thromboxane synthesis. Analgesic nephropathy is a relatively common adverse effect of NSAIDs.

12.What is Ion trapping of salicylic acid? Since PKa of aspirin is 3.5 ,remain unionized and diffusible in gastric juice. But on entering the mucosal cell ( pH 7.1) it ionizes and become in diffusible thus ion trapping in gastric mucosal cell stimulate toxicity.

13.What is lipoxygenase pathway? Lipoxygenase pathway- arachidonic acid is converted to 5-LOX to 5-hydroperoxyeicosatetraenoic acid which is converted to leukotriene B4( LTB4) . LTB4 plays a central role in inflammation- increased microvascular permeability and chemotactic proteins involving neutrophil-endothelial adhesion and neutrophil aggregation and degranulation .

14.What is the role of lipoxygenase enzyme in inflammation? Lipoxygenase located in cells can also metabolise AA to inflammatory mediators like Leukotriene, which are also potent mediators of inflammation. It is more predominantly found in the lungs, WBC. Platelets and liver.

15.What are the important characteristics of NSAIDs? They are primarily weak organic acids possessing antipyretic, analgesic and anti-inflammatory effect -most NSAIDs mediate their primary action through inhibiting cyclooxygenase and reduce synthesis of prostaglandins- provide only symptomatic cure –marked interspecies difference in dosage requirement -highly bound to plasma protein (except very few)- most compound penetrate BBB to act on CNS – prolonged duration of action-adverse effect on G.I tract- do not show respiratory depression. Non narcotic analgesics are weak –no CNS depression, no abuse potential act primarily on peripheral pain mechanism, also act in CNS to raise pain threshold.

**VI. WRITE SHORT NOTE ON:**

1.Anti inflammatory action of NSAIDs: NSAIDs block the first step of PG synthesis by binding to and inhibiting cyclooxygenase ,COX-1 and COX- 2 are inhibited. Some agents like phenylbutazone and flunixin meglumin also reduce formation of PGE 2 in inflammation. A drug that inhibit COX-2 at a lower concentration than that necessary to inhibit COX-1 is probably safer. It also alter cellular and humoral immune response and may suppress inflammatory mediators other than PG-interfere with cell membrane process such as oxidative phosphorylation and cellular adhesion. It disrupt the response of inflammatory cells to extracellular signals. Several neutrophil functions are inhibited. Stabilization of lysosomal membrane - inhibition of complement system, phagocytosis, leucocyte accumulation and synthesis of mucopolysaccharide and histamine. Antagonize brady kinins action , induce oxygen radical scavenger action, uncoupling of oxidative phosphorylation.

2.Aspirin : one of the oldest antipyretic--Acetyl salicylic acid--converted in the body to salicylic acid and salicylates. Readily absorbed from the stomach – t ½ vary between species-5 hours in horse and 30 hrs in cats. Toxic in cats because of limited glucuronidation-high pH enhance absorption. Weak analgesic , antipyretic and anti inflammatory .Cellular metabolism is increased- uncouple the oxidative phosphorylation- increase utilization of glucose. Continued dose cause bleeding and ulcer formation- ion trapping in gastric mucosa. Soluble aspirin contain calcium carbonate and citric acid, long term use reduce the synthesis of cloting factor-vitamin K can prevent this-uricosuric and cholagogue action. Used in minor pain of musculoskeletal origin, dissemination of intravascular coagulation, as an adjuvant therapy in endotoxic shock and reduce formation of mediators. As an antipyretics and to delay labour-acetylate cyclooxygenase enzyme and reduce P.G. synthesis.

3.COX 2 inhibitors: A class of NSAIDS directly target cyclooxygenase -2 , the iso enzyme mainly responsible for inflammation and pain, selective inhibition of COX 2 improve gastrointestinal tolerance and minimizes some side effect with most non selective COX inhibitors. Renal toxicity is not reduced- does not alter platelet function. Toxicity due to inhibition of COIX 1 is minimized . eg. firocoxib, deracoxib.

4.Dimethyl sulfoxide.(DMSO):colourless liquid –anti inflammatory, anti microbial, anti fungal action. Penetrate the skin- used as solvent for many agents, traps free radicals such as super oxide . Used to reduce acute swelling resulting from musculo skeletal trauma, cystitis due to urethral obstruction, superficial burns, swelling, engorgement of mammary gland. While applying rubber gloves must be worn, applied only on clean dry areas-burning sensation- allergic reaction- garlic odor to breath.

5.Diclofenac sodium : it is a phenyl acetic acid with AAA property-primarily inhibits cyclooxygenase enzymes- potency is greater over several other NSAIDs-moderate preference to block COX 2-low G.I. problems than aspirin. It inhibits DNA synthesis, reduce neutrophil chemotaxis and superoxide production at inflammatory site- inhibitory action on lipoxigenase pathway. Used mainly in human medicine in rheumatoid , osteoarthritis, bursitis, spondylitis, polymyosites, dental pain. In veterinary practice used mainly for treatment of uveitis especially when corneal infection is suspected. Side effects include G.I. upset and renal effect . Highly toxic to vultures.

6.Fenamates : Fenamates are anthranilic acid derivative- AAA inhibit cyclooxygenase mainly COX2 there by inhibiting PG and related compounds –antagonise histamine and kinins. Pharmacological action is similar to aspirin. Analgesic action is more than phenyl butazone. Side effect – gastro intestinal disturbances, hepatotoxicity, teratogenicity . used in dogs and horse in inflammatory diseases of musculo skeletal system. Eg.Meclofenamic acid, tolfenamic acid, flufenamic acid.

7.Glycosaminoglycan: (polysulphated glycosaminoglycan) compound chemically similar to heparin and sulphated glycosaminoglycan which form part of the cartilage matrix- extracted from bovine trachea and lungs. Used in horse and dogs for treating degenerative or traumatic arthritis- binds to damaged cartilage matrix presumably because of high negative charge of its sulphate group and leads to reduce cartilage breakdown and stimulate synthesis of new matrix- helps to restore synovial fluid and viscosity.

8.Hyper sensitivity to aspirin: it is associated with the diversion of AA from the PG to leukotriene pathway and the production of mediators that are more inflammatory than the production of PG- H synthesis- thus NSAIDs may cause undesirable effect by augmenting leukotriene synthesis.

9.Mefenamic acid: is an anthranilic acid derivative analgesic antiinflammatory and antipyretic--inhibits cyclooxygenase- mainly COX-2 thereby inhibits PG and related compounds-antagonise histamins and kinins. Pharmacological action similar to aspirin. Analgesic action is more than phenyl butazone. Side effects G.I.disturbances, hepatotoxicity, teratogenicity. Used in dogs and horse mostly for inflammatory diseases of musculo skeletal system. Related compounds are tolfenamic acid, flufenamic acid.

10.Paracetamol ( acetaminophen): Para aminophenol derivative that possess analgesic antipyretic effect-highly toxic in cats- inhibits cyclooxygenase enzyme ,more selective on COX 2 ,mainly affect COX in brain than peripheral tissues- does not produce gastric irritation, erosion or bleeding, no effect on platelets, bleeding time or excretion of uric acid, used in dogs may cause renal and hepatic damage. The toxicity in cats include cyanosis, Heinz body anemia, methaemoglobinemia, jaundice and liver failure and facial oedema . Treatment of toxicity in cats and dogs –Acetyl cysteine can reduce liver injury. Occasionally used in dogs as oral analgesic .

11.Piroxicam: Is an NSAID not structurally related to other NSAIDs- reversible inhibition of cyclooxygenase enzyme- lowers P.G concentration in synovial fluid- inhibit platelet aggregation –high COX 2 : COX 1 inhibition ratio-inhibit superoxide formation- absorbed well from G.I. tract, bound to plasma protein, metabolized by liver- glucuronidase conjugation- excretion via kidney. Undergoes enterohepatic recycling in dogs- hence have long action- toxicity is mainly G.I toxicity.

12.Role of COX in inflammation : Cyclooxygenase one ( COX-1) mediate the formation of constitutive prostaglandin produce by many tissues like G.I. cells, platelets, endothelial cells and renal cells.P.G. generated by COX-1 are constantly present and impart a variety of normal physiological effects like protection of G.I. mucosa, homeostasis. COX-2 catalise the formation of inducible P.G. which are needed only intermittently and are mediators of inflammation- induce vasodilation, change in capillary permeability, chemotaxis. They also potentiate the effect of chemical mediators of inflammation such as histamine and bradykinin which may cause hyperalgia. PGE also modify both T and B cell function in part by inhibition of interleukins-2 secretion.

13.sodium salicylate: White pearly flakes with sweet taste- water soluble- readly absorbed from G.I tract, irritation can be reduced by simultaneous administration of equal amount of Sodium bi carbonate, antipyretic ,analgesic and anti rheumatic(Ephemeral fever in cattle) Cattle and Horse 8-50 gm, Dog 0.15 to 1 gm, Sheep 1 to 3 gm.

14.Tepoxalin: Is NSAIDs causing inhibition of both COX 1 and COX 2 and 5 LOX enzymes - approved for veterinary use in dogs as an anti-inflammatory and analgesic. It is a prodrug. The acid metabolite inhibits cyclooxygenase more selective on COX 1 than COX 2 along with LOX inhibition . reduce the synthesis of PG and leukotrienes. Inhibition of 5 LOX may reduce the GI toxicity associated with other NSAIDs which only inhibits COX. Adverse effect include nausea, vomition, inappetance, diarrhea, gastric ulcers, alopecia and renal toxicity.

**VII. WRITE ESSAYS ON :**

1. How NSAIDs are producing antipyretic anti inflammatory and analgesic effect?

2.Classify NSAIDs describe NSAIDs used in veterinary practice.

3.Classify with examples the non-steroidal anti inflammatory agents, explain their mechanism of action, side effects, and precautions to be observed in treatment.

4.Explain non-selective COX inhibitors as analgesics, anti inflammatory and anti pyretic agents ,what are the remedial measures to reduce their side effects.

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