College of Veterinary Medicine
Department of Physiology, Biochemistry & Pharmacology

autacoids

Dr. Ahmed Salah Naser

Autacoids

are chemical mediators that are synthesized and function in a localized tissue or area and participate in physiologic or pathophysiologic responses to injury.

They act only locally and therefore also termed "local hormone.

Typically, autacoids are short-lived and rapidly degraded.

Major classes.

1. amines: Histamine, serotonin (5hydroxytryptamine)
2. Polypeptides : Bradykinin, angiotensin
3. Lipid-derived : Eicosanoids. Prostaglandins, leukotrienes, thromboxane
4. cytokine . Platelet activating factor, IL, and TNFα.

BIOGENIC AMINES

A. Histamine

1. Biosynthesis. Dietary histidine is decarboxylated by l-histidine decarboxylase to form histamine .

2. Distribution and storage sites.

Mast cell sites

1.pulmonary tissue mucosa of bronchial tree

2.skin

3.GIT:intestinal mucosa

Non mast cell sites

1.CNS

2.Epidermis of skin

3.GIT: intestinal mucosa

4.Basophile(in the blood)

3. Release

a. Immunological mechanism (calcium dependent mechanism) :

When sensitized mast cells or basophils are coupled to IgE antibodies and then exposed to the proper antigen; the mast cell degranulates, thereby releasing histamine and other autacoids.

b. non immuonolgical mechanism (calcium independent mechanism):

1.Drug-induced release. (morphine, polymyxin, tubocurarine, codeine, lidocaine, penicillin), and/or their vehicles are capable of releasing histamine but this release does not involve degranulation or mast cell injury. These drugs displace or compete with histamine for the binding sites with heparin.

2. Plant and animal stings are capable of releasing histamine.

3. Physical injury such as heat, cold, or trauma can disrupt the mast cells thereby releasing histamine.

	Site	Pharmacological effects
H1	1.CNS	Increase Ach and glutamate
	2.SMOOTH MUSCLE	Contraction in all smooth m. except in blood vessels
	3.Excocrine gland	Increase secretion in all these glands like lacrimal g. , bronchial g, salivary g. , gastric gland and nasal gland .
	4.nerve ending	Sever itching
H2	1. Stomach 2. Heart 3. Mast cell	Increase HCL Increase contractility Feedback mechanism
H3	CNS	Opposite H1 effect
H4	IMMUNE CELL	Mast cell chemotaxis and leukotriene B4 production (↑

4. Receptor pharmacology

The guinea pig bronchi are the most sensitive but the bronchi of rabbit, dog, goat, calf, pig, horse, and human also contract.

In contrast, histamine relaxes respiratory smooth muscle in cats (via H1 and H2) and sheep (via H2). .

Histamine antagoinsims

1. Physiologic antagonists to histamine.

The sympathomimetic drugs, for example, epinephrine, phenylephrine, phenylpropanolmaine, and ephedrine . antagonize the actions of histamine by antagonizing histamine's physiological function. These drugs either directly or indirectly activate α- and β-adrenoceptors
to elevate blood pressure and relax the bronchi. This counters the blood pressure lowering and bronchoconstrictive actions of histamine.

2.Antihistamines.

Therapeutically useful antihistamine drugs are H1-antihistamines and H2-antihistamines. At present there are no clinically useful H3 or H4-antihistamines.

a. **Mechanism of action**. it was thought that H1-antihistamines act as competitive antagonists of histamine receptors.

b. **Classification of H1-antihistamines.**

Histamine can be broadly classified into two groups based on usage:

(1) first-generation H1-antihistamines

(2) second generation

First generation	Second generation
diphenhydramine, dimenhydrinate, hydroxyzyline, chlorpheniramine, meclizine, promethazine, and cyproheptadine	Loratidine
Cross BBB	NOT Cross BBB
Lipophilic	Hydrophilic
Have sedation effect	No
Less potent	More potent
Short duration	Long duration
Cheap	Expensive
Have atropine like effect (block muscarinic receptors	No
Block α receptor	No
Block 5HT Receptor	No
The most side effect its sedation	The most side effect is prolong Q T Interval
Have analgesic effect	No

H1-antihistamines.

1. diphenhydramine,
2. dimenhydrinate,
3. hydroxyzyline,
4. chlorpheniramine,
5. meclizine,
6. promethazine,
7. cyproheptadine.

. All H1-antihistamine have this effect, but some of them (diphenhydramine, dimenhydrinate, and meclizine) have more potent antimotion sickness effect than others in the group.

Therapeutic uses.

H1-antihistamines are administered orally, parenterally, or topically for the following conditions.

(1) Treatment of patients with allergic conditions and to reduce or ameliorate the effects due to histamine. Conditions benefited from H1-antihistamines include:

(a) Urticaria and pruritus

(b) Allergic reactions to drugs

(c) Anaphylaxis

(2) Prevention of motion sickness. Diphenhydramine, dimenhydrinate and meclizine are more effective in preventing motion sickness than other H1-antihistamines.

(3) Sedation induction. Promethazine and diphenhydramine are the most potent for inducing sedation.

Pharmacokinetics

(1) All H1-antihistamines are effectively absorbed following oral administration.

(2) All H1-antihistamines are metabolized by cytochrome P450 enzymes .

(3) The first-generation antihistamines are excreted primarily by the kidneys .

(4) The second-generation antihistamines that cause least or no sedation are excreted more into feces when compared with the first-generation drugs.

Adverse effects

(1) CNS depression (lethargy, somnolence, ataxia) .

(2) Antimuscarinic effects (dry mouth, urinary retention) occur with many H1- antihistaqmines.

(3) In high doses CNS stimulation is possible, for example, pyrilamine in the horse.

(4) Some individuals could develop allergy to the use of H1-antihsitamines.

2. H2-antihistamines.

are inhibitors of gastric acid secretion.

Pharmacologic effects.

H2-antihistamines competitively inhibits histamine (H2-receptors) in parietal cell and thereby decreases gastric acid production during basal conditions and when stimulated by food, vagal activity, pentagastrin, gastrin, or histamine.

Therapeutic uses. H2-antihistamines are administered orally to treat gastric, abomasal and duodenal ulcers, drug-induced erosive gastritis, duodenal gastric reflux, and esophageal reflux.

Cimetidine is least potent among the four H2-antihistamines. Lack of therapeutic effect of cimetidine has been reported in dogs.

- **Cimetidine** is least potent among the four H2-antihistamines. Lack of therapeutic effect of cimetidine has been reported in dogs.
- Ranitidine
- Fomotidine
- roxatidine

Pharmacokinetics

(1) well absorbed orally.

(2) metabolized by cytochrome P450 enzymes.

(3 excreted by the kidneys as the primary route.

Drug interactions. Cimetidine can inhibit the hepatic cytochrome P450 enzymes. It may reduce the metabolism of other drugs, which undergo hepatic metabolism, thereby elevating and prolonging their concentration in the plasma.

3. mast cell stabilizer .

Cromolyn sodium , ketotifen
inhibits the release of histamine and other autacoids from mast cells. It does not inhibit H1- and H2-receptors, but opens chloride channel to hyperpolarize the cells.
(1) It is primarily used to treat pulmonary and nasal allergic reactions.
(2) It is not well absorbed from the gut and has no clinical use when given orally.
(3) It is used in a prophylactic manner.
(4) It has been used in the horse where it is nebulized and delivered via a face mask.
(5) The 4% eye drop is used to control allergic conjunctivitis.

Serotonin (5-hydroxytryptamine, 5-HT)

5-HT is present in high concentration in

- platelets,
- the enterochromaffin cells
- myenteric plexus of the GI tract
- CNS.

Its synthesis starts from dietary tryptophan.

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Metabolism, distribution, and function

a. Serotonin is deaminated by monoamine oxidase (MAO) .

b. 90% of the body's serotonin is found in the GIT in enterochromaffin cells. It is involved in regulating motility.

c. Platelets actively transport serotonin and store it. This keeps the concentration of free 5-HT low in the blood flow.

d. Serotonin is synthesized and stored in the CNS where it acts as a neurotransmitter.

e. Serotonin is also found in venoms and stings. Sensory nerve ends are stimulated by serotonin and this action may be responsible in part for the pain and itch of stings

Serotonin receptors.

- 5-HT1
- 5-HT2
- 5-HT3
- 5-HT4–7

Pharmacologic effects.

* Serotonin may produce vasoconstriction or vasodilatation,

* Many smooth muscles (bronchi, uterus, GI) contract in response to serotonin.

*pain : serotonin produce pain and pruritus by stimulating sensory nerve .

* regulating gut motility, body temperature, sleep, aggression, pain, mood, and endocrine function.

Serotonin agonists in nature

Ergot alkaloids (ergotamine, ergonovine, ergocryptine, ergocornine, ergocristine, ergosine) occur in various combinations and are found in the fungi of the genus Claviceps.

Pharmacologic effects.

Ergot alkaloids exhibit a complex pharmacology. They have the ability to act on both adrenergic and serotonergic receptors either as partial agonists or antagonists

Receptor	Site and function	Drug that act on it
$5HT_1$ A B C D E	CNS : sleep, appetite , temperature, thinking. Blood vessels : vasoconstriction	Sumatriptan : agonist on 5HT1D AND 5HT1B (treat migraine). Buspirone : agonist on 5HT1A (decrease anxiety)
$5HT_2$ A B C	CNS Platelet: increase platelet aggregation	Cyproheptadine : antagonism on 5HT2 (appetite stimulant) Ketanserine : antagonism to 5HT2A(Decrease platelet aggregation .
$5HT_3$	CNS vomiting center GIT : REGULATION OF MOTILITY	ONDANSETRON : ANTAGONISM OF 5HT3
$5HT_4$	CNS GIT:regulation of motility CARDIAC MUSCLE	Tegacerod :agonist on 5HT4 (treat IBS) Cisapride : agonist on 5HT4 Metclopromide : agonist on 5HT4
$5HT_5$	CNS	
$5HT_6$-$5HT_7$	CNS	

Serotonin-receptor modifying drugs

1. GI prokinetic agents: These drugs increase GI motility by increasing ACh release from the vagus nerve.

a. Cisapride

Therapeutic uses. It is an agonist for 5-HT4 receptor, and is used for gastric/intestinal stasis, reflux esophagitis, and constipation/megacolon in cats.

b. Metoclopramide

(1) Therapeutic uses. It is a D2-receptor antagonist/**5-HT4** agonist, and is used for treating vomiting disorders, reflux esophagitis, and gastric stasis, or hypomotility.

Adverse effects

(a) In dogs, changes in mental state and behavior (restlessness and hyperactivity to drowsiness/depression . Both dogs and cats can develop constipation while taking this medication.

(b) In adult horses, IV metoclopramide : sedation and excitement, behavioral changes, and abdominal pain.

(c) Other side effects include nausea, diarrhea, transient hypertension, and increased prolactin secretion.

Sumatriptan:

Is a 5HT1D agonist , most effective in the acute attack of migraine via produces constriction of intracranial vessels .

Buspirone :

Is a 5HT1A partial agonist used as non sedative anxiolytic agent .

Tegaserod

is a 5-HT_4 agonist for the management of irritable bowel syndrome and constipation. Approved by the FDA in 2002, it was subsequently removed from the market in 2007 due to FDA concerns about possible adverse cardiovascular effects. Before then, it was the only drug approved by the United States Food and Drug Administration to help relieve the abdominal discomfort, bloating, and constipation associated with irritable bowel syndrome. Its use was also approved to treat chronic idiopathic constipation.[

Cyproheptadine (5-HT2 antagonist and H1-antihistamine)

a. Therapeutic uses. It is useful in cats as an appetite stimulant. It is useful in the treatment of feline asthma or pruritus in cats. It also has H1-antihistamine activity, and thus is useful in managing hives. In horses, it is for treating photic head shaking.

b. Pharmacokinetics. Orally administered cyproheptadine is well absorbed from the gut and is metabolized and excreted in both feces and urine.

c. Adverse effects include sedation, anticholinergic activity, anorexia, and lethargy. Higher doses of cyproheptadine can produce polyphagia.

Ketanserin (5HT2 receptor antagonist)

a. Therapeutic uses. The potential use of ketanserin is to treat ergovaline-induced severe vasoconstriction. It also has significant α-adrenergic blocking activity and thus reduces blood pressure. It can be used to reduce intraocular pressure inglaucoma.

4. Other serotonin modifying drugs used are antidepressants .

Ondansetron :

Blocks 5HT3 receptor , it is used in the preventing and treating vomiting .

POLYPEPTIDES

Angiotensins

are polypeptides that elevate blood pressure by inducing vasoconstriction.

a. **Angiotensinogen** is an α2-globulin synthesized in the liver and is present in the
circulation. It is the precursor for all angiotensins.

b. **Renin** is an enzyme secreted by juxtaglomerular cells in the renal arterioles, which metabolizes angiotensinogen to form angiotensin I.

c. **Angiotensin-converting enzyme (ACE),** an enzyme found in large amounts in lung capillary endothelial cells as well as in other vascular beds, metabolizes angiotensin I to the angiotensin II.

d. Angiotensin II is metabolized by an aminopeptidase to angiotensin III that has less biologic activity than angiotensin II.

Receptors

AT1 receptor and AT2 receptor.

AT1 receptors are stimulatory, whereas AT2 receptors are inhibitory, which mediate effects usually are opposite to those of AT1.

Pharmacologic effects.

Angiotensin II regulates blood pressure and fluid and electrolyte balance.

1. Hypertensin, edema, and electrolyte imbalances can occur from over activity of the renin–angiotensin system.
2. Angiotensin II is 40-times more potent as a vasoconstrictor than norepinephrine.
3. Angiotensin II promotes the synthesis and secretion of aldosterone Aldosterone promotes sodium and water retention and potassium loss .
4. Angiotensin II stimulates the thirst center in the hypothalamus and increases vasopressin (antidiuretic hormone) secretion.

Antagonists of the renin–angiotensin system.

a. ACE Inhibitors. These drugs effectively inhibit ACE, resulting in inhibition of angiotensin II production and accumulation of angiotensin I and bradykinin.

enalapril inhibit the enzymatic conversion of angiotensin I to angiotensin II. Drugs in this class do not block angiotensin II receptors nor do they have agonist activity.

ACE inhibitors produce the following pharmacologic/therapeutic effects:

(a) Decreased retention of sodium and water by reducing the secretion of aldosterone.

(b) An increase in the levels of bradykinin (a vasodilating polypeptide) since bradykinin is inactivated by ACE.

(c) A decrease in blood pressure and fluid retention in patients with elevated angiotensin I blood levels. (See Chapter 8 for detailed information regarding therapeutic uses of ACE inhibitors.)

b. β1-Adrenergic antagonists. The sympathetic nervous system promotes the release of renin from juxtaglomerular cells via β1-receptors. Drugs such as propranolol inhibit activation of β1-receptors and thereby reduce renin release .

c. Angiotensin I (AT1) receptor antagonists. Several AT1 receptor antagonists, including

losartan, candesartan, and valsartan are now added to antihypertensive treatment in human medicine. These drugs do not have the adverse effects associated with chronic use of ACE inhibitors and appear to have a number of ancillary beneficial effects such as anticancer activity and neuroprotective effects in experiment model systems. The veterinary use of AT1 blockers is limited due to the high cost of this class of drugs.

d. Renin receptor inhibitor—<u>aliskiren</u>.

The renin receptor inhibitor aliskiren inhibits the conversion of angiotensinogen to angiotensin I. It is for controlling hypertension in humans.

The kinins: bradykinin and kallidin

are polypeptides that dilate blood vessels.

a. Two distinct enzymes (one from plasma and the other from tissue) called kallikreins catalyze the formation of two polypeptides: bradykinin, and kallidin

b. kininogen serve as the precursor for the synthesis of the two peptides.

c. Proteases inactivate both bradykinin and kallidin. The major peptidase is ACE. ACE inhibitors prolong the duration of action of both peptides and this contributes to their blood pressure lowering activity as well as bronchoconstriction.

2. Mechanism of action. Bradykinin acts on bradykinin-1 (BK1) and bradykinin-2 (BK2) receptors.

3. Pharmacologic effects:

a. vasodilators. The vasodilating effect is due to production of NO and prostaglandins

b. contraction of the smooth muscle .

c. venous contraction .

d. increase vascular permeability and edema .

f. induction of pain.

Icatibant

is medication for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase-inhibitor deficiency . It is a selective and specific antagonist of bradykinin B2 receptors.

III. PHOSPHOLIPID-DERIVED MEDIATORS

Eicosanoids

a. The eicosanoids include the prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LT). They are derived from polyunsaturated acids and arachidonic acid . Its play key role in inflammatory, cardiovascular, and reproductive functions.

b. Arachidonic acid is released from membrane phospholipids primarily by phospholipase A2 in response to physical, chemical, hormonal, and neurotransmitter stimuli.

c. Arachidonic acid can be metabolized by three pathways.

(1) The cyclooxygenase pathway leads to prostaglandin, thromboxane, and prostacyclin production.

(2) The 5-lipoxygenase pathway leads to the synthesis of leukotrienes.

Prostaglandins (PGs) and thromboxanes (TXs)

Pharmacologic effects

(1) Misoprostol. It is a PGE1 analog that has two functions which make it
a useful protective agent for the GI tract. It directly inhibits gastric acid secretion by parietal cells and it facilitates PGE-mediated mucosal defenses

	PGE_1	PGE_2	PGI_2	$PGF_2\alpha$	TXA_2	LTB_4
BLOOD VESSELS	Vasodilation			Vasoconstriction		Vasodilation (inflammatory)
BRONCHEAL MUSCLE	Bronchodilation			Bronchoconstriction		Sever bronchoconstriction
EDEMA	+			-		+++++++
UTERUS	1. NON pregnant >> relaxation 2. Pregnant }}}} contraction			contraction		
Renal blood flow	Increase			Decrease		??????
Platelet			Decrease platelet aggregation		increase platelet aggregation	
Other effect	1. Increase mucuos production in the stomach 2. fever					Chemotaxis

Uses of PGE_1 (alprostadil)

Vasodilation in patient with erectile dysfunction.

Transposition of great vessels .

Induce labor

Uses of PGE_2

Induce labor

Bronchodilation

Uses of PGI_2

TO inhibit platelet aggregation in hemodialysis and open heart surgery .

Uses of $PGF_2\alpha$

- Induction of luteolysis and synchronization of estrus .
- Treatment of pyometra or chronic estrus .
- Expulsion of mummified fetus.
- Induction of abortion .

Leukotriene inhibiters

Leukotriene receptors antagonism

Zafirukast

Montelukast

LOX inhibitor

Zileuton

Uses : asthma

Nonsteroidal Anti-inflammatory Drugs

Mechanisms of action of NSAIDs.

Cyclooxygenase (COX) pathway. Prostanoids are synthesized via the COX pathway; there are two COX isoforms, COX-1 and COX-2. In addition, the recently identified acetaminophen-inhibitable COX-3 isoform is found to be expressed in the canine brain.

a. COX-1 is constitutively expressed in several tissues and is termed "house keeping enzyme" because of its essential role in the maintenance of several homeostatic process including gastric mucosal cytoprotection, renal function, vascular homeostasis, platelet aggregation.

b. COX-2 is an inducible form because it is expressed at the site of injury, inflammation and in certain pathological states such as osteoarthritis. may promote delayed wound healing.

Lipoxygenase (LOX) pathway. AA is converted by 5-LOX to 5-hydroperoxyeicosatetraenoic acid, which is eventually converted to leukotriene B4 (LTB4). LTB4 plays a central role in inflammation, increased microvascular permeability, and chemotactic properties involving neutrophil–endothelial adhesion, and neutrophil aggregation and degranulation.

A. Pharmacological consideration

1. All of them exert analgesic, anti-inflammatory and antipyretic actions by inhibiting

PG synthesis via blocking COX. Some NSAIDs also inhibit LTB4 synthesis by blocking LOX.

2. **Analgesic effects of NSAIDs** are related to blockade of PGE2-mediated enhancement of pain sensitization at the nerve endings in the CNS and at the sites of inflammation.

3. **The antipyretic effects** or temperature-lowering action works only in the presence of a fever, by the three mechanisms :

* inhibit the production of PGE 2 which is responsible for fever.
* desensitization of hypothalamus to IL-1 (endogenous pyrogen).
* cause cutaneousvasodilatation, sweating, and panting.

4. **The anti-inflammatory effect** of NSAIDs is due to inhibition of PGE2 synthesis, which lead to

* decrease chemotaxis .
* decrease capillary permeability.
* stabilization of lysosomal membranes,
* inhibition of the hyaluronidase enzyme which produce by bacteria ,

5. The COX-1 inhibitors decrease blood clotting by

* inhibiting platelet aggregation (they inhibit synthesis of thromboxane A2(TXA2.
* acetylation of cell membrane of platelet leading to decrease aggregation .
* decrease adenosine di phosphate synthesis.

C. Adverse effects

The following are the commonly seen adverse effects of NSAIDs in animals:

1. **vomiting,**
2. **diarrhea,**
3. **GI ulceration,**
4. **hepatotoxicity,**
5. **renal toxicity,**
6. **CNS depression,**
7. **circulatory disturbances**.

Classification of NSAIDs

1. Nonselective COX inhibitors:

a. Enolic acids

Oxicams: Meloxicam

Pyrazolones: Phenylbutazone

b. Carboxylic acid

Nicotinic acid: Flunixin meglumine

Fenamates: Meclofenamic acid

Salicylates: Aspirin

Propionates: Ibuprofen, Naproxen, Ketoprofen, Carprofen

Acetic acid: Etodolac

2. COX-2 selective inhibitors:

Coxibs: Deracoxib, Firocoxib

3. Dual inhibitors: (COX/and 5-LOX):

Propanamide: TepoxalinB.

Aspirin (Acetylsalicylate).

Aspirin is a prototypical NSAID that is effective and inexpensive.

1. Mechanism of action. Aspirin act by **irreversible** inhibition of COX , resulting in decreased PG synthesis. Irreversible inhibition of platelet COX-1 by aspirin is responsible for the blockade of TXA2 production and its associated anticoagulant effects.

2. Therapeutic uses

a. analgesic and an NSAID in dogs and cats, control of osteoarthritis.

b. It can be an adjunct therapy for septic and endotoxic shocks in animals having a heavy infection.

c. Sulfasalazine, an oral salicylate-sulfonamide, is used to treat chronic inflammatory conditions of bowel, for example, ulcerative colitis.

3. Pharmacokinetics

a. Aspirin is readily absorbed from both the stomach and upper intestine.

b. Buffered aspirin. Since the acidity of regular aspirin can irritate stomach, particularly

in dogs and cats, buffered aspirin is preferred for these two species. Although buffered aspirin is more ionized, and thus less rapidly absorbed from the GI tract, the total GI absorption of buffered aspirin is similar to that of regular aspirin.

e. In animals, salicylate metabolism is primarily through glucuronidation

f. Cats have very limited glucuronidation (by glucuronide transferase), and thus are most sensitive to aspirin toxicity. After the exhaustion of glucuronidation, salicylate then form conjugates with glutathione.

4. Adverse effects

a. vomiting, anorexia, GI ulceration,diarrhea.

b. Aspirin-induced paradoxical hyperpyrexia is due to an increase in O2 consumption, leading to increased metabolic rate and increased heat production due to uncoupling of oxidative phosphorylation.

c. In the early phase aspirin-induced acid–base disturbances may be manifested as respiratory alkalosis due to direct stimulation of the medullary receptor center, leading to hyperventilation.

d. Dehydration due to vomiting, sweating, and hyperpyrexia, may be life threatening.
e. Pulmonary edema is seen in sheep.
f. In animals that are placed on chronic aspirin therapy, drug treatment must be discontinued 7 days before surgery to minimize the risk of bleeding during surgery.
g. Drug interactions of aspirin happen most often due to salicylate-mediated displacement of other drugs that compete for the same albumin-binding site, for example, warfarin (in this case the end effect is aggravated due to the additive anticoagulant effects of both drugs).

C. Meclofenamic acid

1. Mechanism of action. Nonselective inhibition of both COX-1 and COX-2 is the primary mechanism of action. Additional effects may include prostaglandin receptor blockade.

2. Therapeutic uses. It is for oral use in the **dog and horse**. It is used in treatment
of osteoarthritis in the horse as well as soft tissue inflammation, (e.g., laminitis)
The onset of action is slow, taking from 36 to 96 hours to develop.

D. Acetaminophen. This drug is unsafe in small animals.

E. Phenylbutazone. *The safety and efficacy profile in addition to its affordability makes it the most commonly used NSAID in the horse.*

1. Mechanism of action. Phenylbutazone, shows COX-2 inhibitory effects and COX-1 sparing effect in both horses and dogs.

2. Therapeutic uses.

lameness , osteoarthritis and other painful conditions of the limbs

Flunixin

It is a nicotinic acid derivative. It has potent anti-inflammatory and analgesic effects and is indicated for the treatment of acute and surgical pain.

Mechanism of action.

1. Flunixin shows greater COX-2 inhibitory effects than COX-1 in horses.

2. In dogs, it appears to exhibit preferential COX-1 inhibitory effects.

Therapeutic uses.

1. Flunixin reduce visceral pain related to colic.
2. In horses flunixin is effective in producing the longest duration of postoperative analgesia .
3. In cattle, it is used for the control of pyrexia associated with respiratory disease and endotoxemia, and for the control of inflammation in endotoxemia and mastitis.

Naproxen

. It is a nonselective COX inhibitor.

Therapeutic uses. It is used orally **in horses** for soft tissue problems, for example,

myositis.

Ibuprofen and indomethacin. These two drugs are not routinely used in veterinary

medicine due to its low safety profile.

Ketoprofen

It is a propionic acid derivative.

. Mechanism of action. is a nonselective inhibitor of COX. Additionally, it also blocks LTB4 biosynthesis via the LOX pathway, which may broaden its efficacy as an anti-inflammatory agent

Etodolac

Etodolac is an indole acetic acid derivative. In dogs, it preferentially inhibits COX-2.

Therapeutic uses

It is for the control of pain and inflammation associated with osteoarthritis in dogs.
It may be used as an analgesic and anti-inflammatory drug for many other conditions.

Deracoxib

Deracoxib is a COX-2 inhibitor.

Therapeutic uses.

A. It is used in dogs for the treatment of pain and inflammation associated with osteoarthritis

B. for the management of postoperative pain and inflammation .

Meloxicam

It is an oxicam derivative, which is a preferential COX-2 inhibitor.

Therapeutic uses.

for the treatment of chronic pain and inflammation associated with osteoarthritis in dogs and cats.

for controlling postoperative pain.

Improved analgesia is seen in dogs given a combination of meloxicam with morphine .

Tepoxalin

* Tepoxalin belongs to the class of dual inhibitors. It is a nonselective COX inhibitor with inhibitory effect on LOX.

1. Mechanism of action

Tepoxalin is a dual inhibitor of both COX and LOX. By inhibiting both COX-1 and COX-2 and 5-LOX at the approved recommended dosage in dogs it may have fewer adverse effects on GI tract.

Tepoxalin reduces the production of PGs associated with pain, hyperpyrexia, and inflammation.

Its inhibition of LOX may reduce leukotrienes synthesis, including LTB4. Since
LTB4contributes to increased GI tract inflammation by increasing cytokine production,
neutrophil longevity and release of proteases, the reduction of LTB4 will help protect GI mucosa. Leukotrienes may also contribute to inflammatory responses seen in osteoarthritis and their inhibition could reduce clinical signs seen with the disorder.

2. Therapeutic uses.

A. To control the pain and inflammation associated with osteoarthritis in dogs.

B. To control allergic conditions in dogs. Because it inhibits leukotrienes synthesis.

C. To control postoperative pain associated with soft tissue surgery.

Thank you