NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN DOMESTIC ANIMALS: I. THEIR CLASSIFICATION, MECHANISM OF ACTION AND PHARMACOLOGICAL EFFECTS

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ABSTRACT
A large number of non-steroidal anti-inflammatory drugs, of different chemical groups are available for veterinary use. These drugs act mainly by inhibiting the formation of endoperoxides (prostaglandins and thromboxanes) through the inhibition of cyclo-oxygenase in the eicosanoid pathway. A wide range of pharmacological effects, including analgesic, antipyretic and anti-inflammatory effects occur as a result of this inhibition. The classification, mechanism of action and pharmacological effects of these drugs are reviewed.

Key words: Non-steroidal anti-inflammatory drugs, review, classification, pharmacology, domestic animals.

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INTRODUCTION
Non-steroidal anti-inflammatory drugs (NSAIDs) have been defined as those substances, other than steroids which suppress one or more compounds of the inflammatory process[25]. The group is generally restricted only to those substances that act by inhibiting components of the enzyme system in the metabolism of arachidonic acid and formation of eicosanoids[16]. Eicosanoids, which include products such as prostaglandins, prostacyclin, thromboxanes and leukotrienes are a potent group of chemical mediators that play a fundamental role in the inflammatory process[15 30 31].

Salicylates, specifically salicylic acid and sodium salicylate, were the first NSAIDs used in veterinary medicine in the latter part of the nineteenth century[1]. These drugs were found to be "specially servicable in combatting the fever and pain of acute rheumatism"[6]. Acetylsalicylic acid, generically known as aspirin (Disprin, R & C Pharmaceuticals) was introduced in 1889 and was followed by the introduction, of a number of new substituted weak organic acids with basically similar actions and side-effects including phenylbutazone (Equipalazone, Centaur), flunixin meglumine (Finadyne, Centaur), naproxen (Nafasol, Lennon) and meclofenamic acid (Arquel granules, Parke-Davis).

The development of NSAIDs was essentially brought about as a result of the therapeutic limitations of corticosteroids and the search therefore for alternative non-steroidal anti-inflammatory drugs[33]. This search still continues and recently the use of a new non-steroidal anti-inflammatory drug, phenylpyrazoline (BW540C) which exerts both cyclo-oxygenase and lipoxygenase inhibition was reported in the horse[17].

The purpose of this paper is to review and summarise the current knowledge on the classification, mechanism of action and pharmacological effects of these drugs in domestic animals.

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CLASSIFICATION
Classical NSAIDs are those drugs which inhibit the cyclo-oxygenase enzyme pathway of arachidonic acid metabolism resulting in anti-inflammatory, analgesic and anti-pyretic effects[15]. However, in future, drugs which inhibit either or both of the cyclo-oxygenase and lipoxygenase pathways in the formation of eicosanoids may also be included. Phenylpyrazolines (eg. BW540C), which are currently being developed are drugs which have broad spectrum inhibition of both pathways[17].

NSAIDs are a heterogenous group of compounds, often chemically unrelated. The main group and subgroups are shown in Fig. 1. Most are substituted organic acids which have been divided into carboxylic and enolic acid groups[25]. Only a few non-acidic NSAIDs exist, including nabumetone and proquamazone[3]. Para-aminophenols although being very weak acids are, however, classified as non-acidic NSAIDs since they have a very large pKa value and would therefore react more like a neutral substance in the body.

MECHANISM OF ACTION
The products of the eicosanoid pathway[34] are responsible for a number of physiological effects. Pharmacologically these effects could be modified or inhibited by specific inhibition of enzymes or neutralization of radicals. The sites at which various drugs can act in the cascade are indicated in blue in Fig. 2. Corticosteroids act by inhibiting phospholipase A[1] and therefore affect both the leukotriene and endoperoxide portions of the pathway. Anti-leukotrienes and dual inhibitors of the cyclo-oxygenase and lipoxygenase enzymes are drugs which are currently under development. Scavengers of free oxygen radicals such as orgoteien, a metallo-protein, prevent the destructive effects of these radicals on cell membranes[1].

Classical NSAIDs act by inhibiting cyclo-oxygenase[16] and thereby prevent the biosynthesis and release of the endoperoxides: prostaglandins (PGE_2, $PGF_{2\alpha}$), prostacycline (PGI_2) and thromboxane (TXA_2) as indicated in red in Fig. 2. Prostaglandins and thromboxanes, as well as other products of the eicosanoid pathway, are part of a physiological control system that is geared to react instantaneously to changes in the homeostasis of organ systems. They affect a wide range of dif-

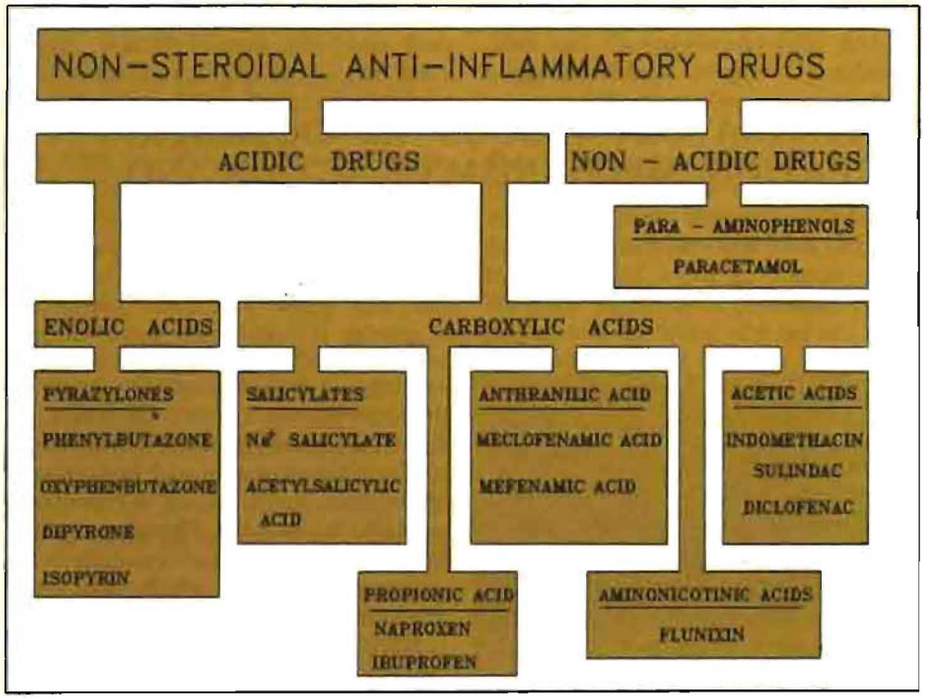

Fig. 1: **Classification of non-steroidal anti-inflammatory drugs (NSAIDs)**

ferent physiological systems with often opposing effects. They are also a group of potent chemical mediators that play a fundamental role in the inflammatory process. Since prostaglandins also potentiate the effects of other inflammatory mediators such as histamine and bradykinin, NSAIDs will also reduce the inflammatory effects of these mediators[37].

Three general types of cyclo-oxygenase inhibition have been described[15 22]. These are reversible competitive inhibition, reversible non-competitive inhibition and irreversible inhibition. Reversible competitive inhibitors include ibuprofen (Brufen, Boots), mefenamic acid (Ponstan, Parke-Davis), some salicylates (Arthridine, Kruger-Med) and indomethacin (Indocid, Logos). The method of inhibition in the case of indomethacin is particularly complex and related to an interaction with the adenylcyclase system by inhibition of phosphodiesterase[15]. Fenemates (mefenamic acid, meclofenamic acid) may also depress prostaglandin actions directly.

Acetaminophen, generically known as paracetamol (Panado, Winthrop), has a reversible non-competitive action, but its action is also partly based on its free radical-trapping properties[22]. It also appears to be more effective against enzymes in the CNS rather than in peripheral tissues. Aspirin, phenylbutazone and flunixin meglumine exert their effects by an irreversible binding to cyclo-oxygenase.

The potency of NSAIDs varies in different animals and this is probably as a result of differences in affinity of the drug for the cyclo-oxygenase enzyme, its effect on the enzyme and differences in plasma binding characteristics. In decreasing potency, in horses the sequences of NSAIDS are: flunixin meglumine, meclofenamic acid, phenylbutazone, naproxen and salicylate[25]. However, potency *per se* does not confer any advantage of one NSAIDs over another. Efficacy is finally determined by the potency versus toxicity ratio.

PHARMACOLOGICAL EFFECTS

Anti-inflammatory

All NSAIDs, except the para-aminophenols have anti-inflammatory activity and provide symptomatic relief of erythema, oedema, fever and pain associated with the acute inflammatory response. Para-aminophenols possess only weak anti-inflammatory activity at the usual dosage rates[22]. NSAIDs exert their anti-anflammatory action by inhibition of the synthesis of cyclo-oxygenase products from arachidonic acid.

The role of eicosanoids in inflammation has recently been reviewed[15]. It is now apparent that members of this group such as PGE_2 and PGI_2 are fundamental to the inflammatory process, particularly in the later stages (3-24 h). Prostaglandins also act synergistically with other mediators such as histamine and bradykinin to potentiate and enhance the inflammatory response[16]. The presence of eicosanoids at the site of inflammation and the persistance or disappearance thereof will therefore affect the progression or resolution of the lesion.

Polymorphonuclear leucocytes are a major source of arachidonic acid metabolites in the acute inflammatory response[19]. Migration of these cells are inhibited by high doses of NSAIDs such as indomethacin, aspirin and flubiprofen[18]. This inhibition was explained by a non-specific inhibition of arachidonic acid peroxidation. Low doses of NSAIDs suppress prostaglandin production but enhance polymorphonuclear leucocyte migration, probably by making more arachidonic substrate available for the uninhibited lipoxygenase pathway[16]. Leukotriene A_4 (LTA_4), which is produced along the lipoxygenase pathway, was found to be one of the most potent endogenous chemotactic factors known[10], and will induce polymorphonuclear leucocyte accumulation.

Analgesia

NSAIDs are effective against pain of low to moderate intensity, particularly pain associated with inflammation or the release of prostaglandins[22]. Prostaglandins alone do not elicit pain but do so in conjunction with other mediators such as histamine and bradykinin[8 9]. Minute quantities of particularly PGE_1, but also PGI_2 have been shown to cause hyperalgesia and to potentiate pain response. Therefore by blocking the formation of these prostaglandins NSAIDs exert their analgesic effect. Several NSAIDs are also effective against kinin-induced pain[22].

Although NSAIDs are generally regarded as being only effective agains pain of somatic and integumental origin flunixin meglumine has been shown tc control visceral pain rapidly and effective ly in equidae[36]. In post operative pair NSAIDs can on occasions be more effec tive than narcotic analgesics eg. ibuprofer vs pentazocine (Sosegon, Winthrop).

In contrast to the weak anti-inflam matory effect of para-aminophenols a normal dosage levels they have gooc systemic analgesic effect. Acetamino phen, the active principle of the para aminophenol analgesics, appears to bc more effective against enzymes in the central nervous system rather than ir peripheral tissues, accounting for its anti pyretic as well as sytemic analgesic ef fect[22]. These drugs are therefore not as ef fective against pain resulting from tissue damage or from the release of inflam matory mediators.

Anti-pyrexia

NSAIDs reset the thermoregulatory areas back towards normal. PGE_1 is a potent pyretic agent[26] and raised concentrations of PGE_2 have been recovered from cerebrospinal fluids of human patients with high body temperatures suffering from a

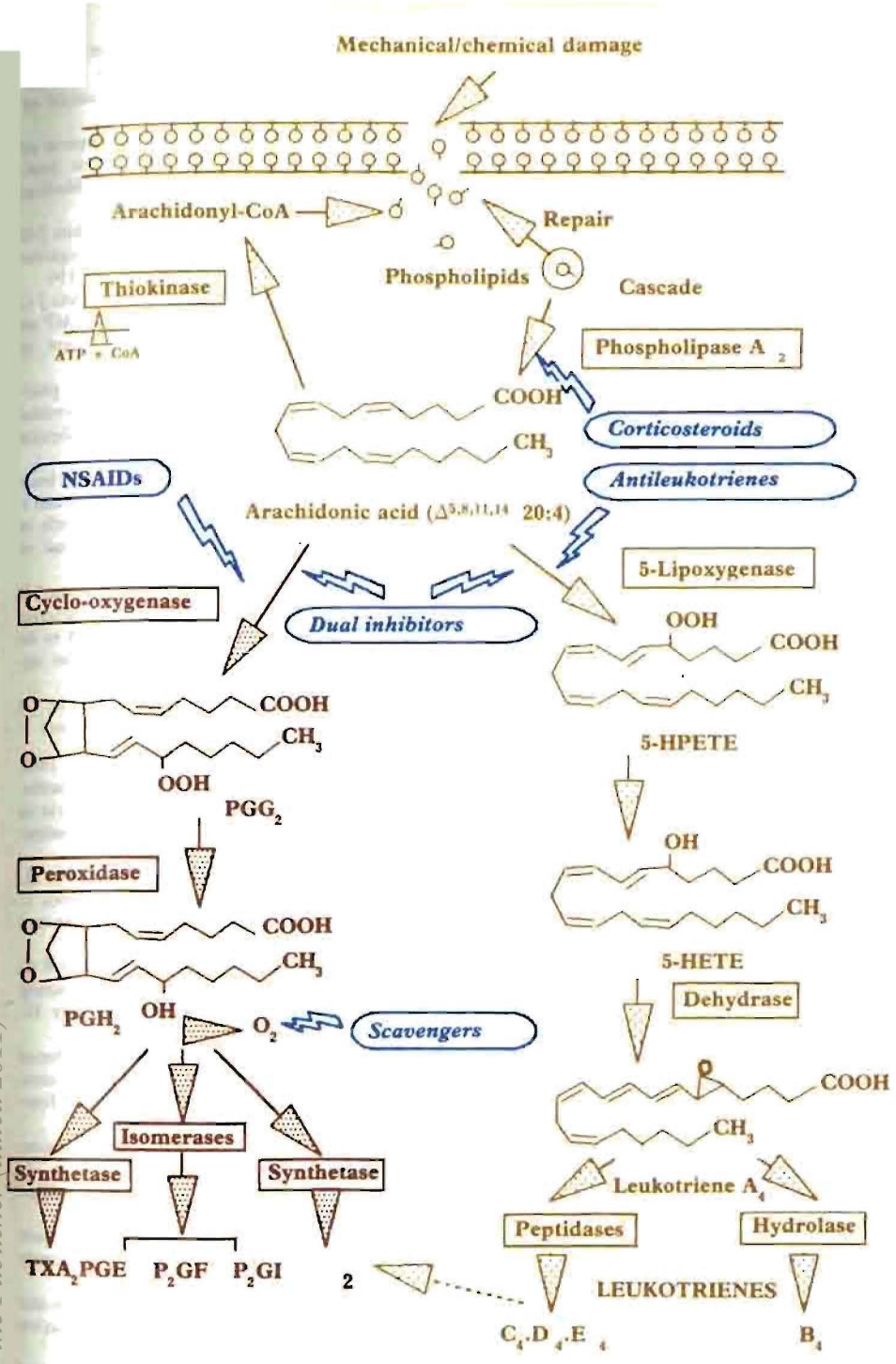

Fig. 2: **Summary of the eicosanoid pathway and sites of action of the various drugs which have an effect on the pathway**

variety of infections, including typhoid and viral encephalitis[32]. The febrile effect of these prostaglandins appears to be as result of a action on the anterior hypothalamus[7]. Blocking the formation of prostaglandins probably accounts for the antipyretic action of many NSAIDs.

Inhibition of platelet aggregation

Aspirin inhibits platelet aggregation by eliminating the release reaction of platelet aggregation induced by adenosine diphosphate and adrenaline. It acts by inhibiting cyclo-oxygenase in the formation of thromboxane A_2[13]. Thromboxane A_2 is a proaggregatory endoperoxide which is metabolised in the platelet from arachidonic acid[14]. Cyclo-oxygenase in platelets is extremely sensitive to inhibition by aspirin and has been estimated as being 20-250 times more sensitive to the inhibitor[4] effects on the enzyme in vascular cells[4]. In contrast to other NSAIDs, aspirin also acts irreversibly in platelets and its inhibition of the cyclo-oxygenase enzyme therefore lasts as long as the platelet survives. Platelets synthetise scant or no new protein. A single ingestion of a therapeutic dose of aspirin thus leads to a platelet defect lasting approximately one week[20].

Prostacycline (PGI_2) also formed along the same cycle-oxygenase pathway possesses the opposite activity on platelets and bloodvessels viz. relaxes bloodvessels and inhibits platelet aggregation[27]. Prostacycline is synthetised in endothelial cells[12] and appears to require at least 10 times more aspirin to completely inhibit its synthesis as compared to the inhibition of platelet cyclo-oxygenase[28]. Prostacycline production furthermore recovers within 6h[21]. Consequently the dose of aspirin has been reduced to selectively inhibit thromboxane A_2 production while preserving prostacycline synthesis[29].

These low doses of aspirin (3-20 mg kg^{-1} in dogs, 25 mg kg^{-1} in cats and 20 mg kg^{-1} in horses) administered once only are effective in inhibiting platelet aggregation for 3-5 d in normal animals of these species[20]. The importance of the platelet endoperoxide pathway differs between and within species[20 23 24].

Pharmacokinetic studies with aspirin provide further support regarding the selective inhibition of thromboxane A_2 production by aspirin. These studies indicate that the irreversible inhibition of cyclo-oxygenase by aspirin occurs predominantly in the pre-systemic circulation[35]. About 60% of the absorbed aspirin is deacetylated to salicylate during the first pass through the liver and the resulting plasma aspirin concentration is probably too low to be associated with any significant cyclo-oxygenase inhibition in systemic tissues, including the vessel wall. Salicylate has a reversible inhibitory effect on cyclo-oxygenase[22].

Uricosuric effect

Salicylate has been shown to alter urate excretion in a number of animals. In man low doses of salicylates decrease renal urate excretion, while in high doses the reverse occurs. Salicylate has little effect on overall urate handling in either Dalmation or other dogs[11].

Phenylbutazone has also been shown to have a uricosuric effect in animals[1]. Sulphapyrasone, a metabolite of phenylbutazone is responsible for the uricosuric effect.

CONCLUSION

Prostaglandins and thromboxanes are responsible for a large number of important and diverse homeostatic physiological functions. Inhibition of their synthesis results in a variety of different pharmacological effects which on the one hand may be used effectively for the treatment of certain conditions such

as inflammation, pyrexia and pain but on the other hand may result in a number of important side effects.

Although the various NSAIDs have the same basic mechanism of action, variation of activity between NSAIDs occur predominantly as result of the type of effect on the cyclo-oxygenase enzyme, due to pharmacokinetic differences and due to other effects such as radical-ion trapping characteristics, effect on the lipoxygenase enzyme and effect on other inflammatory mediators.

The therapeutic indications for use of NSAIDs can be expected to increase in number and diversity as more is understood about the mechanisms by which pain and inflammation is modified[2]. New indications for old drugs are continually being described[5]. Development of drugs with either lipoxygenase inhibition or with dual activity against cyclo-oxygenase and lipoxygenase enzymes will also expand the therapeutic uses of these groups of drugs.

A brief review of the disposition, various therapeutic indications, side and toxic effects and potential drug interaction of NSAIDs is given in part two of this publication.

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