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Analgesics in animal pain management

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Abstract
Non-steroidal anti-inflammatory drugs are the the most widely used over the counter pain relieving agents in the treatment of pain and inflammation associated with surgical, trauma and pathological inflammatory conditions in animals, either as sole agents or in combination to reduce the chances of adverse effects. The opioid are the most powerful pain-relieving compounds used for the systemic treatment of acute pain in many species of animals, mostly in surgical conditions involving deep seated visceral organs and orthopedic surgeries. However, the narcosis and controlled schedule are the disadvantages associated with them. The potential analgesics of therapeutic importance in the management of pain in animals is briefly reviewed n terms of clinical use and the adverse effects in animals.

Keywords: Analgesic, pain, narcotic, non-narcotic, muscle relaxant, coxibs

Introduction
Pain is defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Therapy for the pain generally involves pharmacological agents like opioids, non-steroidal anti-inflammatory drugs (NSAIDs) corticosteroids, local anesthetics, antihistaminics, α_2-agonists, ketamine and gabapentin etc. and non-therapeutic approaches like acupuncture, physiotherapy etc. Concurrent use of more than one type of analgesic agent, may be more effective for pain relief than the use of any single drug type and may allow the dose of each individual drug to be reduced. The most commonly used class of pain-relieving therapeutic agents in domestic animals are opioids (narcotic analgesics) and NSAIDs (non-narcotic analgesics).

Opioids
Opioids are the most powerful pain-relieving compounds available for the systemic treatment of acute pain in many species of animals. Opioids act as agonists, antagonists' partial agonists and mixed agonist/antagonists to four types of opioid receptors (Mu, Kappa, Delta and Sigma), with multiple receptor subtypes. Opioids combine reversibly with specific receptors in the brain, spinal cord, and periphery altering the transmission and perception of pain. In addition to analgesia, opioids can induce other CNS effects that include sedation, euphoria, dysphoria, and excitement.
The important opioid (opiates:synthetic/semisynthetic) analgesics are morphine, oxymorphone, butorphanol, codeine, nalorphine, levallorphan, pethidine, fentanyl, methadone, dextropropoxyphene, pentazocine, cyclazocine, etorphine, buprenorphine, mepiridine(pethidine), sufentanil, methadone, alfentanil, carfentanil, remifenatnil, nalbuphine, tramadol hydrochloride etc.

Charactersetic features
Considerable variation between species and among the different opioids with regard to the effects of opiods.
Use should be reserved for pain that will not respond to other medications or when pets are in terminal condition.
Also, with time, doses have to be increased to obtain comparable pain relief
Schedule II drugs, with potential abuse liability. Hence the owners need to be informed about their ill effects in humans before prescribing and using these agents and the prescribing doctor needs to carefully maintain all the records pertaining to the case to avoid any complications.

Central effects: analgesia, reduced nociception, euphoria (or dysphoria), elevated mood, relief

of the anxiety associated with pain (excessive sedation), respiratory depression, antitussive (cough suppression) effect, bradycardia, hypotension, nausea, vomiton, pica and pupilllary constriction

Peripheral effects: reduced propulsive motility of the GIT, increase in sphincter tone resulting in constipation (hence given in combination with laxative), urinary retention, and hjstamine release (anaphylactoid reaction causing itching or more severe allergic reactions including bronchoconstriction).
The administration of NSAIDS concomitantly with opioids may allow the effective use of lower doses of opioids with fewer side effects and adequate pain management.
Generally produce hyperactivity in ruminants, and particularly chewing behaviour. Doses of opiates required for immobilization may vary considerably between ruminant species In general the dose rate (mg/kg) required increases as the size of the animal decreases.
They should be used with care in acutely uraemic and toxaemic dogs. It has been recommended to administer half of the usual adult dose of opiods to puppies and kittens. Starting at lower doses and increasing to effect is recommended for analgesia.
Opiods are contraindicated in Head injury and raised intracranial pressure, hepatic and renal insufficiency, convulsant states, biliary colic, decreased respiratory reserve as in conditions like emphysema and asthma.

Tramadol hydrochloride: Is a centrally acting analgesic with opioid, monoaminergic, (monoamine reuptake inhibitor) and local anesthetic effects. It has been approved for acute or chronic mild to moderate pain relief in dogs and cats.
It may be combined with other classes of analgesics including steroids, NSAIDs, NMDA antagonists, and gabapentin to allow a lower dose o both drugs to be used.
It should not be combined with group of drugs like tricyclic antidepressants (TCA; eg: clomipramine), selective serotonin reuptake inhibitors (SSRIs; eg: fluoxetine) or monoamine oxidase inhibitors (MAOI; eg: selegiline) due to the risk of serotonin syndrome.
Rare side effects, may include GI disturbances, nausea, pupillary constriction, bradycardia, cough suppression, panting, constipation and sedation, which needs reduction in dosage.
It is not a controlled substance and can be used for pain control in lactating bitches as it is not excreted in milk. It should be used cautiously in animals with a history of seizures as itself can induce seizures.

Non steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs are the most widely prescribed drugs in the treatment of pain and inflammation in many conditions. NSAID have the potential to relieve pain and inflammation without the immunosuppressive and metabolic side effects associated with corticosteroids. The analgesic, antipyretic and anti-inflammatory effects of NSAIDs associated with properties like being devoid of sedation, hypotension, bradycardia and respiratory depression makes them advantageous over opioids, though with lesser analgesic potency. As with the opioids, different animals react differently to NSAIDs.

Mechanism of action: act by inhibition of cyclo-oxygenase (COX) enzyme(s) which leads to a decrease in the synthesis of various prostaglandins and thromboxanes. Some may alsio inhibit phospholipase A enzyme; major mechanism for effects of glucocorticoids on prostaglandin production.
Most of the NSAIDs (aspirin, being the prototype) are nonselective COX inhibitors, with COX 1 inhibition ratio being highest. Meloxicam, nimesulide, etodolac and aceclofenac are considered as preferential COX-2 inhibitors. The newer 'Coxib' class of selective COX-2 inhibitors includes rofecoxib, celecoxib, valdecoxib, parecoxib, deracoxicb, etoricoxib, firocoxib, lumiracoxib etc are thought to inhibit COX-2 selectively. Paracetamol (acetaminophen) is a selective COX-3 inhibitor with only analgesic and antipyretic actions, devoid of/with minimal anti-inflammatory action.

Pharmacological Effects: All NSAID, except for acetaminophen exhibit antipyretic, analgesic, and anti-inflammatory properties. In general, NSAID provide only symptomatic relief from pain and inflammation and do not significantly alter the course of pathologic damage. As analgesics, they are generally less potent than opioids and are therefore more effective against mild to moderate pain.

Adverse effects
1) Cellulitis, thrombophlebitis and tissue necrosis with intramuscular or perivascular injections
2) Gastric ulceration by inhibiting the production of PGE and PGI_2. The only exception would appear to be paracetamol as it does not inhibit peripheral oxygenase. The ulcerogenic potential of NSAIDs in any species is increased by concurrent corticosteroid treatment, dehydration, hypovolaemic shock and disruption to normal gut blood flow (empty stomch). Agents such as H_2 receptor antagonists (eg: ranitidine), proton pump inhibitors (eg: omeprazole) or cytoprotective drugs (eg: misoprostol, suclralfate) are administered to prevent/heal the gastric ulceration effect of NSAIDs.
3) Renal toxicity: Renal toxicity as a result of reduced renal blood flow and glomerular filtration rate secondary to inhibition of synthesis of renal prostaglandins, that are involved in maintaining renal blood flow via their vasodilatory actions.

Contraindications
1) in gastrointestinal bleeding, blood dyscrasia., cardiac, hepatic or renal impairment (insufficiency), dehydraion, hypovolaemia or hypotension
2) Concurrent use of potentially nephrotoxic drugs (eg: aminoglycosides, diuretics,) should be avoided with these agents.
3) Not advisable in in pregnant animals and animals nearing the oestrus as COX-2 induction is necessary for ovulation and implanation of the embryo. 4) Nearing term, as they delay the parturition

Specific nonsteroidal anti-inflammatory drugs
Aspirin is used in veterinary medicine primarily for the relief of mild to moderate pain associated with musculoskeletal inflammation or osteoarthritis. In cats, aspirin may be used for its anti-platelet effects in thromboembolic disease, every 48 hr, to allow for prolonged metabolism. Vomiting and melena may be seen at higher doses. Aspirin overdose in any species can result in salicylate poisoning, characterized by severe acid-base abnormalities, hemorrhage, seizures, coma, and death

Acetaminophen: Has little ulcerogenic potential, with no effect on platelets or bleeding time. It is more effective in inhibiting COX-3, in the brain rather than in the periphery.
Dose-dependent adverse effects include depression, vomiting, and methemoglobinemia. Use in cats is contraindicated due to a lack of glucuronosyl transferase and the potential for hemolytic anemia and centrilobular hepatic necrosis.

Meloxicam: Is recommended to dogs, as a one-time loading dosage of 0.2 mg/kg, PO, followed by 0.1 mg/kg, PO, sid. Once a therapeutic effect is seen, the dosage can be titrated to the lowest possible dose. Once absorbed, meloxicam is highly protein bound (97%) and has a relatively long elimination half-life (12+ hr). GI safety appears to be greater for meloxicam than for nonspecific NSAID, and meloxicam has been shown to be chondroneutral in rodent studies.

Carprofen: Is approved to manage pain and inflammation associated with osteoarthritis and acute pain associated with soft-tissue and orthopedic surgery in dogs. The exact mechanism of action of carprofen is unclear. Although it has greater selectivity for COX-2 over COX-1, carprofen is considered a weak COX inhibitor. Labrador Retrievers are most susceptible for hepatopathies with carprofen, although a true breed predisposition has not been established.

Flunixin meglumine: Is used for pain relief in the treatment of colic. It is used for protection from septic/endotoxic shock due to any gastro-intestinal insult either post-surgical or medical such as in cases of peritonitis or diarrhoea. Chronic flunixin meglumine administration in dogs results in severe GI ulceration and renal damage

Piroxicam is used for pain due to osteoarthritis., and to in many types of tumors in dog and cats, including nasal epithelial tumors, mammary tumors, colorectal tumors, oral squamous cell carcinoma, oral melanoma, prostatic carcinoma, transitional cell carcinoma (TCC) of the urinary bladder, osteosarcoma. and some rectal neoplasms.

Phenylbutazone: Is generally a safe and effective drug in the horse, in which it is commonly used for lameness, resulting from from soft tissue injury, muscle soreness, bone and joint problems, and laminitis. Phenylbutazone may be given intravenously or orally; pain relief and fever reduction usually starting within one to two hours. In Dogs it is for the longer-term management of chronic pain particularly due to osteoarthritis. It can cross the placenta and is found in milk. It should be avoided or used with caution in pregnant or nursing animals. It may affect blood levels and duration of action of phenytoin, penicillin G, sulfonamides, sulfonylurea antidiabetic agents, barbiturates, promethazine, rifampin, chlorpheniramine, diphenhydramine etc.

Nimesulide: Is used in dogs for relief of pain associated with musculo-skeletal inflammation.It is not indicated for use in puppies younger than 4 months/ dogs under 5kg; cats, and pregnant and lactating bitches.

Ketoprofen: Is most commonly prescribed for musculoskeletal pain from soft tissue injury, osteoarthritis or other bone and joint problems. It is a potent inhibitor of COX and bradykinin and may also inhibit some lipoxygenases. Its efficacy is comparable to that of opioids in the management of pain following orthopedic and soft-tissue surgery in dogs. sIt may be used to reduce or control fevers due to viral or bacterial infections. In dogs and cats it is used for the short-term management of post-surgical pain and occasionally the longer-term management of chronic pain particularly due to osteoarthritis. It can be also used in the management of colic for protection from bacterial toxins (endotoxemia).

Aceclofenac: Has a faster, more potent analgesic, antipyretic and anti-inflammatory activities, It is superior from other common NSAIDs as it has selectivity for COX-2, and is well tolerated, with better GI tolerability and improved cardiovascular safety when compared to other selective COX-2 inhibitors. It also shows increased matrix component synthesis and protection of chondrocytes against apoptosis. It efficiently interferes with neutrophils adhesion to endothelium and this effect may represent an additional relevant mechanism in its anti-inflammatory activity.

Carprofen: Is an NSAID of the arylpropionic acid class available in the USA in chewable tablet formulations. This has been approved by the FDA to manage pain and inflammation associated with osteoarthritis and acute pain associated with soft-tissue and orthopedic surgery in dogs. The recommended dosage is 4.4 mg/kg/day or divided bid, PO. In Europe and other countries, carprofen is also registered for use in horses and cattle and for short-term therapy in cats. Although it has greater selectivity for COX-2 over COX-1, carprofen is considered a weak COX inhibitor.
Other mechanisms of action include inhibition of PLA_2, which may be responsible for its anti-inflammatory effects. Potentially serious idiosyncratic hepatopathies, characterized by acute hepatic necrosis, have been reported in Labrador Retrievers, although a true breed predisposition has not been established.

Etodolac: Is the pyranocarboxylic acid etodolac is approved for use in dogs in the USA. Allowing dosing at 10–15 mg/kg/day, PO. Extensive enterohepatic recirculation has been reported in dogs, followed by elimination of etodolac and its metabolites in the liver and feces. It has shown to inhibit macrophage chemotaxis and has demonstrated efficacy for the treatment of lameness associated with hip dysplasia.

Vedaprofen: Is the arylpropionic acid derivative vedaprofen is available in *Europe in a gel formulation* for horses and dogs and in an injectable formulation for horses. Vedaprofen is indicated for the treatment of pain and inflammation associated with musculoskeletal disorders in dogs

Deracoxib: Is the first NSAID of the coxib class approved for use in dogs, is available in a beef-flavored chewable tablet formulation in the USA. It Inhibits COX-2–mediated PGE_2production. COX-1:COX-2 ratios reported for deracoxib in -indicate it is 1, 275-fold more selective for COX-2.
Indicated for the control of postoperative pain and inflammation associated with orthopedic surgery at a dosage of 3–4 mg/kg/day for up to 7 days, PO, and for the control of pain and inflammation associated with osteoarthritis at a dosage of 1–2 mg/kg/day, PO.

Firocoxib: Is a coxib-class NSAID approved in the USA and Europe for the control of pain and inflammation associated with osteoarthritis and for the control of postoperative pain

and inflammation associated with soft-tissue and orthopedic surgery in dogs.

Robenacoxib: Is a coxib-class highly selective COX-2 inhibitor, structurally related to the human NSAIDs diclofenac and lumiracoxib. Used for the control of pain and inflammation associated with osteoarthritis, orthopedic and soft-tissue surgery in dogs, and for musculoskeletal disorders and soft-tissue surgeries in cats GI safety appears to be greater than that of nonselective NSAIDs. Administration with food decreases bioavailability of robenacoxib.

Mavacoxib: Is a new coxib-class COX-2 inhibitor recently approved in Europe and Australia for the control of pain and inflammation associated with degenerative joint disease in dogs. It is structurally related to the human NSAID celecoxib; however, substitution of a methyl group with a single fluorine atom has conferred great resistance to metabolism, resulting in an elimination half-life of 17 days in young Beagle dogs. Unlike the major route of elimination of other NSAIDs, that of mavacoxib is biliary excretion of the parent molecule. In field trials conducted in aged dogs with osteoarthritis, the half-life was found to be even longer at 44 days, and in these older dogs, approximately 1 in 20 exhibited a half-life of >80 days

Tepoxalin: A dual inhibitor of both cyclooxygenases (COX-1 and COX-2) and 5-lipoxygenase (5-LOX). From a mechanistic perspective, its LOX activity (reduction of leukotriene production) may reduce components of inflammation not controlled by COX isoenzyme inhibition. The metabolite, tepoxalin pyrazol acid, lacks the LOX activity of the parent molecule. Both tepoxalin and its active metabolite are highly bound to plasma protein (98%–99%).
Many of the commercially available NSAIDs formulations are also available in combination with other suitable agents for their synergestic action in pain relieving. These include muscle relaxants like chlorzoxazone, carisoprodol, chlomezanone, methocarbamol, tizanidine and anti-inflammatory enzymes like serratiopeptidase.

CINODS
Naproxcinod: Is the first in a new class of analgesic and anti-inflammatory drugs called COX-inhibiting nitric oxide donators (CINODs), devoid of renal adverse effects due to nitric oxide moiety. It is indicated for the treatment of acute and chronic nociceptive pain, such as post-operative and arthritic pain.

Piprants
Grapiprant: Is the first piprant (a prostaglandin EP4 receptor antagonist) class of anti-inflammatory and analgesic drug It acts by specifically blocking the EP4 receptor which is the primary mediator of osteoarthritis pain in dogs and is approved as a veterinary drug by FDA for the control of pain and inflammation associated with osteoarthritis.

Adjuvant analgesic drugs
They are generally not considered to be primary first choice analgesics, but used in combination with other analgesic drugs in acute pain states to manage severe pain, so as to reduce the dose of the primary analgesic

Methocarbamol: Is a muscle relaxant that exerts its effect by acting on the CNS rather than on the muscles themselves; may relieve muscle tension associated with arthritis in pets. It has weak sedative properties and may make the urine appear darker.

Xylazine and Medetomidine hydrochloride: Given by intramuscular injection at less than sedative doses, are effective pain relievers.

NMDA Receptor Antagonists: They block pain by binding to the N-methyl-D-aspartate (NMDA) receptor. These include ketamine, dextromethorphan, memantine, and amantadine. Ketamine, commonly used as a general anesthetic in cats, reduces pain when it is applied to the skin as a specialty compounded gel or paste. Amantadine, originally an antiviral compound is most commonly used to treat drug reactions that affect coordination (extrapyramidal reactions) and pain in dogs. Side effects are may include agitation or diarrhoea.

Gabapentin: Is a structural analogue of GABA, an inhibitory neurotransmitter. It is originally a newer anticonvulsant, used in dogs and cats for the treatment of chronic pain, particularly of neuropathic origin and also used in chronic arthritic pain and pain associated with malignancy. It appears to be most effective when combined with other types of analgesic agents, as with NSAIDs, permitting the use of lower doses. The most common side effects are mild sedation and ataxia. Care to be taken in animals with decreased liver or renal function. It should not be discontinued abruptly because withdrawal may precipitate seizures or rebound pain. The dosage should be decreased over the course of two to three weeks. It crosses the placenta and gets excreted in milk, thus needs careful monitoring during pregnancy or lacatation.

Local anaesthetics: Are peripherally acting alnalgesics. Long acting agent bupiavcaine is used along with lidocaine for long acting pain relief. A single dose of bupivacaine injected at a local site will provide local analgesia for 6-10 hours. Lidocaine is administetred as an intravenous constant rate infusion (50-70µg/kg/minute in dogs, 10µg/kg/min in cats) is effective in the treatment of neuropathic pain, periosteal and peritoneal pain. It may also reduce the opioid requirement after surgery when administered as constant rate infusion.

Corticosteroids: Are the most effective blockers of inflammation and resulting pain. However, they all have major side effects when given over extended periods of time. When they must be used, they should be given in the minimal amount that will control and inflammation and should not be given more than two or three times a week.
Other adjunctive drugs less commonly employed for the relief of chronic pain can include chondroprotectives, anxiolytics and sedatives like benzodiazepines (eg: diazepam, midozolam), tricyclic antidepressants (eg: amitryptilline, imipramine), doxycycline, omega-3 fatty acids, magnesium, immunonutritional modifiers and bioflavinoids.

Conclusion
The target of recently developed NSAIDs has been attributed to COX-2 inhibiton, with the theory being that the analgesia and suppression of inflammation without the inhibition of physiologically important prostaglandins. However, evaluations have showed that they are not necessarily more effective than older drugs, but could be safer for the gastrointestinal tract.

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