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Advanced Anaesthesia for Nurses Mini Series

Session Three: Multimodal Analgesia for Anaesthesia

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Multimodal Analgesia

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What is pain?

Pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP, 1994).

The inability to communicate does not negate the possibility that an individual is experiencing pain and is in need of pain relieving treatment (McMillan, 2016).

Analgesia is the absence of pain in response to a stimulus that would normally elicit pain (IASP, 1994). There are many pharmacological analgesic agents available however the veterinary nurse's role in analgesia is about so much more than the individual drugs (McMillan, 2016).

In the perioperative period our goal as nurses is to encourage the adoption of a multi-modal approach to pain and nociceptive stimuli to make our patients as comfortable as possible post-operatively. A multi-modal approach should involve the use of drugs from different classes, administered by different routes to block the maximum amount of pain pathways possible This should be the case whether you work in a small general practice or large referral hospital. List all the analgesic agents and routes of administration that you could use and then cross off any that are contraindicated in your patient! You can then decide on what level of analgesia is appropriate for that case. Combining therapies in this way will have additive or synergistic effects allowing you to reduce the dosages of individual drugs. Intra-operative analgesia will also help you to achieve a smoother anaesthetic and recovery.

The Pain Pathway

Transduction - noxious stimulus is converted into a chemical signal at the nociceptor.

The signal is then **transmitted** along the nerve fibre to the dorsal horn of the spinal cord and through the spinal cord to the brain.

Modulation occurs at various sites in the spinal cord and brain with signals either being enhanced (sensitisation) or inhibited (hypoalgesia).

Perception - conscious organisation of the information that has been transmitted and modulated.

Pain perception in the unconscious patient

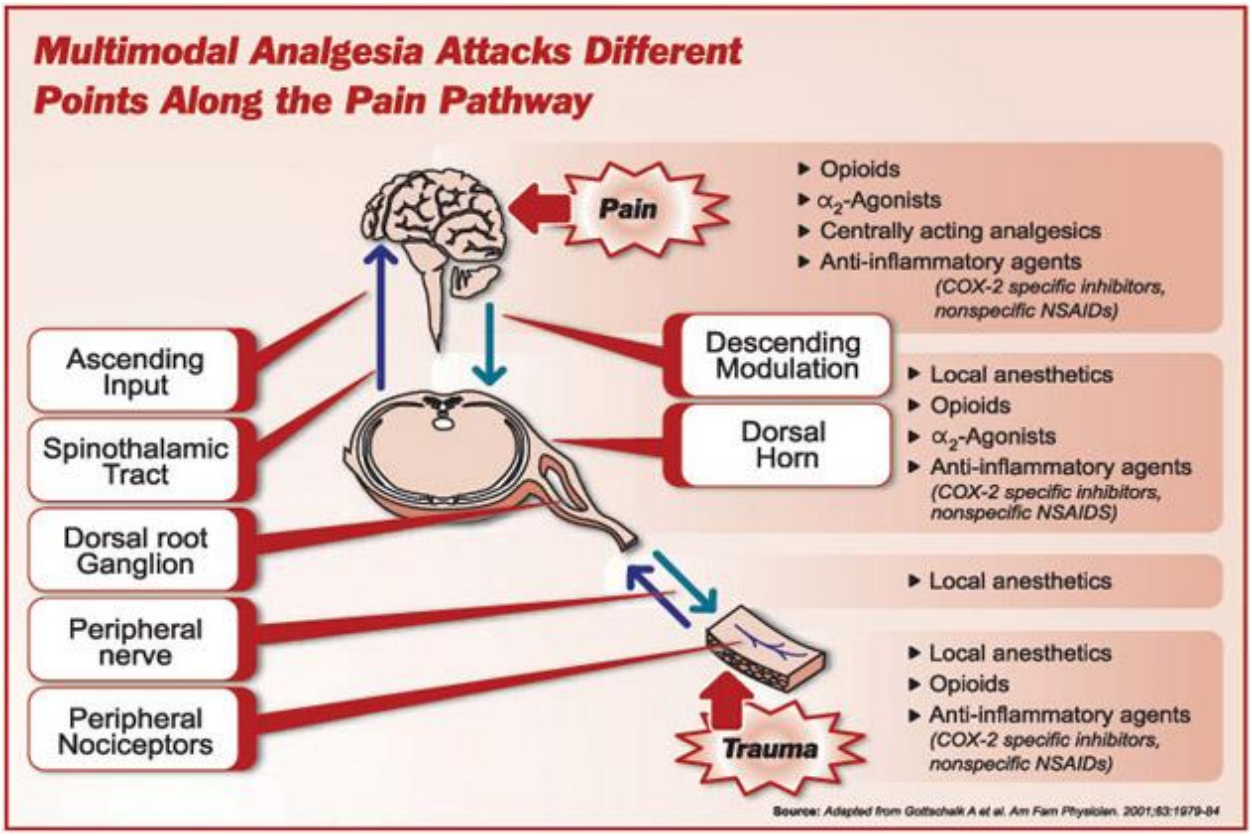
Nociception - neural process of encoding noxious stimulation and denotes the response of the central nervous system to actual or potential tissue damage (**noxious stimulus**). This process encompasses the transduction, transmission and modulation of the noxious stimulus but does not include perception (McMillan, 2016).

Hyperalgesia increased sensitivity to a noxious (painful) stimulus.

Allodynia pain evoked by a stimulus that would not normally be painful.

Multimodal analgesia –utilising analgesic agents in combination to target the nociceptive pathway at different points and providing more effective pain management (McMillan, 2016).

Pre-emptive or preventative analgesia - analgesic agents are given prior to anticipated noxious (painful) stimulus.



Premedication

Pre-emptive analgesia, i.e. administration of analgesia prior to a painful or nociceptive stimulus, should be our main aim. This optimises analgesia during surgery and reduces the dose and potentially of postoperative analgesics. Remember that nociceptive input to the CNS continues throughout the surgical procedure and may lead to sensitisation. Postoperative pain is much more difficult to manage once sensitisation has occurred.

Analgesic agents should be included in premedication protocols for all surgeries even those considered to be mildly painful. This contributes to a balanced anaesthetic technique and as a result reduces the dose of other anaesthetic agents required for induction and maintenance.

How can we administer Analgesia?

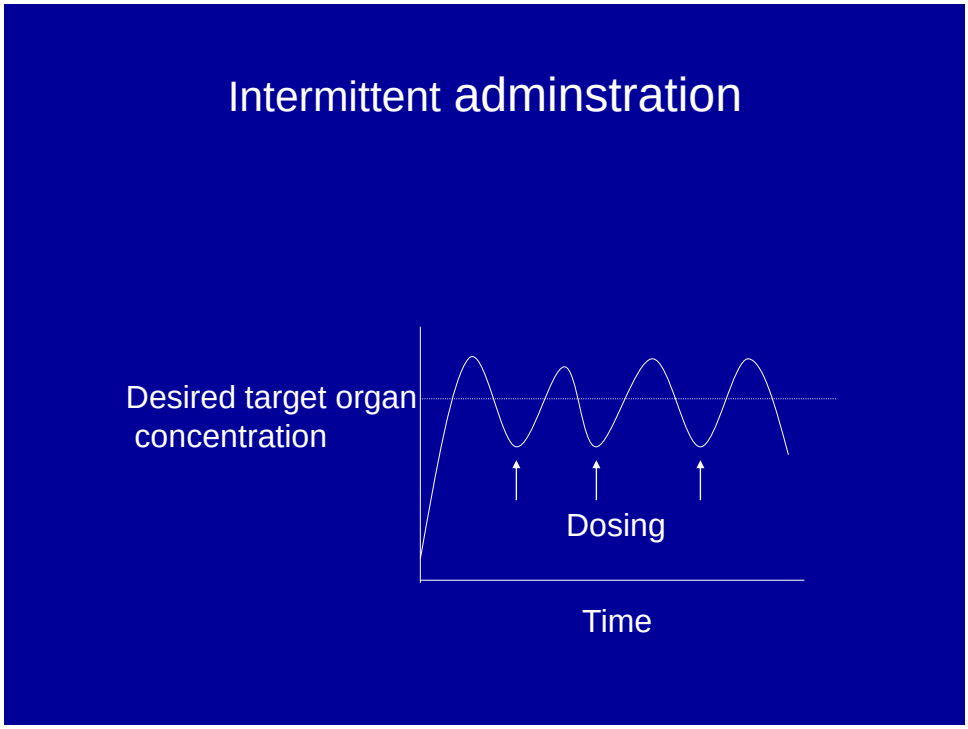
- **Oral/ Transmucousal**
- NSAIDs, gabapentin, tramadol, buprenorphine, paracetamol
- **Injectable Bolus**
- I/V, I/M, S/C, via chest drain/ wound soaker catheter/ continuous nerve block catheter, epidural catheter
- NSAIDs, opioids, ketamine, LA, paracetamol, α2 agonists
- **CRI**
- I/V e.g. fentanyl, ketamine, lidocaine, α2 agonists
- Wound soaker catheter
- **Transdermal**

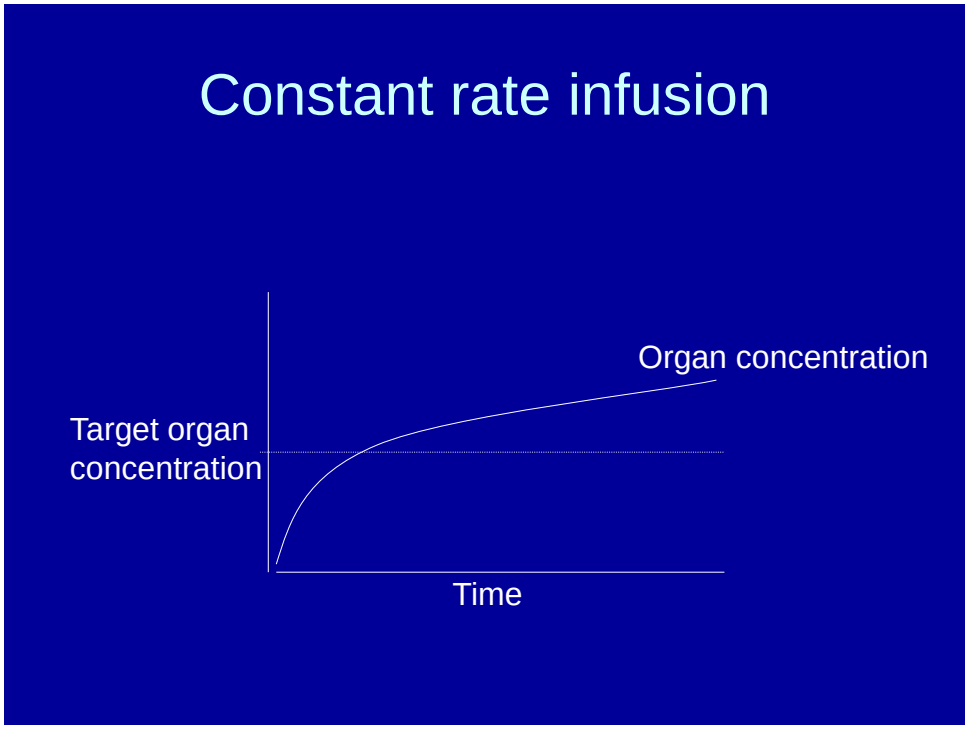
– fentanyl, buprenorphine, lidocaine

- **LA techniques**

Why Use CRIs

- Bolus injections cause peaks and troughs in drug plasma concentration
- CRI will give constant plasma levels
- Eliminates waning analgesic effect
- Dose can be more accurately titrated
- BUT
  - Requires close patient monitoring
  - Way of accurately giving drugs - equipment





Drug Therapy

The main pharmacological classes of analgesic to consider are:

- **Opioids**
- **Non-steroidal anti-inflammatory drugs (NSAIDs)**
- **Alpha- 2 agonists**
- **NMDA receptor agonists e.g. Ketamine**
- **Local analgesics**
- **Other agents**

These different classes of drugs influence pain processing through different mechanisms at different levels of the pain pathways. This means that they can be effectively used in combination to provide multi-modal analgesia protocols.

OPIOIDs

Opiates are drugs derived from the poppies *Papaveretum somniferum* (morphine, codeine) or *Papavertum bracteatum* (thebaine).

Opioids are drugs that act on opioid receptors and can include semisynthetic or synthetic versions of opiates.

Structurally opioids are benzylisoquinoline alkaloids which act on the opioid receptors (OP) of which there are four main types mu (MOP or OP3), kappa (KOP or OP2), delta (DOP or OP1) and nociceptin (NOP or OP4). Originally there was a sigma but this has been reclassified as it cannot be antagonised by naloxone.

Opioid receptors are G-protein coupled receptors that have a number of downstream events when activated

- Inhibit adenyl cyclase
- Facilitate the opening of synaptic K+ channels- hyperpolarising membranes
- Inhibit neurotransmitter release via inhibiting the function of voltage gated Ca++ channels (Ca++ influx is crucial for neurotransmitter release from vesicles in presynaptic nerve terminals)

MOP- endogenous ligand = endorphin - mediate central, spinal and peripheral analgesia and respiratory depression. Found in Periaquaductal grey matter, pre + post synaptic membranes of afferent neurones, Nucleus raphe magnus, rostral ventral medulla, thalamus and cortex.

KOP- endogenous ligand = dynorphin - mediates sedation, spinal and peripheral analgesia. Found in the hypothalamus and nociceptin areas.

DOP- endogenous ligand = encephalin - mediates spinal and peripheral analgesia. Found in olfactory bulb, cerebral cortex, pre + post synaptic membranes of afferent neurones

NOP- endogenous ligand = Orphanin FQ - role unknown but may be involved in the anti-analgesic effects. Found in primary afferent neurones and the nucleus raphe magnus

Individual, breed and species differences in opioid PKPD exist. In the dog canine l-opioid receptor gene mutations may cause increased dysphoria (Labradors, sled dogs)

Structural groups

Morphine analogues	Thebaine derivatives	Phenylpiperidines	Anilinopiperidines	Diphenylheptanes
MORPHINE	**BURPRENORPHINE**	**PETHIDINE**	**FENTANYL**	**METHADONE**
CODEINE	OXYCODONE		**ALFENTANIL**	
BUTORPHANOL			**REMIFENTANIL**	
			SUFENTANIL	

Potency

Drug	Approx potency	Unionised	Protein binding	Lipid solubility
Pethidine	0.1	+	+++	++
Morphine	1	++	++	++
Methadone	1-2.5 (L 50x > D)		++++	++++
Burprenorphine	5			
Alfentanil	10	++++	++++	+++
Fentanyl	100	+	+++	++++
Remifentanil	50-250 (clinically perhaps < than fentanyl?)	+++	+++	++
Sufentanil	500	++	++++	++++
Etorphine	1000			

Desired effects

Analgesia with central, spinal and peripheral effects

Sedation

Anaesthetic/sedative sparing

Reduce neuroendocrine stress response to anaesthesia and surgery (although ADH and cortisol can increase in response to opioid administration in some species)

Depressed airway reflexes

Adverse effects

Dysphoria/euphoria

Nausea and vomiting (morphine)

Ileus (via MOP receptor activation in GI tract, reduces secretions, peristalsis and sphincter tone)

Hypoventilation

Decrease thermoregulatory thresholds in the thalamus

Chest wall muscle rigidity (mechanism unknown and unclear if occurs in animals)?

Reduce central sympathetic outflow

Vagal excitation (except pethidine which has mild vagolytic/antimuscarinic effects)

Histamine release (morphine & pethidine especially) direct non opioid receptor effects on mast cells.

Depressed airway reflexes

Reduced urine output through ADH stimulation (though effects are unclear)

Urinary retention (extradural/spinal especially seems to increase sphincter tone)

Immunomodulation (affects acquired and innate immune system. Natural killer cell activity, T-cell proliferation, antibody production, phagocytic cell function, and cytokine production have all been shown to be affected by opioids)

Opioids are the cornerstone of acute pain management in small animals and man.

Individual drugs

MORPHINE

Description

- Prototypical opioid agent against which all other opioids are compared.
- Widely used and studied but not licensed in any species.
- Schedule II controlled drug.
- P-glycoprotein substrate
- Available with preservative for systemic administration and preservative free for the epidural route

- Also available in a liposomal encapsulated sustained release formulation. The morphine is encapsulated in an aqueous chamber within a lipid vesicle, the vesicles accumulate together into a non-concentric matrix (like a ball of foam), from which morphine is slowly released lasts 48+h (60h in beagles). The product has a slower onset of action than morphine (1-2h not 20-30 minutes)
- Not licensed in any species

Routes

- Shown to be effect systemically, via extradural and intrathecal routes and peripherally (intra-articularly).
- Has poor oral bioavailability in most veterinary species.

Actions

- Pure opioid agonist at MOP, KOP, DOP and NOP.
- Vomiting caused by action at CTZ as crosses the BBB slowly, has antiemetic effects at the vomiting centre. Increasing dose paradoxically reduces incidence of vomiting probably due to bigger concentration gradient across BBB and faster onset of antiemetic action at the vomiting centre.

Speed of onset and duration of action

- Speed of onset (SOO) 10-15minutes with peak analgesia at 1h following IV administration
- Extradurally it takes 20-30mins (longer in the liposomal encapsulated form)
- Duration of action (DOA) about 4h in most species perhaps longer in cats?
- Prolonged duration of action when administered extradurally and spinally (up to 24h) due to its hydrophilic nature meaning it has greater persistence in CSF compared to other opioids. This also means it has a greater area of spread up the cord.

Metabolism

- Undergoes glucoronidation with 80% making morphine-3-glucoronide (M3G) and 10% morphine-6-glucoronidide (M6G). Remainder undergoes sulphonation (this is more significant in cats as their ability to glucoronidate is poor), is demethylated to normorphine or is excreted unchanged in urine. Conjugate morphine is excreted in urine.

Active metabolites?

- M6G is more potent than morphine (exact potency regarding analgesia has not been investigated) and has a longer elimination half life. This may mean a reduced efficacy of morphine in cats due to less M6G being produced.

Species and breed differences

- There is a single point mutation recognised in the canine mu-opioid receptor gene that causes increases dysphoria in Labradors, Huskies and Malamutes.

Methadone

Description

- Methadone is a synthetic diphenylheptane with similar (or possibly slightly higher) potency than morphine.
- It is made of 2 enantiomers D- and L- methadone.
- Methadone is licensed in the UK (Comfortan) for analgesia in dogs and cats
- Schedule II controlled drug.
- P-glycoprotein substrate

Routes

- Methadone has been shown to be efficacious systemically and extradural/intrathecally. It has a shorter onset of action and shorter duration than morphine (15min).
- It has shown to have good bioavailability via the oral transmucosal route in the cat but has low bioavailability PO due to rapid first pass metabolism (unlike in man).

Actions

- Methadone is a MOP agonist (L-methadone more potent).
- NMDA antagonistic effects (D-methadone more potent)
- Seratonin and noradrenaline reuptake inhibition and may increase serotonin release
- nACh antagonism
- These other actions may reduce opioid tolerance and reduce post-operative opioid requirements but there are no good studies in veterinary species.
- Crosses blood brain barrier rapidly therefore has an antiemetic effect

Speed of onset and duration of action

- Speed of onset slightly faster than morphine due to high lipophilicity
- Duration quite variable, especially between individuals, and also route specific. In dogs between 1.75-4h IV and 2-12h SC. May last up to 12h via extradural route.
- May inhibit its own metabolism and accumulate after multiple dosing so individually tailored analgesia is important.

Metabolism

- Hepatic metabolism via cytochrome P450 demethylation (CYP3A4, CYP2B6 and to a lesser extent CYP2D6).
- P450 metabolism may be induced by phenobarbitone (CYP2B6 & CYP3A4), St John's Wort (CYP3A4) and dexamethasone (CYP2D6), and inhibited by ketoconazole, erythromicin, diltiazem and verapamil, cimetidine, buprenorphine (CYP3A4) and buprenorphine, cimetidine & SSRIs (CYP2D6).

Active metabolites

- No known active metabolites.

Species and breed differences

- Efficacy and duration of action be effected by interbreed P-glycoprotein and cytochrome P450 differences.

Pethidine (meperidine)

Description

- Synthetic, phenylpiperidine derivative opioid with a lower potency than morphine.
- Pethidine is licensed in the UK for the use in the dog and cat for analgesia.
- Schedule II controlled drug.

Routes

- Causes profound histamine release IV so should not be used
- IM or extradural use

Actions

- MOP agonist
- Sodium channel blocker
- Alpha-2 agonist (α_{2B})- may account for better sedation?
- mACh antagonist (antimuscarinic)
- NMDA antagonism?
- Seratonin/noradrenaline reuptake inhibition?
- Antispasmodic action?
- Negative inotropic effects

Duration

- 60 minutes in the dog
- 90-120 minutes in the cat

Metabolism

- Vary amongst species
- Demethylated to norpethidine in the liver which in turn is hydrolysed and excreted by the kidney

Active metabolites

- Norpethidine is an active metabolite with lower efficacy than pethidine.
- May cause seizures if accumulates in patients with renal disease

Drug interactions

- May cause serotonin syndrome in patients receiving monoamine oxidise inhibitors

Species and breed differences

- Effect metabolism and therefore duration of action

Fentanyl

Description

- A short acting, synthetic anilinopiperidine derivative which is more potent than morphine
- Summary of product characteristics (SPC) and market authorisation for IV use in the dog (Fentadon)
- SPC and market authorisation as a transcutaneous liquid preparation (a patchless patch) for perioperative analgesia in the dog
- *Schedule* II controlled drug

Routes

- Classically delivered either systemically IV or extradurally.
- Also useful transcutaneously as very lipid soluble, relatively small molecular size and high potency (efficacy at low plasma levels). Until recently this has been as a patch (depot with a rate limiting membrane). However a “patchless” system has just gained market authorisation for dogs in the EU (Recuvyra), it is formulated as a highly concentrated solution with a lipid soluble carrier (octyl salicylate) and isopropyl alcohol (evaporates increasing concentration gradient). When absorbed this forms a depot of fentanyl in the stratum corneum which provide analgesia for 72h.
- Can be administered as a bolus or CRI

Actions

- MOP agonist
- May have serotonin reuptake inhibitory effects

Speed of onset and duration of action

- SOO within 5 min when administered IV, also rapid via the extradural route
- DOA 15-30min (generally about 20min) after a single bolus due to rapid redistribution to fat and muscle
- Context sensitive half time (CSHT) increases dramatically after 2h of steady state infusion as peripheral sites become saturated and elimination relies more on hepatic metabolism and renal excretion. At 2h CSHT is 50min but reaches 3h after 8h infusions.
- Transdermal fentanyl in the form of recuvyra follows “flip-flop” kinetics where the absorption in much longer than the elimination (plasma levels become absorption dependent).

Metabolism

- Metabolised in the liver via cytochrome P450 pathways (CYP3A4?). Norfentanyl is hydroxylated and renally excreted
- May be induced by Phenobarbital or inhibited by ketoconazole, erythromicin, diltiazem and verapamil, cimetidine, buprenorphine and potentially methadone?
- Metabolites are not active and are excreted via the kidney.

Drug interactions

- *May impair midazolam metabolism*
- *MAO inhibitors?*

Alfentanil

Description

- A short acting, synthetic anilinopiperidine derivative which is more potent than morphine but less potent than fentanyl.
- Fentanyl is its parent drug.
- Not licensed in any form for any species

Routes

- IV only real studied route

Actions

- MOP agonist
- May have serotonin reuptake inhibitory effects

Speed of onset and duration of action

- Peak effect 90s
- DOA 5-10 minutes after bolus.
- CSHT is 50mins after 2h infusion and does not increase so becomes context insensitive.

Metabolism

- Metabolised in the liver via cytochrome P450 pathways (CYP3A4?). Noralfentanil is hydroxylated and renally excreted
- May be induced by Phenobarbital or inhibited by ketoconazole, erythromicin, diltiazem and verapamil, cimetidine, buprenorphine and potentially methadone?
- Metabolites are not active and are excreted via the kidney.

Drug interactions

- *MOA inhibitors*

Remifentanil

Description

- An ultra-short acting, synthetic anilinopiperidine derivative with a methyl ester linkage which is more potent than morphine but clinically is probably less potent than fentanyl.
- Fentanyl is its parent drug.
- Not licensed in any form for any species

Routes

- *IV only as an infusion*

Actions

- MOP agonist
- May have serotonin reuptake inhibitory effects

Speed of onset and duration of action

- Almost immediate SOO
- Duration of action ultra-short so always administered as an infusion
- Context insensitive due to its ultra-rapid, non-hepatic dependent metabolism. CSHT is about 5min

Metabolism

- Undergoes rapid de-esterification by plasma, red cell and tissue esterases
- Although plasma esterases are liver dependent red cell and tissue esterases are not and therefore offset is reliable in patients with impaired liver function
- May be some “ultra-fast” metabolisers

Drug interactions

- *MOA inhibitors*

Buprenorphine

Description

- Buprenorphine is a long acting, semi-synthetic thebaine derivative which is slightly more potent than morphine
- Buprenorphine is licensed as an analgesic in dogs, cats (multiple forms with and without preservative)
- Schedule III controlled drug but it is advised to keep it in a locked cupboard.

Routes

- Buprenorphine can be administered by all routes including IV, IM, SC, OTM, intrathecal/extradural, transcutaneously
- As a weak base with a pKa 8.24 it is unionised in cats saliva (pH 9) allowing a rapid and complete uptake (bioavailablity ~100%)
- Higher doses are required to get a clinical effect in dogs (6x the IV dose)

Action

- Buprenorphine is classically described as a partial MOP agonist. Experimental studies using canine spinal cord indicated the substance's action as partial agonist and an inverted U- or bell- shaped dose-response curve is reported in rodents.
- Buprenorphine binds avidly (but slowly) to MOP receptors and dissociates slowly
- Buprenorphine is a potent local anaesthetic and blocks voltage-gated Na(+) channels via the local anaesthetic binding site.
- Buprenorphine induces pronounced antihyperalgesia

Speed of onset and duration of action

- Delayed SOO approx 1h
- DOA 6-12h

Drug interactions

- Buprenorphine exhibits a pronounced antihyperalgesic (shown in cats when combined with carprofen) effect that might indicate potential advantages in the treatment of neuropathic pain
- Concern has been over co-administration with other opioids. Studies with sufentanil in bitch spays showed that higher doses of sufentanil were required with buprenorphine than saline control. Another study compared it with morphine for thoracotomies and there was no difference in fentanyl usage.

Metabolism

- Buprenorphine is metabolised by the liver, via CYP3A4 (also CYP2C8 seems to be involved), into norbuprenorphine (by *N*-dealkylation).
- Both buprenorphine and norbuprenorphine are metabolised by glucuronidation. These glucuronides are then eliminated mainly through excretion into the bile.
- Due to the mainly hepatic elimination, there is no risk of accumulation in patients with renal impairment.

Active metabolites

- Norbuprenorphine and glucuronide metabolites of buprenorphine are biologically active at doses relevant to metabolite exposures
- Buprenorphine's main active metabolite, norbuprenorphine, is a μ-opioid, δ-opioid, and nociceptin receptor full agonist, as well as a κ-opioid receptor partial agonist

Controversy

- Current receptor based theory suggests drug receptor interactions to be context sensitive (depend on the exact response you are measuring) so the term partial agonist should only be used in a very specific context
- It is the consensus in human anaesthesia and pain medicine that buprenorphine clearly behaves as a full μ-opioid agonist for analgesia in clinical practice, with no ceiling effect
- The effects of buprenorphine can be completely reversed by naloxone

- No problems have encountered when switching to and from buprenorphine and other opioids, or in combining them
- Perhaps as effective as morphine epidurally?

Species and breed differences

- Several studies have suggested that buprenorphine may act as a full agonist in the cat
- Bioavailability is poor via the SC in cats

Butorphanol

Description

- Butorphanol is a morphinian type, synthetic opioid agonist-antagonist
- It is licensed for sedation and analgesia in dogs and cats

Routes

- Systemically IV, IM or SC
- Oral form used as antitussive

Actions

- Agonist at KOP
- Antagonist at MOP
- Good sedative

Speed of onset and duration of action

- Rapid SOO probably within 2-5min depending on route
- DOA 45-90mins, but maybe longer with higher doses

Metabolism

- Hydroxylated and glucoronidated in the liver

Species and breed differences

- As good or better as buprenorphine in some cats? Useful as a “triple combo” with ketamine and medetomidine or a “quad combo” with additional midazolam.

Non-Steroidal Anti-Inflammatory Drugs

NSAIDs are analgesic and anti-inflammatory drugs commonly used in both large and small animal medicine. Despite differences in chemical structures and other potential mechanisms of action, these compounds share the effect of inhibiting the production of eicosanoids downstream of phospholipase (downregulated by steroidal anti-inflammatory) by targeting the **cyclo-oxygenase (COX)** pathway. Eicosanoids are products of the breakdown of arachidonic acid which in turn is produced by the action of phospholipase-A (the target for glucocorticoid steroids) on phospholipids released from damaged cell membranes.

COX

- Cyclooxygenase is present in most tissues within the body and can become up-regulated with a variety of stimuli.
- Two primary forms of COX have been identified, COX-1 and COX-2. Initially, COX-1 was identified as a constitutive isoform whereas COX-2 was identified as an inducible isoform, but further studies have shown that both isoforms are constitutive and inducible.
- COX-3 has been identified in the cerebral cortex of dogs but its role is unknown and it may just be a central COX-1 variant.
- COX-1 produces many different eicosanoids, but prostaglandin (PG) E2 and thromboxane A2 produce many clinically important effects.
- PGE2 produces numerous physiologic responses including vasodilation, sensitization of nociceptors enhancing both peripheral and central sensitization, and a number of effects in the GI tract including increased mucus production, decreased gastric acid secretion, increased secretion of bicarbonate in the duodenum, and increased turnover of mucosal cells.
- Thromboxane A2 is primarily associated with platelets and results in increased platelet aggregation and vasoconstriction enhancing coagulation and blood clot formation with the result that exclusive inhibition of COX-1 produces an anticoagulant effect. COX-1 is also constitutively expressed in the cerebral cortex where its inhibition may contribute to the central analgesic and antipyretic effects of NSAIDs.
- COX-2 also produces a variety of eicosanoids with PGE2, prostacyclin (PGI2) and 15-epi-lipoxinA4, also known as aspirin triggered lipoxin (ATL)
- PGE2 produced by COX-2 results in the same physiologic effects as PGE2 produced by COX-1.
- PGI2 is produced in endothelial cells and results in vasodilation and inhibition of platelet aggregation, producing an antagonistic effect to thromboxane A. Therefore exclusive inhibition of COX-2 produces a pro-coagulant effect. PGI2 has also been identified in inflamed tissues and in the GI tract where it produces similar gastroprotective effects as PGE2.
- PGE2 and PGI2 also alter renal physiology by increasing sodium excretion, inhibiting sodium reabsorption, and altering chloride transport.
- PGE2 and PGI2 also stimulate renin release and profoundly alter total renal blood flow and regional blood flow within the kidneys of dogs
- COX-2 is associated with both central and peripheral sensitisation.
- COX-2 is constitutively expressed in the dorsal horn of the spinal cord and contributes to the propagation of nociceptive (pain) stimuli with the result that inhibition of COX-2 can also produce central analgesic effects.
- COX-2 expression is increased in injured tissue, producing PGE2 and PGI2 resulting in sensitization of peripheral nociceptors coupled with enhanced pain transmission as with COX-1
- COX-2 is also up-regulated in the endothelial cells within the hippocampus during fevers, which may explain the antipyretic effect of some NSAIDs

Lipoxins

- Lipoxins are eicosanoids produced via COX pathways that produce anti-inflammatory effects and are thought to be produced to modulate the inflammatory response Aspirin Triggered Lipoxins (ATLs).
- ATLs are potent anti-inflammatory and gastroprotective products of COX-2. ATLs have antagonistic effects on leukotriene C4 induced bronchoconstriction and vasoconstriction and they also antagonize the effect of leukotriene D4 mediated decreases in glomerular filtration rate

LOX

- The 5-lipoxygenase (LOX) pathway of the arachidonic acid cascade also produces a variety of leukotrienes.
- Leukotrienes have been associated with vasoconstriction, increased vascular permeability, bronchoconstriction, and attraction of inflammatory cells such as neutrophils, lymphocytes, and eosinophils. (Use of COX inhibitors may shift arachidonic acid metabolism into the LOX pathway and lead to bronchoconstriction hence the caution in human medicine in administering NSAIDs to asthmatics)
- Leukotriene production in the GI tract may be increased when non selective COX inhibitors are administered due to a shunting of the arachidonic acid pathway through LOX

Additional MOA

- Some NSAIDs, carprofen/flunixin for example, have been documented to inhibit the activation of Nuclear Factor kappa–B (NFκB), which regulates proinflammatory enzymes, cytokines, chemotactic factors, and cellular adhesion molecules- iNOS gene activation is reduced
- Endotoxin increases COX-2 gene expression via NFκB (TLR4 mediated LPS response). Therefore eicosanoid production is increased. NSAID inhibition of COX-2 therefore may have an “anti-endotoxic” effect.
- This may explain the ability of flunixin meglumine and other NSAIDs to be an effective inhibitor of the effects of endotoxin in horses with endotoxemia
- Some in vivo studies have suggested that carprofen does not inhibit PG synthesis and therefore has a MOA unassociated with COX inhibition
- Studies have also found that certain NSAIDs may alter the function or expression of a variety of ion channels
- However, the extent of these non-cyclooxygenase NSAID effects is yet to be fully elucidated.

Molecular structure

Class	Group	Drug example 1	Drug example 2	Drug example 3
ENOLIC ACID	**Oxicams**	Meloxicam		
ENOLIC ACID	**Pyrazolones**	Phenylbutazone	Metamizole	
CARBOXYLIC ACID	**Proprionic acid**	Carprofen	Ketoprofen	Vedaprofen
CARBOXYLIC ACID	**Acetic acid**	Etodolac	Ketorolac	
CARBOXYLIC ACID	**Phenylacetic acid**	Paracetamol		
CARBOXYLIC ACID	**Fenamic acid**	Tolfenamic acid	Meclofenamic acid	
CARBOXYLIC ACID	**Aminonicotinic acid**	Flunixin		
CARBOXYLIC ACID	**Salicylic acid**	Aspirin		
COXIBS	**Diaryl-substitutes**	Robenacoxib	Firocoxib	Mavacoxib

Selectivity

- The COX-1/COX-2 inhibitory ratio, also known as the IC50 ratio (the ratio of 50% inhibition of COX-1 and COX-2), is often referenced as a measure of NSAID safety. The higher the ratio above 1 the more COX-2 specific the NSAID is
- Such statements must be interpreted cautiously due to numerous limitations
- COX-2 selective, COX-2 preferential and COX-1 sparing NSAIDs are described in the literature
- This nomenclature is not well defined and they seem to be used interchangeably and this can be confusing
- The COX selectivity or COX sparing concept only applies to the potential decrease in the frequency of GI adverse effects in healthy GI tissues, and has no association with renal or hepatic adverse effects, effects on diseased or injured gastrointestinal tracts, nor to efficacy.
- The renal adverse effects of NSAIDs may be more related to COX-2 inhibition and all commercially available NSAIDs inhibit COX-2.
- Hepatic adverse effects may be related to production of reactive metabolites and be independent of COX inhibition as idiosyncratic toxicity has been observed with all licenced NSAIDs in the USA
- COX-1/COX-2 ratios are difficult to interpret due to variations in the assay employed, species differences, and laboratory to laboratory variability
- The ratios are often determined in vitro, with purified enzymes or whole blood, which may or may not predict in vivo effects
- The IC50 ratio is often referenced as a measure of NSAID safety, the clinical applicability of this ratio is questionable the apparent COX selectivity determined in vitro by IC50 ratios may not correspond to effective doses or minimize adverse effects
- The magnitudes of in vitro COX inhibitory ratios (COX-2 selective versus COX-1 sparing) are not predictive of the magnitude of differences in GI or other adverse effects
- Comparison of IC50 or IC80 ratios is also dependent on parallel inhibitory curves for COX-1 and COX-2 inhibition which do not always occur
- Species specific differences in the COX inhibitory concentrations have also been documented for some NSAIDs

- The COX selectivity of an NSAID has no association with efficacy; there have been no studies indicating one specific NSAID to be consistently more effective than another. It is important to remember that an individual patient may, however, have a better response to one NSAID than to another
- Similarly, a specific patient may develop adverse effects to one NSAID but not to another, and some patients may not tolerate any NSAID. It is also important to realize that COX selectivity is dependent on dose and all NSAIDs become nonselective COX inhibitors at high concentrations
- However, studies have demonstrated that drugs which maintain some activity of COX-1 (i.e. COX-2 selective or COX-2 preferential inhibitors) have decreased frequencies of gastrointestinal adverse effects and subsequently a better GI adverse effect profile than NSAIDs which inhibit both COX isoforms when assessed in vivo

General PK

- Generally good bioavailability in monogastric species after oral dosing because of medium to high lipid solubility. Dissolution in stomach impaired by acidic pH.
- Good bioavailability after parenteral (intramuscular and subcutaneous) dosing
- Medium to high lipid solubility, therefore penetrate blood–brain barrier readily
- Low volume of central compartment
- Low volume of distribution but some exceptions
- As weak acids may penetrate poorly into cells because of relatively acid pH of intracellular fluid (pH 7.40 in plasma vs. pH 7.00 in cells)
- High degree of plasma protein binding of all drugs (except salicylate) in all species: limits passage from plasma into interstitial and transcellular fluids but facilitates passage into inflammatory exudates. Therefore plasma concentration may not correlate to due to high concentration at tissue inflammation sites (maybe due to protein binding?)
- Renal excretion of parent drug markedly limited by plasma protein binding (only free fraction available for ultrafiltration in glomerular capillaries) may be increased by urinary alkalinization (due to ion trapping of the weak acids)
- Hepatic elimination is the primary route of elimination for NSAIDs via biliary secretion, conjugation reactions, and metabolic reactions such as cytochrome P450 metabolism, usually to inactive compounds, but some metabolites are active: Aspirin - salicylate
- Marked species (and possibly breed and strain) differences in: Clearance, Terminal half-life
- Reduced clearance, increased half-life in neonates

Side effects

- GI effects can be the result of mucosal irritation due to the weakly acidic nature of the drugs or due to eicosanoid suppression
- The high concentrations of NSAIDs in the gastrointestinal tract after oral administration or due to biliary secretion within the duodenum is also hypothesized to contribute to the direct irritant effects of NSAIDs to the GI tract
- PGE2 and PGI2, have important gastroprotective effects including increased mucosal blood flow, increased mucus production, increased bicarbonate production, decreased acid secretion and increased turnover of gastrointestinal epithelial cells
- Both COX-1 and COX-2 are constitutively expressed in the canine GI tract and the inhibition of these enzymes can lead to GI adverse effects including gastritis, enteritis, ulceration, and perforation
- Inhibition of COX-1 or COX-2, exclusively, results in minimal GI adverse effects
- The lower frequency of GI adverse effects when only one isoform of COX is inhibited is thought to be due to up-regulation of the other isoform since both COX-1 and COX-2 produce PGE2

- Newer more selective NSAIDs appear to exhibit decreased incidence of adverse GI effects. This may be due to less than complete inhibition of COX-1, resulting in continued PGE2 production in the GI tract by COX-1
- COX-2 is up-regulated in damaged and healing tissues within the GI tract, increasing angiogenesis at the edge of gastric ulcers by inhibiting cellular kinase activity and increasing production of PGE2 and vascular endothelial growth factor (VEGF). It is through these mechanisms that COX-2 is thought to promote ulcer healing
- Cyclooxygenase is constitutively expressed in the kidneys and is up-regulated in ischemic and hypotensive states.
- PGE2 and prostacyclin (PGI2) alter renal physiology by increasing sodium excretion, inhibiting sodium reabsorption, and altering chloride transport
- PGE2 and PGI2 also stimulate renin release and profoundly alter total renal blood flow and regional blood flow within the kidneys of dogs
- Species specific differences in the renal anatomic distribution of constitutive COX isoforms occur in animals and humans
- COX-1 and COX-2 are involved in renal blood flow regulation and tubular function, therefore it cannot be assumed that COX-1-sparing NSAIDs infer greater safety in the kidney
- Neither meloxicam or carprofen alter renal function in hypotensive anaesthesia in dogs (Bostrum et al)
- Most references advise avoiding in hypotension or if renal compromise already apparent
- Impairs bone healing experimentally but unsure if clinically significant

Drug Data of common (or different) NSAIDs

Aspirin

- Not used commonly as an anti-inflammatory but rather as a platelet inhibitor
- Irreversibly binds to COX enzyme in platelets with a covalent bond
- Reduces TXA production and therefore platelet aggregation is inhibited
- Given mainly to small animals with risk of thromboembolic disease- currently there is a double blinded randomised clinical trial comparing aspirin to clopidigrel (FATCAT) being undertaken

Carprofen

- Propionic acid derivate
- Mixed reports on its COX-1 and COX-2 inhibition, in vitro appears to be COX-2 > COX-1 but in vivo one study found that PG/TBX synthesis not effected
- Inhibits NFκB
- Oral and injectable forms
- Higher peak plasma concentrations PO than SC
- Highly protein bound in the blood
- Half life 8h
- Efficacious for 18h+
- Undergoes hepatic metabolism
- Much of the drug is eliminated in the faeces (60% to 75%)
- the remaining amounts are eliminated in the urine
- Long-term oral administration of carprofen, compared with other NSAIDs, appears to have fewer GI side effects, possibly due to sparing the COX-1 isoenzyme (LUNA et al., 2007) and seems to cause less GI ulceration
- Widely publicised idiosyncratic hepatic reaction (said to be mainly in Labradors but are a common breed and are over represented in arthritic dogs) but this can be seen with other NSAIDs

Ketoprofen

- Anecdotally as good as flunixin at masking signs of endotoxaemia in equine colic
- Wider safety margin than phenylbutazone or flunixin for chronic use (but not licensed for this)
- Licensed for post-op use only due to reportedly causing coagulopathy
- Touted as a dual inhibitor of COX and LOX but evidence here is weak
- Glucoronidated in the liver

Meloxicam

- Enolic NSAID, classified as an “oxicam”
- COX-2 >> COX-1
- Half life 12h but 24h dosing- tissue half life likely longer
- Metabolism via cytochrome P450 pathways
- Has NFκB inhibitory effects so is anti-endotoxic

Paracetamol

- Little anti-inflammatory effects
- Exhibits a central analgesic and antipyretic effect
- May block peroxidise enzyme component of prostaglandin H2 synthesis
- May block COX1 variant COX3 (central COX1)
- May stimulate serotonin receptors
- Perhaps acts as a prodrug for a cannabinoid- N-arachidonoylphenolamine (weakly binds CB1 but inhibits anantamide reuptake a more potent CB1 agonist)
- Limited data in dogs
- Relatively safe in dogs even at high doses but very easily kills cats
- Normally metabolised by conjugation via glucoronidation pathways
- In cats or in overdose this shifts to oxidation pathways forming n-acetyl-p-benzoquinone-imine (NAPQI)
- NAPQI is a potent highly reactive oxidant
- Glutathione deactivates in normal circumstances but in overdose or cats (low glutathione reserves) this is deactivation is overrun and oxidative damage ensues.
- Red cells and hepatocytes are injured leading to the formation of methaemoglobin and hepatic necrosis
- N-acetyl-cysteine is a glutathione precursor which blocks oxidation and increases sulphonation of NAPQI
- Used as an antidote sometimes alongside ascorbic acid which may help convert methaemoglobin back to haemoglobin

Robenacoxib

- New coxib NSAID
- Developed solely for companion animal use
- Highly selective for the cyclo-oxygenase (COX)-2 enzyme in dogs with minimal COX-1 effects.
- Onset 1h
- Robenacoxib persists longer and at higher concentrations at sites of inflammation than in blood. No evidence for persistence in other tissues.
- Terminal half life is approx 1h, but tissue persistence for 24h
- 99% protein bound
- Excreted predominately via the biliary route (65 %) and the remainder via the kidneys
- Superior analgesia in one study for cats (most of them had ovariohysterectomy)
- No difference in side effect profile in dogs compared to carprofen (non-inferiority**)**

Tepoxalin

- Dual COX:LOX inhibitor
- Only parent drug has LOX effects and tepoxalin is rapidly metabolised to an active metabolite with COX activity only
- COX1>COX2 but seems to have a similar GI profile to COX2 selective NSAIDs
- Clinical relevance of LOX effects remain uncertain

Other Agents

Ketamine

- Phencyclidine derivative
- Can be administered IV/IM/SC/epidurally/perineurally but stings
- Relatively rapid onset of action ~2 minutes (although not considered to be within one arm-brain circulation time)
- Antagonistic at NMDA receptor (non-competitive binds to allosteric site rather than at glycine/glutamate receptors)
- Also works by inhibiting voltage gated Na^+,K^+ and Ca^{2+} channels, mAchR
- Binds to MOP receptors
- Analgesia at sub-anaesthetic levels
- Somatic over visceral analgesia
- Muscle rigidity, convulsions, hyperexitability seen but reduced by the co-administration of alpha 2 or benzodiazepines
- Recovery via redistribution from CNS
- Metabolised to norketamine an active metabolite which is then conjugated via mainly glucoronidation pathways. Ketamine, norketamine and conjugates can be excreted
- Cats are poor conjugators so get increased norketamine and elimination depends more on renal excretion than metabolism
- Indirect CV stimulation- acts directly as a myocardial depressant but sympathetic effects (decrease reuptake of catecholamines increases sympathetic efferent activity) generally outweigh this. A subsequent increase in myocardial work and $V\dot{O}2$ due to increased cardiac output (HR + SV) and afterload
- Suppresses NFκB- decreases effect of sepsis and endotoxaemia by reducing the amplification of the inflammatory cascade in sepsis (reduces iNOS and COX etc) – experimental model
- May reduce the need for inotropes in sepsis
- Depletion of catecholamine stores or an exhausted sympathetic nervous system may cause myocardial depression – not sure of clinical relevance
- Respiratory- does not depress the respiratory response to hypoxaemia. RR and V_{min} drop initially but normally return to baseline. Apneustic (prolonged inspiration/ inspiratory hold) may occur as well as other abnormal breathing patterns
- May not obliterate cranial nerve reflexes so may still swallow and have active palpebral
- Increased ICP seen (but generally associated with an increase in $PaCO_2$). Increases cerebral metabolic oxygen demand. EEG shows seizure like patterns- increased activity. May be neurotoxic or neuroprotective which depends on dose (NMDA receptor involved with apoptosis and shifts in intracellular Ca^{2+})
- May increase IOP (effect lost with benzodiazepines in dogs)
- Reduces gut motility
- May increase uterine tone

Nitrous Oxide

Nitrous oxide is a gaseous inhalant which has been quite widely used as an analgesic adjunct during anaesthesia as part of a balanced anaesthetic technique to reduce the volatile agent required. Nitrous oxide should make up 50-60% of fresh gas flow during anaesthesia in order to achieve this. An upper limit of 66% must be observed to avoid hypoxemia. Nitrous oxide is contraindicated in patients with raised ICP, pnemothorax, GDV, anaemia, intestinal obstruction and lung pathology.

Gabapentin

Gabapentin was originally used as an anticonvulsant drug in human medicine but has been found to provide analgesia for neuropathic pain in humans and small animals. The mechanism of action is currently unknown but it is thought to produce clinical effects secondary to an increased synthesis of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Analgesia may also be produced through blockage of calcium channels. In acute pain gabapentin should be combined with other analgesics. It is only available in oral form. It does not undergo significant hepatic metabolism but is excreted by the kidneys so patients should have normal renal function. The major side effect of gabapentin is its sedative effect although this is usually short lived.

Tramadol

Tramadol is categorized as an atypical, centrally acting opioid analgesic. Central analgesic effects are produced through activity of the parent drug and its active metabolites at μ receptors. Tramadol is approximately 1/6000th that of morphine with the metabolite being four (to 200!) times more potent and eliciting most of the opioid effects). Tramadol inhibits serotonin and noradrenaline reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. Tramadol also causes seratonin release. The serotonergic-modulating properties of tramadol give it the potential to interact with other serotonergic agents. There is an increased risk of serotonin toxicity when tramadol is taken in combination with serotonin reuptake inhibitors (e.g., SSRIs), since these agents not only potentiate the effect of 5-HT but also inhibit tramadol metabolism. Tramadol is also thought to have some NMDA antagonistic effects, which has given it a potential application in neuropathic pain states.

The relative degree of contribution of each mechanism toward pain control is not fully understood. The contribution of non-opioid activity is demonstrated by the fact that the analgesic effect of tramadol is not fully antagonised by the μ-opioid receptor antagonist naloxone. Also acts as an NMDA receptor antagonist.

Tramadol is not currently a controlled drug in the UK and is available in oral and parenteral forms making it an excellent analgesic for mild to moderate postoperative pain.

Other Analgesic adjuncts

- Amantadine – antagonism of NMDA receptors
- Tri-cyclic antidepressants - Amitriptyline
- Capsaicin
- Fish oils
- Acupuncture

Nursing Considerations in Preventing/ Relieving Pain

- Comfortable bedding – mattresses, thick vet beds
- Patient contact TLC, grooming, stroking, mental stimulation
- Providing home comforts – toys and blankets from home?
- Physiotherapy
- Cryo/ heat therapy
- Owner visits?
- Preventing urine scalding
- Turning regularly

Constant Rare Infusions (CRIs)

Constant rate infusions are frequently required during anesthesia whether it is for total intravenous anesthesia (TIVA), an analgesic infusion or the need to administer local anesthesia via a wound soaker catheter.

The rate of administration of many drugs at their original formulation strength would often be very low so it can be necessary to dilute them to improve accuracy. This is typically done using normal (0.9%) saline or lactated Ringer's solution. Care should be taken to adjust the volume in the syringe or bag before adding the drug to ensure accuracy. For example, if 5 mL of a drug needs to be made up to 500mL then 5mL of the contents of a 500mL bag would need removing before the drug was added. Similarly to make 50 mL using 2.5mL of a drug then 47.5mL fluid and 2.5mL of drug would be added to the syringe.

From the mg/kg/hr or mcg/kg/hr or mg/kg/min or mcg/kg/min the amount of drug to be administered per hour can be calculated. This is done in the same way as the drug dosage.

Example:

A 10kg dog is to be administered ketamine at an intraoperative rate of 10mcg/kg/min so the drug dosage would be:

10kg x 10mcg = 100mcg/min

The concentration of the ketamine is 100mg/mL

There are 1000mcg in a mg so 1000 x 100 = 100,000mcg/mL

100mcg per min/ 100,000 mcg per mL = 0.001mL/min of ketamine at the current dilution.

If the dilution of the ketamine is considered and changed to 1mL (100mg) of ketamine to 499mLs of fluid then the drug concentration has been changed to 100mg/500mL:

100mg/500mL =0.2mg/mL

To get to mcg:

1000 x 0.2mg = 200mcg/mL

Then to find out how much of the new dilution the dog needs:

100mcg per min/ 200mcg/mL = 0.5mL/min of the new diluted ketamine.

This can then be scaled this down to avoid wastage so for a 2 hour surgery:

2hours x 60 minutes = 120 minutes

120minutes x 0.5mL/min ketamine = 60 mL of solution required.

It is likely that a 50mL syringe would be made up and then more if needed so if there was 100mg/500mL ketamine for the 0.5mL/min administration rate and only 50mL is needed then:

500mL/50mL = 10

100mg/10 = 10mg

10mg/ 100mg/mL = 0.1 mL of ketamine to be added to the 50mL syringe with 49.9mL fluid.

To work this back to check it:

0.1mL ketamine at 100mg/mL

100mgx0.1mL =10mg ketamine in 50 mL

To convert to mcg 10x1000 = 10,000mcg in 50mL

10,000mcg/50mL = 200mcg/mL

100mcg/min (original dose of ketamine worked out for dog)/ 200mcg/mL = 0.5mL/min solution

This can be done for any drug with any volume of fluid. If there were no syringe driver available to administer accurate volumes then the drug could be added to a fluid bag, however the use of a fluid pump is advised to prevent overdosing. Analgesic drugs can in this way be added to maintenance (or higher) patient fluid requirements.

For example:

A 25kg dog is to receive 4mL/kg/hr fluids postoperatively and it is advised that postoperative ketamine is administered within these fluids at 2mcg/kg/min.

To calculate:

First the amount of fluid per hour must be calculated:

4mL/hr x 25kg = 100mL/hr

Then the amount of ketamine per hour must be calculated:

2mcg x 25kg x 60 minutes = 3000mcg

The mcg can then be converted to mg by dividing by 1000:

3000mcg/1000 = 3mg/hr

The ketamine per hour can then be calculated in mL where ketamine is 100mg/mL:

3mg per hour/ 100mg per mL = 0.03mL ketamine per hour

This will also be 0.03mL ketamine per 100mL because the dog requires 100mL fluid per hour.

It then needs to be decided if a 1Litre or 500mL bag should be made up and calculations are as follows:

For a 500mL bag:

500mL/100mL = 5 hours – this bag will last for 5 hours and needs 5 hours of the ketamine dose to be added:

5 x 0.03mL = 0.15mL ketamine added to 500mL bag of fluid (withdraw 0.15mL fluid first)

For a 1 litre bag:

1 litre = 1000mL

1000mL/100mL = 10 hours – the bag will last for 10 hours and needs 10 hours of the ketamine dose to be added:

10 x 0.03mL = 0.3mL ketamine added to a 1000mL (1 Litre) bag of fluid (withdraw 0.3mL fluid first).

The same calculation can be done for any fluid amount and for any drug. Alternatively there are many drug calculators available on the internet for CRI some of which can be found at http://www.vasg.org/drug_delivery_calculators.htm. It is important to ensure that the anesthetist has the ability to thoroughly check these calculations though.

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