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Invited review

State of the art analgesia—Recent developments pharmacological approaches to acute pain management in dogs and cats: Part 2

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ABSTRACT

There has been considerable interest in the area of acute pain management over recent years, focusing on pain assessment, pharmacological and non-pharmacological interventions. The evidence base for our clinical decision making and treatment of patients is ever increasing and becoming more robust. There is still a tendency to base some aspects of pain management on poor quality evidence and this requires further input in years to come. With new literature come new ideas and this review will detail the current knowledge base behind pharmacological management of acute pain in dogs and cats. The known mechanisms of action of each analgesic and its evidence will be considered. The second part of this review will consider the non-traditional analgesics, describing their component drugs individually, thereby focusing on their mechanisms of action and the current evidence for their use in acute pain management.

Introduction

The aim of this review is to assess recent developments in pharmacological approaches to acute pain management in cats and dogs, which has seen considerable interest in recent years. This has been centered around the use of the non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics. A recent review (Gurney, 2012) described new concepts in acute pain management, highlighting the investigating authors use of new analgesic medications as well as re-focusing on currently utilized classes of analgesics. For information on other, non-pharmacological methods of pain management the reader is directed towards the other reviews in this special edition.

Appropriate analgesia should be used in combination with adequate and effective pain assessment. A multi-modal approach to good pain management is essential to ensure a successful outcome and avoid over reliance on pharmacotherapy. The reader is referred to elsewhere in this special edition for information on pain assessment.

The literature search was performed for the preceding 5-year period (2012–2017) and appropriate studies on acute pain management in dogs and cats were selected and a narrative review style decided upon, due to the evidence available being of insufficient quality to permit a systematic review. In addition to this 5-year period, key references from earlier in the literature were also included when considered appropriate, i.e. to illustrate an analgesic mechanism of action.

The second part of this review will consider the non-traditional analgesics, covering the *N*-methyl D-aspartate receptor antagonists (NMDA), IV use of local anaesthetics, gabapentanoids and alpha-2 adrenoreceptor antagonists. The review will describe the component drugs individually, focusing on their mechanisms of action and the current evidence for their use in acute pain management. Information provided in this part will be focused on comparative data given the lack of animal specific evidence. The reader is referred to elsewhere in this special edition for information on non-pharmacological methods and management of chronic pain.

N-methyl D-aspartate receptor antagonists

Ketamine

Ketamine exerts a pain-modifying effect via its NMDA receptor antagonist actions. These ionotropic receptors, located throughout the nervous system, are an important component of glutamatergic neurotransmission. At the spinal level, NMDA receptor activation results in the development of central sensitisation manifest clinically as hyperalgesia and allodynia. Activation of NMDA receptors via glutamate release from excitatory synapses augments the propagation of nociceptive information and is therefore

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linked to acute and chronic pain states as well as opioid-induced tolerance and hyperalgesia.

The evidence relating to ketamine in the management of pain in people is eloquently summarised by Schug et al. (2015) who detail its main role as an adjuvant in the treatment of pain associated with central sensitisation, such as in severe acute pain, neuropathic pain and "opioid-resistant" pain. In people, perioperative IV ketamine reduces opioid consumption, time to first analgesic request and post-operative nausea and vomiting when compared to placebo with benefits seen particularly in patients with severe pain. Ketamine is particularly effective after thoracic, upper abdominal and major orthopaedic surgery. Contrary to popular belief IV ketamine does not appear to increase intracranial pressure (ICP) or reduce cranial perfusion pressure compared to opioids (Wang et al., 2014), therefore providing some evidence to support its use in cases of suspected raised ICP.

Further studies in dogs demonstrate that low dose ketamine reduces minimum infusion rate of propofol (Reed et al., 2015) and that it reduces the minimum alveolar concentration required to abolish the sympathetic response to surgical stimulus (MAC-BAR) of sevoflurane (Love et al., 2011) although this is not direct evidence of an analgesic or anti-nociceptive effect. Bergadano et al. (2009) demonstrated an anti-nociceptive effect using nociceptive withdrawal reflex thresholds following 0.5 mg/kg ketamine IV but this did not appear to be sustained with a continuous rate infusion (CRI) of 10 mcg/kg/min. Kaka et al. (2016) elucidated the serum ketamine concentration to produce mechanical antinociceptive effects in conscious dogs. Not all studies (Gutierrez-Blanco et al., 2015; Chiavaccini et al., 2017) show clear benefits in nociceptive pain, as might be anticipated. Ketamine's analgesic effect has not yet been studied in a feline surgical model, although its clinical use has been described in a very small number of surgical cases (Steagall and Monteiro-Steagall, 2013).

Note that in a more recent study (Kaka et al., 2016) serum ketamine concentrations were maintained at >200 ng/mL (nociceptive threshold 100–200 ng/mL) when 0.5 mg/kg ketamine IV bolus followed by CRI of 30 mcg/kg/min was administered for 120 min.

WSAVA Guidelines for recognition, assessment and treatment of pain (Matthews et al., 2014) advise that ketamine is indicated as part of a multimodal perioperative pain management plan for major surgery, in trauma patients or as part of a desensitization treatment for chronic pain patients. The use of ketamine as part of the management of acute pain can therefore be recommended based on the current literature.

Magnesium

Magnesium influences neuronal calcium influx and is regarded as an NMDA-receptor antagonist but has also anti-inflammatory effects mediated by a reduction in plasma concentrations of interleukin-6 and tumour necrosis factor-alpha in the post-operative setting. Multiple meta-analyses, cited by Schug et al. (2015) show that magnesium IV has an opioid-sparing effect in people. It has also opioid sparing in the early post-operative period when used as an IV adjunct to spinal anaesthesia. Its long terms effects when administered neuraxially or peri-neurally have yet to be determined. Intra-thecal magnesium combined with lipophilic opioid, prolongs the duration of spinal analgesia in non-obstetric populations (cited by Schug et al., 2015).

Veterinary evidence is limited, Rioja et al. (2012) showed that magnesium IV failed to decrease isoflurane requirements, postoperative pain and stress hormone concentrations during ovariohysterectomy in dogs and the authors concluded that it had no clinical advantage. One study (Bahrenberg et al., 2015) has investigated the antinociceptive effects of magnesium sulphate when administered epidurally alone, and in combination with morphine in dogs. It produced an antinociceptive effect of similar magnitude to that of epidural morphine with no motor effects; no potentiation of morphine anti-nociception was observed. A further study (Adami et al., 2016) added magnesium sulphate to spinally-administered ropivacaine and demonstrated a lower intra-operative fentanyl requirement, lower pain scores and analgesia of longer duration but with increased duration of motor blockade.

Based on the current literature, the routine use of magnesium for acute pain management cannot be recommended.

Local anaesthetics

Lidocaine

Lidocaine, a local anaesthetic agent, has been investigated as an analgesic agent and more extensively for minimum alveolar concentration (MAC) reduction during anaesthesia and surgery in dogs. Ortega and Cruz (2011) reported significantly lower intra-operative supplemental analgesia requirements in dogs having surgery and receiving lidocaine CRI (2 mg/kg then CRI 50 mcg/kg/min) compared to saline recipients.

Gutierrez-Blanco et al. (2013) demonstrated that lidocaine (2 mg/kg, then CRI 100 mcg/kg/min) and a combination of lidocaine, ketamine (1 mg/kg, CRI 40 mcg/kg/min) and dexmedetomidine (1 mcg/kg, CRI 3 mcg/kg/h) had an isoflurane sparing effect in dogs undergoing ovariohysterectomy, the magnitude of the effect being greater with the combination. Acevedo-Arcique et al. (2014) in a non-surgical model, assessed the effects of lidocaine (2 mg/kg, CRI 100 mcg/kg/min), dexmedetomidine (2 mcg/kg, CRI 2 mcg/kg/h), or their combination on MAC of isoflurane. Lidocaine, dexmedetomidine and their combination significantly reduced MAC by 27.3%, 43.4% and 60.9% respectively, when compared to baseline. Moran-Muñoz et al. (2014) employed the same methodology to assess the effects on the MAC of sevoflurane and demonstrated that lidocaine, dexmedetomidine and their combination reduced this by 26.1, 43.7% and 54.4% respectively. Suarez et al. (2017) documented clinically important sevoflurane sparing effects with fentanyl (15 mcg/kg, CRI 6 mcg/kg/h), lidocaine (2 mg/kg, CRI 6 mg/kg/h), and the fentanyl–lidocaine combination. The measured MAC decreased by 39%, 21%, and 55% for fentanyl, lidocaine, and the fentanyl-lidocaine combination, respectively.

Given that MAC reduction is not synonymous with analgesia, other studies have sought to demonstrate that lidocaine has anti-nociceptive or analgesic effects. Kaka et al. (2015) reported that in minimally anaesthetised dogs subject to electric stimulation, lidocaine (2 mg/kg, CRI 50 and 100 mcg/kg/min), ketamine (3 mg/kg, CRI 10 and 50 mcg/kg/min), and morphine (0.2 mg/kg) depressed the median frequency resulting from the post treatment stimulation. This suggested anti-nociceptive effects and the authors concluded that there was a role for these drugs in post-operative analgesic provision.

Tsai et al. (2013) evaluated the post-operative analgesic effects of meloxicam IV (0.2 mg/kg) or lidocaine IV (1 mg/kg, CRI 25 mcg/kg/min) and their combination, concluding that IV lidocaine and meloxicam provide similar and adequate post-operative analgesia in healthy dogs undergoing ovariohysterectomy. The pain scoring system used in this study was however, not validated.

Gutierrez-Blanco et al. (2015) evaluated the following analgesic approaches in dogs undergoing ovariohysterectomy. Butorphanol (0.4 mg/kg), fentanyl (5 mcg/kg, CRI 10 mcg/kg/h to end anaesthesia then 2.5 mcg/kg/h for 4 h), ketamine (1 mg/kg, 40 mcg/kg/min, then 10 mcg/kg/min as previously), lidocaine (2 mg/kg, 100 mcg/kg/min, then 25 mcg/kg/min as previously), dexmedetomidine (1 mcg/kg then 3 mcg/kg/h, then 1 mcg/kg/h as previously) or a

combination of LKD at the aforementioned doses. Interestingly, given the results reported by Tsai et al. (2013), this study showed that only lidocaine/ketamine/dexmedetomidine and fentanyl resulted in adequate postoperative analgesia.

Guimarães Alves et al. (2014) showed no differences in pain score and postoperative opioid requirements in dogs that underwent fracture repair and received a CRI IV of lidocaine (1.0 mg/kg, CRI 50 mcg/kg/min) or morphine (0.1 mg/kg/h) or a combination of lidocaine and morphine at the same doses. Lewis et al. (2014) were unable to detect a benefit of a CRI of morphine, lidocaine and ketamine (morphine 0.24 mg/kg/h, lidocaine 3 mg/kg/h and ketamine 0.6 mg/kg/h), a lumbosacral epidural with morphine (0.2 mg/kg) and ropivacaine (0.2 mg/kg) or both treatments (i.e. constant rate infusion and lumbosacral epidural at the same doses) over IM premedication with morphine alone in dogs undergoing stifle arthrotomy.

Pypendop and Ilkiw (2005) demonstrated that although lidocaine CRI reduced isoflurane requirement in cats, it resulted in greater cardiovascular depression than isoflurane alone to maintain equipotent levels of anaesthesia. Pypendop et al. (2006) demonstrated that at the same plasma concentrations of lidocaine used in the above study there was no difference in thermal threshold compared to the saline control group or between the different concentrations.

Thus, the literature remains inconclusive in respect to the efficacy of lidocaine CRI as an analgesic agent in the dog, however there is considerable evidence of efficacy as a MAC sparing adjunct to anaesthesia. The use of lidocaine CRI in cats is not recommended.

Gabapentinoids

The gabapentionoids (gabapentin and pregabalin) are anticonvulsants with analgesic properties. They are derivatives of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and have multiple, as yet not totally elucidated, mechanisms of action. They exhibit a selective inhibitory effect on trafficking of the voltage-gated calcium channels containing the α2δ-1 subunit in a state dependent manner thus suppressing the production of excitatory neurotransmitters glutamate, substance P and calcitonin gene related peptide from primary afferent nerve fibres (Kukkar et al., 2013). They may also have some effect on the GABA-A receptor complex in the dorsal horns of the spinal cord and activates the descending inhibitory pathway by inducing norepinephrine release which subsequently induces analgesia resultant to spinal alpha 2 adrenoceptor stimulation (Takeuchi et al., 2007). There is an overall decrease in neuronal excitability, modulation of central sensitisation, hyperalgesia and allodynia. They exhibit only minor effects on normal nociceptive pathways and are thus unlikely to be of benefit as sole analgesic agents.

Gabapentin

Gabapentin elimination half-life is 5–7 h in man compared to a terminal half-life of about 3.3 h in dogs (Kukanich and Cohen, 2011); which means that frequent dosing is needed to maintain minimum targeted plasma concentrations. Efficacy in humans is associated with 2 mcg/mL plasma concentrations, but the effective concentrations are unknown in the dog. Data (Vollmer et al., 1986; Kukanich and Cohen, 2011) suggest 10–20 mg/kg every 8 h would maintain 2 mcg/mL plasma concentrations in dogs.

Two studies assessed the clinical benefit of gabapentin in dogs undergoing thoracic limb amputation (Wagner et al., 2010) and intervertebral disc surgery (Aghighi et al., 2012). Gabapentin 10 mg/kg orally twice daily did not result in a detectable reduction in pain behaviour in disc surgery dogs, compared to background opioid analgesia alone, although a trend ($p < 0.1$) was noted. Effective background analgesia or an ineffective dose may explain the result. In Wagner et al.'s (2010) study the dose of gabapentin (5 mg/kg twice daily) was possibly too low to be efficacious. The small sample size and a number of other confounding factors, such as multimodal analgesia also limited the likelihood of detecting a benefit of gabapentin.

In the cat clearance is much lower (Siao et al., 2010), neither effect on thermal threshold (Pypendop et al., 2010) nor MAC reduction has been shown (Reid et al., 2010). There is a small case series of reported efficacy in chronic musculoskeletal pain in cats following acute traumatic injury (Lorenz et al., 2013).

A recent clinical study investigating the use of gabapentin in combination with buprenorphine when compared with buprenorphine alone, or buprenorphine with meloxicam in cats undergoing ovariohysterectomy failed to show a difference between groups in requirement for rescue analgesia or in pain scores when utilizing multi-dimensional composite pain scales. Ironically when the validated Glasgow composite pain scale was used, gabapentin recipients had lower pain scores (Steagall et al., 2017). This study had a small sample size and a type II error was likely so results should be interpreted with caution.

Pregabalin

Pregabalin is structurally similar to gabapentin but has higher oral bioavailability and a longer half-life (Salazar et al., 2009). Whilst it has been used clinically in Chiari malformation cases (Plessas et al., 2012) and there is one case report of efficacy in a cat (Clark et al., 2017), there are no controlled studies evaluating the efficacy of pregabalin to treat pain in veterinary patients.

Whilst strong human evidence clearly supports further clinical investigation of these drugs for acute and chronic pain management in domestic species, more robust pharmacokinetic and pharmacodynamic data is required. Based on current evidence the use of gabapentin can be considered in both species when additional analgesia is required or in the face of intolerance to other more commonly used agents. Further studies are required to demonstrate the effectiveness of pregabalin, although the case reports in the literature are promising.

Alpha-2 adrenoreceptor agonists

Medetomidine and dexmedetomidine

The alpha-2 adrenoreceptor agonists, medetomidine and dexmedetomidine are extensively used in veterinary medicine to provide both sedation and analgesia and as part of premedication protocols prior to general anaesthesia. They are known to produce sedation and analgesia by their interaction with central and spinally located alpha-2 receptors and mediate their cardiovascular effects by their interaction with both peripheral and centrally located alpha-2 receptors (Cullen, 1996; Murrell and Hellebrekers, 2005).

Their sedative, minimum alveolar concentration (MAC) reducing and analgesic effects have been studied in dogs and cats, although their cardiovascular effects still limit their use in certain clinical situations. The literature contains a variety of both nociceptive studies and clinical analgesic studies, all measuring outcome either by threshold testing or utilising pain assessment tools.

A recent clinical analgesic study investigated the use of dexmedetomidine by either the intramuscular route or into the Governing Vessel 20 acupuncture point. Sedation and analgesia scored using a numerical rating scale revealed superior sedation and analgesia when administered into GV20 (Pons et al., 2017) compared to IM dosing. Whereas another clinical study in cats and

dogs prior to elective surgery evaluating buprenorphine combined with either dexmedetomidine or acepromazine failed to show a difference in level of analgesia using pain assessment, physiological variables and mechanical nociceptive threshold (Hunt et al., 2013). A study in dogs comparing the administration of either dexmedetomidine or morphine or a combination of both administered by the intra-articular route following stifle surgery resulted in longer lasting analgesia when the combination was used (Soto et al., 2014).

A number of different studies have demonstrated a reduction in MAC isoflurane with the use of dexmedetomdine. In cats, this resulted in a dose dependent decrease in isoflurane MAC as the plasma concentration of dexmedetomidine increased (Escobar et al., 2012). A 2014 study in dogs resulted in the same dose dependent reduction in isoflurane MAC following dexmedetomdine administration (Acevedo-Arcique et al., 2014).

Dexmedetomidine has also been shown to have a dose dependent effect when thermal threshold was used to assess thermal nociception in cats. The temperature difference (deltaT) increased as dexmedetomidine dose plasma concentration increased. This also correlated with the assessed level of sedation (Pypendop and Ilkiw, 2014).

Route of administration, with regard to analgesic effect has also been investigated. A 2014 nociceptive study in cats compared IM and oral transmucosal (OTM) administration of dexmedetomidine and buprenorphine (Porters et al., 2014). They found no difference in both sedation and antinociceptive scores between groups using a mechanical stimulus and an ear pinch test. A nociceptive study (Slingsby et al., 2009) also found no difference between groups in the level of anti-nociception when dexmedetomidine alone was administered. These results contrast to those of a study (Santos et al., 2010) that compared route of administration with the combination of dexmedetomidine and buprenorphine but used a lower dose of dexmedetomidine and found the OTM route resulted in less favourable levels of sedation and reduced ability to restrain the cats. Nociception was not specifically investigated as an outcome measure.

Further clinical work, utilising pain assessment tools is required to assess the benefits and possible concerns with the use of the alpha-2 adrenoreceptor agonists in pain management in both dogs and cats. Species differences may reveal this class of analgesic to have particular benefit in the management of feline acute pain but will require further evidence to ensure this is based on good science.

Neurokinin type-1 receptor antagonists

Maropitant

Maropitant is a neurokinin type-1 (NK_1) receptor antagonist with a licence to prevent and treat emesis in dogs. It has a high bioavailability in dogs following administration by the subcutaneous route, but poor bioavailability following oral administration and a half-life of 7.75 h when dosed at 1 mg/kg (Benchaoui et al., 2007). A similar pharmacokinetic profile is seen in cats with a half-life of 13–17 h and a lower bioavailability following oral administration compared to the subcutaneous (SC) route (Hickman et al., 2008). It has been investigated for its anti-emetic properties and possible effects on regurgitation during anaesthesia (Claude et al., 2014).

Maropitant's NK_1 receptor antagonism results in blockage of the effects of substance P and a multiple clinical and experimental studies have investigated the potential visceral analgesic effects. Unfortunately, differences in methodology in the experimental research make it difficult to directly compare results and form conclusions regarding its use in pain management. Fukui et al. (2017) demonstrated a significant reduction in sevoflurane requirements following SC maropitant (1 mg/kg) administration compared to saline, which was of similar magnitude to the reduction seen with carprofen. Another MAC (sevoflurane) study demonstrated a 16% reduction in MAC following administration of 5 mg/kg maropitant IV followed by a continuous infusion (Alvillar et al., 2012). Another study used a model of nociception following ovarian ligament traction on MAC (sevoflurane). Once again there was a reduction in sevoflurane MAC between 24 and 30% following IV maropitant administration (Boscan et al., 2011). Clinical pain studies have also differed in outcome, again likely due to differences in methodology. One study compared maropitant at 1 mg/kg with morphine at 0.5 mg/kg, both administered SC, and reported lower isoflurane requirements during canine ovariohysterectomy and better post-operative pain scores in the maropitant group (Marquez et al., 2015). All monitored physiological variables and rescue analgesia requirements were similar between groups. This is comparable to a study by Swallow et al. (2017) that reported lower isoflurane requirements following SC administration of 1 mg/kg maropitant compared to saline during canine ovariohysterectomy. Premedication in this study consisted of acepromazine and methadone, with meloxicam administered prior to surgical intervention. Although isoflurane requirements were lower in the maropitant group, no differences in monitored physiological variables or pain assessment were reported in the study.

The clinical pain studies on the analgesic properties of maropitant further highlight the question, is a reduction in inhalational agent requirement the same as provision of analgesia? Further investigation is required into the use of maropitant to provide visceral analgesia before it can be routinely recommended in canine patients. There are no experimental or pain studies in cats at this current time.

Conclusions

There is a wealth of published information detailing pharmacological interventions for the treatment of acute pain in dogs and cats. The literature provides an ever-stronger evidence base for our clinical decision making and patient treatment, but still requires further good quality studies. Currently the evidence behind our clinical decision for a number of the new and upcoming drugs is weak. There is a positive sense though, that we are now armed with multiple options for treatment of acute pain and have opportunities to provide good analgesia even when certain drug classes may be contraindicated in a particular situation. In conclusion, a stronger evidence base is required, containing good quality studies that may then be reviewed in a more systematic approach.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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