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Managing orthopaedic pain in horses

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Introduction

Orthopaedic pain is a broad term applied to pathology of the musculoskeletal system, potentially involving bones, joints, tendons, ligaments and muscles and consequently incorporating both soft and hard tissues. When thinking in terms of appropriate therapeutics, it may therefore be more useful to define it as deep somatic pain to distinguish it from superficial (cutaneous) somatic pain and visceral pain.

Musculoskeletal pain may result from trauma (including planned surgical intervention), overuse, inflammation, infection, neoplasia, osteolysis, ischaemia or neuronal damage. Common equine orthopaedic conditions such as degenerative joint disease, navicular syndrome and laminitis often present several of these aspects in combination and can be challenging to manage. Difficulty can be compounded by occurrence of acute-on-chronic flare-ups (see Box 1 for some definitions associated with pain).

The nature, severity and types of pain all must be taken into consideration when deciding how to provide effective analgesia.

Pain recognition

One of the biggest challenges in veterinary medicine is the recognition and quantification of pain. Assessment of pain in non-verbal species (and non-verbal humans) is difficult and subjective, typically relying on a combination of physiological variables, behaviour assessment and a degree of anthropomorphism. Several attempts have been made to devise pain scales for use in horses to identify the site and type of pain, but as yet none of these has been fully validated. This is further complicated by the fact that horses as a species tend not to be overtly demonstrative of pain unless

it is moderate to severe, show considerable variation in the way they respond and alter their behaviour in the presence of an observer. Different assessors may therefore attribute very different levels of pain to the same animal, leading to very different assessments of the requirement for analgesia. In the current context, lameness scores are crude but clinically useful and widely employed. Manifestation of musculoskeletal pain may be obvious in the case of a single limb lameness, less so in mild multiple limb lameness, post surgically, or in cases of axial rather than appendicular pathology.

Box 1.

Types of Pain

Acute pain - Acute pain is the normal physiological response to application of a noxious stimulus. It is designed to be protective, being linked to the withdrawal reflex, preventing further tissue damage and triggering behavioural changes intended to maximise healing. This type of pain is typically of short duration, persisting only as long as the original insult. This is the type of pain associated with the early stages of tissue injury or surgery and is relatively easy to treat.

Chronic pain – this is pain that persists beyond the time frame expected for the relevant condition, a period of three to six months is often quoted. Thus may be due to acute injury or disease that is not resolving, ongoing degenerative conditions such as arthritis, or failure to manage acute pain adequately in the early stages of treatment. Achieving satisfactory analgesia can be extremely difficult in chronic pain states as the nervous system undergoes maladaptive changes – a process called neuroplasticity. This can result in sensitisation of the nervous system, when normally innocuous sensory input becomes perceived as painful (termed allodynia) or an exaggerated response to normally painful stimuli (termed hyperalgesia). Sensitisation may occur in both peripheral and central components of the nervous system and involves increased reactivity of peripheral nociceptors and central pain neurons, recruitment of additional nociceptors to generate pain signals and upregulation of pain receptor expression, so reinforcing the pain transmission pathways. In cases where chronic pain develops, pain ceases to become simply an indicator of a disease process and becomes part of the disease process itself. The longer pain is left untreated or inadequately controlled the more difficult it becomes to obtain a satisfactory outcome.

Neuropathic pain – this is pain caused by direct peripheral or central nerve injury resulting in hyperalgesia, allodynia and chronic, spontaneous ectopic generation of pain signals in the absence of any external stimuli.

Strategic Analgesia

A good analgesic plan will consist of systemically administered drugs, if possible in combination with local or regional analgesic techniques. Drugs chosen should ideally be those licensed for analgesia in the horse by the prescribed route, however licensed drugs administered by an unlicensed route, or unlicensed drugs may on occasion be indicated and appropriate. The key is in understanding the types of pain that may be present, the mode of action of the drugs that are available and how these drugs may be employed to maximise their effect on the case in question. In this way a multi-modal therapeutic plan can be formulated, incorporating the most appropriate drugs, designed to target as many aspects of the pain pathway as accurately as possible.

Systemic administration of analgesic agents in the short term is typically by the intravenous (IV) or intramuscular (IM) route, with oral medication often being relied on for more protracted courses of treatment. Whilst a combination of these routes will probably prove adequate in the majority of cases, other methods of drug delivery may allow for more effective provision of analgesia in specific cases.

The **oral-transmucosal** (OTM) absorption of some drugs can result in rapid uptake and high bioavailability as it avoids first pass metabolism which enterally absorbed drugs administered per os (PO) are subject to. Although potentially very effective, drugs administered this way may be swallowed or spat out, resulting in imprecise dosing, restricting this method to either highly concentrated formulations or highly potent drugs, where a small total volume can be given. Although several drugs can be effectively administered this way, only the alpha 2 agonist detomidine has a formulation licenced specifically for this route.

Transdermal drug delivery systems have been developed for a number of classes of drugs in the human market and include patches, creams and gels for external application designed to have either systemic or local effects. Transdermal drug absorption avoids first pass metabolism and gives the potential for prolonged drug administration with minimal patient handling. However drug uptake is highly dependent on sustained contact with the skin and that the area of application is healthy and has a good blood supply. Several human preparations have been evaluated in veterinary species and a specific veterinary formulation of fentanyl (licenced for use in dogs) is now available.

Epidural drug administration (Fig 1) provides the opportunity for a more targeted effect and is becoming more commonly employed. Use of local anaesthetics, alpha 2 agonists, opioids, ketamine and tramadol has been reported in the horse by this route. Depending on the characteristics of the drug, there will be varying systemic uptake, and onset and duration of effect may differ significantly from those familiar from conventional systemic administration, which can be advantageous. For prolonged analgesia, epidural catheters can be placed which facilitate provision of extended

targeted pain management (Fig 2). Commercial kits (Fig 3) for this procedure are available (B Braun Medical Ltd, Yorkshire, UK; Smiths Medical, Kent, UK) and have been used successfully in several cases at the author's hospital. These catheters require very careful management, with maintenance of patency and sterility being the main problems, however with proper management it is possible to maintain these in situ for up to 10 days in clinical cases.

Diffusion (soaker) catheters offer the potential for prolonged, precise administration of local anaesthetic agents. Their potential has yet to be fully realised and they are discussed in more detail below with local anaesthetic drugs.

With the high prevalence of developmental, degenerative and traumatic disease affecting the joints of horses, as well as the frequency of diagnostic and therapeutic surgical procedures involving joints and other synovial structures, **intra-synovial** administration of analgesic agents is an attractive and effective method of achieving targeted pain relief. Administration of a number of drugs by this route has been described, including morphine, corticosteroids and local anaesthetic agents.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

There are several non-steroidal anti-inflammatory drugs licenced for use in horses in the UK and these often form the first line and mainstay of analgesia provision. Action is by inhibition of cyclo-oxygenase enzymes both peripherally and centrally, thereby interrupting the arachidonic acid cascade that results in production of prostacyclin, prostaglandins and thromboxanes. These substances are potent inflammatory mediators, which result in sensitisation and recruitment of peripheral nociceptors and transmission of central pain pathways. Many disease processes and certainly surgical interventions will induce an inflammatory response, so incorporating an anti-inflammatory drug is eminently appropriate.

Many are available for administration by IV injection and as powders and/or pastes for oral administration, making them convenient for both acute and chronic pain management, although palatability may be problematic with some of the powdered preparations designed to be mixed with food. Choice largely comes down to familiarity, availability and cost. Anecdotally, some horses will respond better to one than another so it may be worth trying an alternative if response to one is unsatisfactory. Data sheets tend to advise leaving 24 hours between dosing if changing to an alternative to avoid inadvertent overdose. The potential for toxicity also need to be considered in the context of long term treatment, particularly as this may be continued by the owner of the horse for extended periods, outside the direct control of the veterinary surgeon. Doses should be carefully calculated and dosing regimes clearly stipulated. Toxicity may manifest as blood dyscrasias and gastrointestinal ulceration, with the glandular region of the stomach, proximal duodenum and right dorsal colon being particularly affected. Renal papillary necrosis has also been reported in horses receiving clinically relevant doses of phenylbutazone (Read 1983). This is particularly relevant as the aminoglycoside antimicrobial gentamicin, commonly used as a first line treatment in cases of synovial sepsis is also known to be nephrotoxic.

Paracetamol (acetaminophen)

Veterinary licensed oral preparations of paracetamol are available for dogs (in combination with codeine) and pigs in the UK, but not horses. This is not a typical NSAID and the exact mechanism of action is undetermined but thought to act centrally on serotonergic, opioid, nitric oxide and cannabinoid pathways as well as effects on prostaglandin production (Sharma and Mehta 2013). Its successful use as an adjunctive analgesic medication has been reported (20mg/kg PO twice daily) in a laminitic pony showing pain refractory to NSAIDs, lidocaine and morphine analgesia (West and others 2011).

Corticosteroids

Corticosteroids act by inhibiting both cyclo-oxygenase and lipoxygenase pathways of the arachidonic acid cascade, exerting potent anti-inflammatory activity as well as a wide range of other effects. Most commonly utilised when discrete foci of inflammation can be precisely targeted using small volumes, such as vertebral or limb synovial or ligamentous structures. Methylprednisolone and dexamethasone are licenced for systemic and intra-synovial use in horses. Data sheets invariably carry warnings about the risk of inducing or exacerbating laminitis and total dose and frequency of administration should be carefully considered. Triamcinolone although not licenced is also frequently used.

Opioids

This is a versatile group of drugs offering IV, IM, OTM, transdermal, epidural and intra synovial routes of administration. Action is primarily by central modulation of the pain pathways although opioid receptors are also present outside the central nervous system in tissues such as the myenteric plexus and synovial membranes, with expression being upregulated in inflammatory states.

Butorphanol, pethidine and buprenorphine are licensed for use in horses in the UK and all demonstrate different receptor activity and affinity.

Pethidine (meperidine) is a mu receptor agonist, making it potentially the most efficacious of the licenced options. Used at 1mg/kg IM it was shown to improve experimentally induced foot lameness, but only at 2-3hrs post administration (Foreman and Ruemmler 2013). Despite its theoretical promise, several factors limit its clinical utility. It is only licenced as a visceral analgesic, IV administration is contra-indicated due to potential for histamine release and seizure-like activity, it can cause pain on IM injection and large volumes need to be injected due to its low potency. It is also a Schedule 2 Controlled Drug, with the associated administrative requirements. Epidural

administration of pethidine (0.8mg/kg) has been reported, giving a fast onset (12 minutes) and 4 to 5 hour duration of action (Skarda and Muir 2001).

Buprenorphine (a Schedule 3 Controlled Drug) is a partial mu agonist, with some potentially attractive attributes and is licenced for post-operative analgesia at a dose of 10µg/kg IV. It is highly potent, requiring small volumes of administration and somatic analgesia of 6hrs duration (assessed experimentally using thermal threshold testing) is reported at this dose (Carregaro and others 2007). Buprenorphine also shows very good absorption by the OTM route, facilitating administration to needle shy horses. A sublingual dose of 6µg/kg is reported to have produced effective sedation and analgesia lasting up to 12hrs in a case of trauma-associated musculoskeletal pain (Walker 2007). The author has used it with apparent good effect by this route. Data sheet recommendations state buprenorphine should only be administered after an intravenous sedative agent and cardiovascular stimulation and locomotor excitement lasting for over 12hours have been reported following the recommended dosing regimen (Carregaro and others 2006, 2007) and the author has seen horses compulsively box-walking following use in clinical cases.

Butorphanol is a mu receptor antagonist and kappa receptor agonist. Whilst analgesia is reported as excellent or good in clinical colic cases (Stout and Priest 1986), it does not perform so well for somatic pain. In experimental horses Kalpravidh and others (1984a, 1984b) demonstrated only moderate analgesia lasting 15-30 minutes, assessed using thermal threshold testing. Increased heart rate and locomotor activity may also be seen, although in the author's experience this is not as marked as that seen following buprenorphine administration. Epidural administration of butorphanol failed to produce detectable analgesia (Natalini and Robinson 2000), suggesting that horses do not possess kappa receptors in the spinal cord. It is then logical to assume that kappa agonists will only have a supraspinal effect.

Unlicenced opioids.

In the author's hospital, morphine (0.1-0.3mg/kg) is routinely given systemically (IM and IV) for perioperative analgesia and managing pain not controlled by NSAID administration. Morphine and methadone are also administered regularly by the epidural route for painful hindlimb orthopaedic conditions. Epidurally, morphine (0.1–0.2 mg/kg) (Sysel and others 1996, Goodrich and others 2002) shows a slow onset (up to 6 hours) and a duration of action of around 5 hours (Natalini and Robinson 2000), but can possibly last up to 12 - 18 hours. Epidural methadone (0.1mg/kg) has an onset of around 15 minutes and lasts about 5 hours (Olbrich and Mosing 2003). In the author's hospital it is routine to combine methadone and morphine (0.1mg/kg of each) to obtain the theoretical advantage of providing rapid onset of analgesia with extended duration in the acute setting. Methadone also has activity at the N-methyl-D-aspartate (NMDA) receptor, therefore has an additional mechanism for contributing to analgesia. Where sustained provision of targeted analgesia is required, morphine can be administered at 0.1-0.2mg/kg twice daily via an indwelling epidural catheter. It is important to ensure strict aseptic technique and that preservative free solutions are used where possible.

Intra-synovial administration of 0.05mg/kg morphine has also been demonstrated to provide analgesia for potentially 24 hours in experimentally induced radio-carpal joint synovitis (Lindegaard and others 2010a and 2010b).

The availability of fentanyl patches offers the attractive prospect of providing extended opioid analgesia with minimal intervention. Maxwell and others (2003) showed rapid uptake by the transdermal route with all horses exceeding the 1ng/mL plasma level consistent with that reported to provide analgesia in other species, which was maintained for 32 hours. Orsini and others (2006) examined the pharmacokinetics of transdermal fentanyl using commercially available patches targeted to deliver 60µg/kg and found a large variation in onset of absorption (up to 5 hours), time to peak concentration (8.5-14.5 hours) and maximum plasma concentration achieved (0.67-5.12ng/mL). One third of horses failed to achieve the 1ng/mL plasma concentration considered to be

analgesic. A large variation in onset, maximum concentration (0.1-28.7ng/mL) and time to maximum concentration (8-24 hours) has also been reported in neonatal foals treated with fentanyl patches designed to deliver 100µg/hr (Eberspacher and others 2008). The site of patch application is known to affect the rate and uptake of transdermally delivered fentanyl (Mills and Cross 2007).

Combination therapy with NSAIDs has been reported in clinical cases refractory to NSAID treatment alone (Thomasy and others 2004). Again, a large variation in maximum concentration and time to achieve this were reported, but some, although weak, evidence of analgesic effect was claimed. A solution of fentanyl (50mg/mL) is licenced for transdermal use in dogs where it is claimed to provide analgesia for a minimum of 4 days post-application, but this has not been evaluated in horses at the time of writing.

Alpha 2 adrenergic agonists

Frequently used as sedative agents, alpha 2 agonist compounds also provide analgesia by a mechanism similar to, and synergistic with, that of the opioids (Hellyer and others 2003). Duration and quality of analgesia is controversial (England and Clarke 1996), but appears to be better for visceral, rather than somatic pain. Some authors have reported no detectable influence on somatic analgesia (Elfenbein and others 2009), whilst others have found that the effect depends not only on the drug used, but also on the type of stimulus applied (Moens and others 2003, Rohrbach and others 2009). Given systemically, analgesia is best considered to be of short duration, peaking later than sedative effects and not lasting as long, making them of most use during surgical procedures.

All alpha 2 agonists have profound effects on the cardiovascular system which should also be taken into account, as should the difficulty of assessing adequate analgesia in a sedated animal.

Epidurally, xylazine (0.17mg/kg up to 0.25mg/kg) is safe and effective (LeBlanc and Carron 1990; Skarda and Muir 1996; LeBlanc and others 1998). Detomidine (30µg/kg) in combination with

0.2mg/kg morphine produces analgesia (Skarda and Muir 1996, Sysel and others 1996, Goodrich and others 2002) and reduces post-operative lameness after hindlimb surgery (Sysel and others 1996, Goodrich and others 2002). High lipid solubility facilitates systemic absorption from the epidural space, especially of detomidine (Skarda and Muir 1996), causing sedation following epidural administration. Loss of tail and perineal muscle tone may become evident due to local anaesthetic-like properties (particularly with xylazine). Onset is rapid (approximately 12 minutes) and duration of effect is 2.5-3.5 hours (LeBlanc and others 1998, Skarda and Muir 1996).

Local Anaesthetic Agents

Local anaesthetics have the potential to completely abolish pain by interrupting neuronal signal transmission, rather than just obtunding it. They affect both sensory and motor neurons, consequently their use will not be appropriate for all sites of pain or surgery, but where applicable they offer considerable benefit. They can be administered topically, perineurally, epidurally, intra-synovially, systemically and directly infiltrated into tissues. Mepivacaine, lidocaine and procaine are all licenced for use in horses in the UK. Of these, only mepivacaine is supplied without adrenaline or preservative and is licensed for infiltration, perineural, intra-articular and epidural administration, making it an extremely versatile preparation. Lidocaine without adrenaline is also available from pharmaceutical suppliers as a 2% solution for injection and as a 0.2% solution in 5% glucose for IV infusion, but not licenced for use in horses.

Lidocaine administration has been described by continuous IV infusion (loading dose of up to 2mg/kg followed by infusion at 50µg/kg/minute). Its use in this manner is most often associated with gastrointestinal tract surgery, however somatic analgesia as assessed by thermal threshold testing has been demonstrated experimentally (Robertson and others 2005).

Epidurally, care needs to be taken with the total volume injected to avoid cranial spread which may impair motor function to the hindlimbs (Goodrich and others 2002, Olbrich and Mosing 2003). Preservative free preparations of bupivacaine 0.5%, lidocaine 2% and mepivacaine 2% solutions (5-10mL) have been used by the author.

Transdermal patches containing 5% lidocaine are used to treat a range of chronic neuropathic and musculoskeletal pain in humans, with systemic uptake having been proven. Application of two 700mg patches to the limbs of horses for 12 hours failed to demonstrate systemic uptake in a study by Bidwell and others (2007). Doubling the number of patches for 24 hours gave variable systemic uptake (Andreoni and Giorgi 2009). If the skin was subjected to an alcohol scrub prior to patch placement there was a tendency for a more rapid and pronounced, but less sustained uptake. Antinociceptive effects assessed by pricking the skin under the patch at removal showed no difference in sensation between horses which had had a patch applied and control animals. This application therefore appears to be of little benefit.

Diffusion catheters (Fig 4) are another method of providing targeted pain relief. These are available commercially (Mila International Inc, Kentucky, USA) or can be improvised from narrow gauge plastic tubing or intravenous cannulae. The use of these for prolonged perineural administration of lidocaine, mepivacaine and bupivacaine to the palmar metacarpal nerves has been investigated experimentally in horses (Driessen and others 2008). Although regional anaesthesia was achieved, significant oedema developed, necessitating discontinuation of the infusions, limiting their clinical potential. Alternatively, catheter implantation during wound closure, allowing local anaesthetic to be instilled directly at the surgical site for post-operative pain management has been described in small animals (Abelson and others 2009) with no associated risk of wound complications and has been successfully used in horses at the author's hospital to provide analgesia for 48 hours following surgical resection of thoracolumbar spinous processes (Fig 5).

Prolonged intra-synovial administration of local anaesthetic agents in human patients has been associated with chondrolysis, with bupivacaine appearing to exhibit the greatest degree of chondrotoxicity. This effect appears to be dose and time dependent, being particularly pronounced with formulations containing adrenaline. Consequently a number of local anaesthetic agents have been tested in animal models and chondrocyte cultures, with mixed results; *in vitro* results not always supporting *in vivo* ones (Webb and Ghosh 2009; Dragoo and others 2010). An *in vitro* study of bupivacaine, lidocaine and mepivacaine on equine chondrocyte cultures showed mepivacaine to be the least chondrotoxic, with cell viability on exposure to this agent approaching that of the saline control (Park and others 2011). Single intra-synovial injection of local anaesthetic solution is performed regularly at the author's hospital to provide targeted pain relief following arthroscopic surgery, with no apparent problem.

Ketamine

Used at sub-anaesthetic doses, this NMDA receptor antagonist has potent analgesic properties and may counteract central sensitization, so making it potentially useful in the management of chronic as well as acute pain. Infusions of 0.4 and 0.8mg/kg/hour have been shown to be tolerated well in conscious horses, with excitement seen at 1.6mg/kg/hour, although no somatic analgesia was demonstrated (Fielding and others 2006). Peterbauer and others (2008) however, did demonstrate analgesic properties in conscious horses after 0.6mg/kg IV bolus followed by 20µg/kg/minute infusion. Analgesia is mainly somatic rather than visceral and is mediated by a number of mechanisms in addition to NMDA receptor activity. In addition to infusion administration, IM bolus dosing at 0.2-0.5mg/kg has been practiced by the author to manage acute episodes of pain, or acute-on-chronic episodes in cases of laminitis or following surgical intervention. Epidural administration (0.5, 1.0 and 2.0mg/kg) has been shown to provide analgesia lasting 30 to 75 minutes (De Segura and others 1998).

Tramadol

Tramadol is a synthetic analogue of codeine which has been used in the management of acute and chronic moderate to severe pain in humans. It is a centrally acting analgesic that has agonist activity at mu opioid receptors and also inhibits the reuptake of noradrenaline and serotonin. Although not licenced in the horse, the pharmacokinetics and pharmacodynamics of intravenously, intramuscularly and orally administered tramadol have been investigated in this species (Shilo and others 2007, Cox and others 2010, Dhanjal and others 2009, Knych and others 2013a 2013b, Giorgi and others 2007, Stewart and others 2011). Minimum plasma tramadol levels which provide analgesia in people vary greatly between 100 and 600ng/mL, with much of the analgesic effect of tramadol being attributed to the M1 metabolite (O-desmethyltramadol) which has 200 times the affinity for the mu opioid receptor than the parent drug. In people there is genetically predetermined variation in the ability to produce this metabolite, making some individuals poorly responsive to the drug. It is unknown whether this is also true in horses, although a large individual variation in plasma concentrations of MI (and several other metabolites) has been demonstrated (De Leo and others 2009, Knych and others 2013a, 2013b, Giorgi and others 2007). Oral bioavailability following a 5mg/kg dose has been reported as approximately 65% in fasted horses, increasing to approximately 85% in fed horses (Giorgi and others 2007), whilst Shilo and others (2007) reported only 3% following 2mg/kg administered to fasted horses. Knych and others (2013a) used doses of 3, 6 and 9mg/kg PO which showed a very wide variation in plasma levels, with only the 9mg/kg dose consistently achieving plasma concentrations within the human analgesic range. No adverse events were reported apart from mild signs of colic and increased pacing behaviour in 1 horse at the higher dose. Intramuscular administration of 2mg/kg resulted in rapid and complete absorption with attainment of useful plasma concentrations and no adverse effects (Shilo and others 2007). Cox and others (2010) and Shilo and others (2007) reported side effects including ataxia, muscle twitching

and sweating for 15 minutes after 2mg/kg IV and Giorgi and others (2007) reported confusion, agitation, tremor and tachycardia after 5mg/kg IV but not PO. Dhanjal and others (2009) reported side effects following 2mg/kg IV and were unable to demonstrate an antinociceptive effect using a noxious thermal stimulus. Guedes and others (2012) administered 5mg/kg PO twice daily to horses with chronic laminitic pain and showed only weak evidence of analgesia, whilst ketamine showed a much greater effect. Epidural administration of 1mg/kg tramadol produced analgesia after 30 minutes with effects lasting for 4 hours (Natalini and Robinson 2000).

Gabapentin

Originally used as an adjuvant anticonvulsant, gabapentin was subsequently shown to be effective in treating a range of chronic pain syndromes in people. It is a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) but neither parent drug nor metabolites show affinity for, or activity at $GABA_A$ or $GABA_B$ receptors. The major mechanism of action is currently thought to be via voltage dependent calcium channels, thereby reducing neurotransmitter release (Kong and Irwin 2007). Pharmacokinetics of a single dose of 5mg/kg PO (Dirikolu and others 2008) and 20mg/kg PO and IV (Terry and others 2010) have been evaluated in horses. No adverse events were noted after either dose or route of administration although sedation was evident for 1 hour after the IV dose. Rapid but poor absorption (compared with humans, rats, dogs and monkeys) followed PO administration with a bioavailability of only 16% following the higher dose. Gabapentin is not licensed for veterinary species but there are case reports of its use in horses. Davis and others (2007) describe its use in a heavily pregnant mare with suspected neuropathic pain at 2.5mg/kg PO every 8 hours, increasing dosing interval over 6 days, with apparent beneficial effect and no detriment to the foetus. It is also reported as a component of a multimodal approach to provision of analgesia in the management of severe laminitis associated hoof pain, at doses between 3.3mg/kg every 8 hours and 2mg/kg every 12 hours PO (Dutton and others 2009).

Bisphosphonates

Bisphosphonates have been shown to reduce pain in human patients with osteoarthritis and cancer pain and improve joint mobility. These drugs inhibit osteoclast proton secretion, reducing the acidity of the microenvironment associated with bone resorption, so reducing activation of acid sensitive ion channels in sensory neurons. A direct anti-inflammatory effect is also demonstrated by inhibiting osteoblast secretion of vascular endothelial growth factor, reducing cytokine release from activated macrophages (Silvina and Barbara 2014). Tiludronic acid is licenced for treatment of inflammatory and degenerative joint disease in horses at a dose of 1mg/kg by intravenous infusion over 30 minutes. Improvement of lameness in horses suffering from bone spavin (Gough and others 2010) and navicular disease (Denoix and others 2003) has been demonstrated in tiludronate treated horses.

Isoxsuprine hydrochloride is licenced for the treatment of navicular disease in horses. Its action causes vasodilation, lowers blood viscosity and inhibits platelet aggregation, thereby potentially improving circulation in the affected area. Some, but inconsistent evidence of clinical efficacy has been shown (Rose and others 1983; Turner and Tucker 1989).

Conclusion

The World Health Organisation 'pain ladder' (Fig 6) describes a graded approach to administration of analgesic agents, combined with adjunctive therapies and provides a useful framework to follow for pain management. Originally designed to provide guidance managing cancer pain in people, is now much more widely applied. The number of drugs available for use in horses is limited, however by understanding the action of what is available and adopting a multi-modal approach, additive or synergistic activities can be exploited to maximise effect whilst minimising the risk of side effects. Adjunctive therapies can equally be vital in achieving a successful outcome (Fig 7). These range from

simple bandaging, hot and cold compresses or using ice, physiotherapy, acupuncture, corrective or remedial farriery up to surgical interventions such as hoof wall resection, and salvage procedures such as neurectomy (sometimes in conjunction with fasciotomy) and arthrodesis. Novel attributes of drugs used for other indications can also be exploited for good effect, for example the use of tricyclic antidepressants for chronic pain management in people and small animals. However evidence of safety and efficacy in the horse in this regard is often lacking.

Quiz

1. In addition to being a general anaesthetic agent, ketamine provides profound analgesia via its action at NMDA receptors. Which of the following drugs also has NMDA receptor activity?
   a) Gabapentin
   b) Methadone
   c) Paracetamol
   d) Tramadol

2. Which of the following statements is **true** of alpha 2 agonists?
   a) They provide reliable somatic analgesia
   b) The analgesia they provide lasts as long as the sedative effects
   c) They are all licensed for administration by the oral transmucosal route
   d) It is possible to achieve sedation by administering them into the epidural space

3. The following classes of drugs can effectively be administered epidurally, **except** for which one?
   a) Alpha 2 agonists
   b) Non-steroidal anti-inflammatories
   c) Opioids

d) Local anaesthetics

4. Which of the following statements is **true** regarding intra-synovial administration of analgesic agents?

a) Local anaesthetics should never be used due to their chondrotoxic effects

b) There are no drugs licenced for use by this route in the horse

c) Total dose of corticosteroids should be restricted due to the potential for adverse systemic side effects

d) There are no opioid receptors present in synovial tissue therefore these drugs will not be effective by this route

Answers: 1 b), 2 d), 3 b), 4 c).

Contributorship

The author is the sole contributor to this article and accepts responsibility for its content.

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Further reading

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Figure 1.

Epidural injection (here shown being performed at the sacro-coccygeal/first inter-coccygeal space) is a useful technique for achieving more targeted drug delivery. It is important to observe good hygiene and where possible to use preservative free drugs.

Figure 2.

Epidural catheter placed at the sacro-coccygeal/first inter-coccygeal space. Note the bacterial filter and sterile dressing to maintain cleanliness. With appropriate care, these can be maintained for several days for extended pain management without the requirement for repeated needle puncture.

Figure 3.

Commercially available epidural catheter kits. Several makes are available and contain all the necessary components.

Figure 4.

Commercially available wound diffusion catheters. These are available with different diffusion lengths so can be chosen to suit the extent of the surgical field. Home-made ones can be constructed from long intravenous cannulae or dog urinary catheters.

Figure 5.

Commercial wound diffusion catheter in-situ following spinous process resection. The catheter is placed during wound closure and exited through a stab incision distant from the surgical site. Note the bacterial filter to preserve sterility of injected local anaesthetic agent.

Figure 6.

World Health Organisation 'Pain Ladder'. Originally designed for guidance in managing cancer pain in people, it describes a logical, progressive approach to provision of analgesic agents when managing many types of clinical pain.

Figure 7.

Severe case of laminitis. These cases can be extremely challenging to manage, often presenting with complex pain that is refractory to conventional analgesic protocols. Adjunctive approaches are as important as pharmacological therapy, with hoof wall resection and provision of adequate mechanical support illustrated here.

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Managing orthopaedic pain in horses

Introduction

Orthopaedic pain is a broad term applied to pathology of the musculoskeletal system, potentially involving bones, joints, tendons, ligaments and muscles and consequently incorporating both soft and hard tissues. When thinking in terms of appropriate therapeutics, it may therefore be more useful to define it as deep somatic pain to distinguish it from superficial (cutaneous) somatic pain and visceral pain.

Musculoskeletal pain may result from trauma (including planned surgical intervention), overuse, inflammation, infection, neoplasia, osteolysis, ischaemia or neuronal damage. Common equine orthopaedic conditions such as degenerative joint disease, navicular syndrome and laminitis often present several of these aspects in combination and can be challenging to manage. Difficulty can be compounded by occurrence of acute-on-chronic flare-ups (see Box 1 for some definitions associated with pain).

The nature, severity and types of pain all must be taken into consideration when deciding how to provide effective analgesia.

Pain recognition

One of the biggest challenges in veterinary medicine is the recognition and quantification of pain. Assessment of pain in non-verbal species (and non-verbal humans) is difficult and subjective, typically relying on a combination of physiological variables, behaviour assessment and a degree of anthropomorphism. Several attempts have been made to devise pain scales for use in horses to identify the site and type of pain, but as yet none of these has been fully validated. This is further complicated by the fact that horses as a species tend not to be overtly demonstrative of pain unless

it is moderate to severe, show considerable variation in the way they respond and alter their behaviour in the presence of an observer. Different assessors may therefore attribute very different levels of pain to the same animal, leading to very different assessments of the requirement for analgesia. In the current context, lameness scores are crude but clinically useful and widely employed. Manifestation of musculoskeletal pain may be obvious in the case of a single limb lameness, less so in mild multiple limb lameness, post surgically, or in cases of axial rather than appendicular pathology.

Box 1.

Types of Pain

Acute pain - Acute pain is the normal physiological response to application of a noxious stimulus. It is designed to be protective, being linked to the withdrawal reflex, preventing further tissue damage and triggering behavioural changes intended to maximise healing. This type of pain is typically of short duration, persisting only as long as the original insult. This is the type of pain associated with the early stages of tissue injury or surgery and is relatively easy to treat.

Chronic pain – this is pain that persists beyond the time frame expected for the relevant condition, a period of three to six months is often quoted. Thus may be due to acute injury or disease that is not resolving, ongoing degenerative conditions such as arthritis, or failure to manage acute pain adequately in the early stages of treatment. Achieving satisfactory analgesia can be extremely difficult in chronic pain states as the nervous system undergoes maladaptive changes – a process called neuroplasticity. This can result in sensitisation of the nervous system, when normally innocuous sensory input becomes perceived as painful (termed allodynia) or an exaggerated response to normally painful stimuli (termed hyperalgesia). Sensitisation may occur in both peripheral and central components of the nervous system and involves increased reactivity of peripheral nociceptors and central pain neurones, recruitment of additional nociceptors to generate pain signals and upregulation of pain receptor expression, so reinforcing the pain transmission pathways. In cases where chronic pain develops, pain ceases to become simply an indicator of a disease process and becomes part of the disease process itself. The longer pain is left untreated or inadequately controlled the more difficult it becomes to obtain a satisfactory outcome.

Neuropathic pain – this is pain caused by direct peripheral or central nerve injury resulting in hyperalgesia, allodynia and chronic, spontaneous ectopic generation of pain signals in the absence of any external stimuli.

Strategic Analgesia

A good analgesic plan will consist of systemically administered drugs, if possible in combination with local or regional analgesic techniques. Drugs chosen should ideally be those licensed for analgesia in the horse by the prescribed route, however licensed drugs administered by an unlicensed route, or unlicensed drugs may on occasion be indicated and appropriate. The key is in understanding the types of pain that may be present, the mode of action of the drugs that are available and how these drugs may be employed to maximise their effect on the case in question. In this way a multi-modal therapeutic plan can be formulated, incorporating the most appropriate drugs, designed to target as many aspects of the pain pathway as accurately as possible.

Systemic administration of analgesic agents in the short term is typically by the intravenous (IV) or intramuscular (IM) route, with oral medication often being relied on for more protracted courses of treatment. Whilst a combination of these routes will probably prove adequate in the majority of cases, other methods of drug delivery may allow for more effective provision of analgesia in specific cases.

The **oral-transmucosal** (OTM) absorption of some drugs can result in rapid uptake and high bioavailability as it avoids first pass metabolism which enterally absorbed drugs administered per os (PO) are subject to. Although potentially very effective, drugs administered this way may be swallowed or spat out, resulting in imprecise dosing, restricting this method to either highly concentrated formulations or highly potent drugs, where a small total volume can be given. Although several drugs can be effectively administered this way, only the alpha 2 agonist detomidine has a formulation licenced specifically for this route.

Transdermal drug delivery systems have been developed for a number of classes of drugs in the human market and include patches, creams and gels for external application designed to have either systemic or local effects. Transdermal drug absorption avoids first pass metabolism and gives the potential for prolonged drug administration with minimal patient handling. However drug uptake is highly dependent on sustained contact with the skin and that the area of application is healthy and has a good blood supply. Several human preparations have been evaluated in veterinary species and a specific veterinary formulation of fentanyl (licenced for use in dogs) is now available.

Epidural drug administration (Fig 1) provides the opportunity for a more targeted effect and is becoming more commonly employed. Use of local anaesthetics, alpha 2 agonists, opioids, ketamine and tramadol has been reported in the horse by this route. Depending on the characteristics of the drug, there will be varying systemic uptake, and onset and duration of effect may differ significantly from those familiar from conventional systemic administration, which can be advantageous. For prolonged analgesia, epidural catheters can be placed which facilitate provision of extended

targeted pain management (Fig 2). Commercial kits (Fig 3) for this procedure are available (~~Fig 3~~ B Braun Medical Ltd, Yorkshire, UK; Smiths Medical, Kent, UK) and have been used successfully in several cases at the author's hospital. These catheters require very careful management, with maintenance of patency and sterility being the main problems, however with proper management it is possible to maintain these in situ for up to 10 days in clinical cases.

Diffusion (soaker) catheters offer the potential for prolonged, precise administration of local anaesthetic agents. Their potential has yet to be fully realised and they are discussed in more detail below with local anaesthetic drugs.

With the high prevalence of developmental, degenerative and traumatic disease affecting the joints of horses, as well as the frequency of diagnostic and therapeutic surgical procedures involving joints and other synovial structures, **intra-synovial** administration of analgesic agents is an attractive and effective method of achieving targeted pain relief. Administration of a number of drugs by this route has been described, including morphine, corticosteroids and local anaesthetic agents.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

~~The first line and mainstay of analgesia provision, t~~There are several non-steroidal anti-inflammatory drugs licenced for use in horses in the UK and these often form the first line and mainstay of analgesia provision. Action is by inhibition of cyclo-oxygenase enzymes both peripherally and centrally, thereby interrupting the arachidonic acid cascade that results in production of prostacyclin, prostaglandins and thromboxanes. These substances are potent inflammatory mediators, which result in sensitisation and recruitment of peripheral nociceptors and transmission of central pain pathways. Many disease processes and certainly surgical interventions will induce an inflammatory response, so incorporating an anti-inflammatory drug is eminently appropriate.

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Many are available for administration by IV injection and as powders and/or pastes for oral administration, making them convenient for both acute and chronic pain management, although palatability may be problematic with some of the powdered preparations designed to be mixed with food. Choice largely comes down to familiarity, availability and cost. Anecdotally, some horses will respond better to one than another so it may be worth trying an alternative if response to one is unsatisfactory. Data sheets tend to advise leaving 24 hours between dosing if changing to an alternative to avoid inadvertent overdose. The potential for toxicity also need to be considered in the context of long term treatment, particularly as this may be continued by the owner of the horse for extended periods, outside the direct control of the veterinary surgeon. Doses should be carefully calculated and dosing regimes clearly stipulated. Toxicity may manifest as blood dyscrasias and gastrointestinal ulceration, with the glandular region of the stomach, proximal duodenum and right dorsal colon being particularly affected. Renal papillary necrosis has also been reported in horses receiving clinically relevant doses of phenylbutazone (Read 1983). This is particularly relevant as the aminoglycoside antimicrobial gentamicin, commonly used as a first line treatment in cases of synovial sepsis is also known to be nephrotoxic.

Paracetamol (acetaminophen)

Veterinary licensed oral preparations of paracetamol are available for dogs (in combination with codeine) and pigs in the UK, but not horses. This is not a typical NSAID and the exact mechanism of action is undetermined but thought to act centrally on serotonergic, opioid, nitric oxide and cannabinoid pathways as well as effects on prostaglandin production (Sharma and Mehta 2013). Its successful use as an adjunctive analgesic medication has been reported (20mg/kg PO twice daily) in a laminitic pony showing pain refractory to NSAIDs, lidocaine and morphine analgesia (West and others 2011).

Corticosteroids

Corticosteroids act by~~By~~ inhibiting both cyclo-oxygenase and lipoxygenase pathways of the arachidonic acid cascade, ~~these drugs~~ exerting potent anti-inflammatory activity as well as a wide range of other effects. Most commonly utilised when discrete foci of inflammation can be precisely targeted using small volumes, such as vertebral or limb synovial or ligamentous structures. Methylprednisolone and dexamethasone are licenced for systemic and intra-synovial use in horses. Data sheets invariably carry warnings about the risk of inducing or exacerbating laminitis and total dose and frequency of administration should be carefully considered. Triamcinolone although not licenced is also frequently used.

Opioids

This is a versatile group of drugs offering IV, IM, OTM, transdermal, epidural and intra synovial routes of administration. Action is primarily by central modulation of the pain pathways although opioid receptors are also present outside the central nervous system~~CNS~~ in tissues such as the myenteric plexus and synovial membranes, with expression being upregulated in inflammatory states.

Butorphanol, pethidine and buprenorphine are licensed for use in horses in the UK and all demonstrate different receptor activity and affinity.

Pethidine (meperidine) is a mu receptor agonist, making it potentially the most efficacious of the licenced options. Used at 1mg/kg IM it was shown to improve experimentally induced foot lameness, but only at 2-3hrs post administration (Foreman and Ruemmler 2013). Despite its theoretical promise, several factors limit its clinical utility. It is only licenced as a visceral analgesic, IV administration is contra-indicated due to potential for histamine release and seizure-like activity, it can cause pain on IM injection and large volumes need to be injected due to its low potency. It is

also a Schedule 2 Controlled Drug, with the associated administrative requirements. Epidural administration of pethidine (0.8mg/kg) has been reported, giving a fast onset (12 minutes) and 4 to 5 hour duration of action (Skarda and Muir 2001).

Buprenorphine (a Schedule 3 Controlled Drug) is a partial mu agonist, with some potentially attractive attributes and is licenced for post-operative analgesia at a dose of 10µg/kg IV. It is highly potent, requiring small volumes of administration and somatic analgesia of 6hrs duration (assessed experimentally using thermal threshold testing) is reported at this dose (Carregaro and others 2007). Buprenorphine also shows very good absorption by the OTM route, facilitating administration to needle shy horses. A sublingual dose of 6µg/kg is reported to have produced effective sedation and analgesia lasting up to 12hrs in a case of trauma-associated musculoskeletal pain (Walker 2007). The author has used it with apparent good effect by this route. Data sheet recommendations state buprenorphine should only be administered after an intravenous sedative agent and cardiovascular stimulation and locomotor excitement lasting for over 12hours have been reported following the recommended dosing regimen (Carregaro and others 2006, 2007) and the author has seen horses compulsively box-walking following use in clinical cases.

Butorphanol is a mu receptor antagonist and kappa receptor agonist. Whilst analgesia is reported as excellent or good in clinical colic cases (Stout and Priest 1986), it does not perform so well for somatic pain. In experimental horses Kalpravidh and others (1984a, 1984b) demonstrated only moderate analgesia lasting 15-30 minutes, assessed using thermal threshold testing. Increased heart rate and locomotor activity may also be seen, although in the author's experience this is not as marked as that seen following buprenorphine administration. Epidural administration of butorphanol failed to produce detectable analgesia (Natalini and Robinson 2000), suggesting that horses do not possess kappa receptors in the spinal cord. It is then logical to assume that kappa agonists will only have a supraspinal effect.

Unlicenced opioids.

In the author's hospital, morphine (0.1-0.3mg/kg) is routinely given systemically (IM and IV) for perioperative analgesia and managing pain not controlled by NSAID administration. Morphine and methadone are also administered regularly by the epidural route for painful hindlimb orthopaedic conditions. Epidurally, morphine (0.1–0.2 mg/kg) (Sysel and others 1996, Goodrich and others 2002) shows a slow onset (up to 6 hours) and a duration of action of around 5 hours (Natalini and Robinson 2000), but can possibly last up to 12 - 18 hours. Epidural methadone (0.1mg/kg) has an onset of around 15 minutes and lasts about 5 hours (Olbrich and Mosing 2003). In the author's hospital it is routine to combine methadone and morphine (0.1mg/kg of each) to obtain the theoretical advantage of providing rapid onset of analgesia with extended duration in the acute setting. Methadone also has activity at the N-methyl-D-aspartate (NMDA) receptor, therefore has an additional mechanism for contributing to analgesia. Where sustained provision of targeted analgesia is required, morphine can be administered at 0.1-0.2mg/kg twice daily via an indwelling epidural catheter. It is important to ensure strict aseptic technique and that preservative free solutions are used where possible.

Intra-synovial administration of 0.05mg/kg morphine has also been demonstrated to provide analgesia for potentially 24 hours in experimentally induced radio-carpal joint synovitis (Lindegaard and others 2010a and 2010b).

The availability of fentanyl patches offers the attractive prospect of providing extended opioid analgesia with minimal intervention. Maxwell and others (2003) showed rapid uptake by the transdermal route with all horses exceeding the 1ng/mL plasma level consistent with that reported to provide analgesia in other species, which was maintained for 32 hours. Orsini and others (2006) examined the pharmacokinetics of transdermal fentanyl using commercially available patches targeted to deliver 60µg/kg and found a large variation in onset of absorption (up to 5 hours), time to peak concentration (8.5-14.5 hours) and maximum plasma concentration achieved (0.67-

5.12ng/mL). One third of horses failed to achieve the 1ng/mL plasma concentration considered to be analgesic. A large variation in onset, maximum concentration (0.1-28.7ng/mL) and time to maximum concentration (8-24 hours) has also been reported in neonatal foals treated with fentanyl patches designed to deliver 100µg/hr (Eberspacher and others 2008). The site of patch application is known to affect the rate and uptake of transdermally delivered fentanyl (Mills and Cross 2007). Combination therapy with NSAIDs has been reported in clinical cases refractory to NSAID treatment alone (Thomasy and others 2004). Again, a large variation in maximum concentration and time to achieve this were reported, but some, although weak, evidence of analgesic effect was claimed. A solution of fentanyl (50mg/mL) is licenced for transdermal use in dogs where it is claimed to provide analgesia for a minimum of 4 days post-application, but this has not been evaluated in horses at the time of writing.

Alpha 2 adrenergic agonists

Frequently used as sedative agents, ~~these~~ alpha 2 agonist compounds also provide analgesia by a mechanism similar to, and synergistic with, that of the opioids (Hellyer and others 2003). Duration and quality of analgesia is controversial (England and Clarke 1996), but appears to be better for visceral, rather than somatic pain. Some authors have reported no detectable influence on somatic analgesia (Elfenbein and others 2009), whilst others have found that the effect depends not only on the drug used, but also on the type of stimulus applied (Moens and others 2003, Rohrbach and others 2009). Given systemically, analgesia is best considered to be of short duration, peaking later than sedative effects and not lasting as long, making them of most use during surgical procedures.

All alpha 2 agonists have profound effects on the cardiovascular system which should also be taken into account, as should the difficulty of assessing adequate analgesia in a sedated animal.

Epidurally, xylazine (0.17mg/kg up to 0.25mg/kg) is safe and effective (LeBlanc and Carron 1990; Skarda and Muir 1996; LeBlanc and others 1998). Detomidine (30µg/kg) in combination with 0.2mg/kg morphine produces analgesia (Skarda and Muir 1996, Sysel and others 1996, Goodrich and others 2002) and reduces post-operative lameness after hindlimb surgery (Sysel and others 1996, Goodrich and others 2002). High lipid solubility facilitates systemic absorption from the epidural space, especially of detomidine (Skarda and Muir 1996), causing sedation following epidural administration. Loss of tail and perineal muscle tone may become evident due to local anaesthetic-like properties (particularly with xylazine). Onset is rapid (approximately 12 minutes) and duration of effect is 2.5-3.5 hours (LeBlanc and others 1998, Skarda and Muir 1996).

Local Anaesthetic Agents

Local anaesthetics have the potential to completely abolish pain by interrupting neuronal signal transmission, rather than just obtunding it. They affect both sensory and motor neurons, consequently their use will not be appropriate for all sites of pain or surgery, but where applicable they offer considerable benefit. They can be administered topically, perineurally, epidurally, intra-synovially, systemically and directly infiltrated into tissues. Mepivacaine, lidocaine and procaine are all licenced for use in horses in the UK. Of these, only mepivacaine is supplied without adrenaline or preservative and is licensed for infiltration, perineural, intra-articular and epidural administration, making it an extremely versatile preparation. Lidocaine without adrenaline is also available from pharmaceutical suppliers as a 2% solution for injection and as a 0.2% solution in 5% glucose for IV infusion, but not licenced for use in horses.

Lidocaine administration has been described by continuous IV infusion (loading dose of up to 2mg/kg followed by infusion at 50µg/kg/minute). Its use in this manner is most often associated with gastrointestinal tract surgery, however somatic analgesia as assessed by thermal threshold testing has been demonstrated experimentally (Robertson and others 2005).

Epidurally, care needs to be taken with the total volume injected to avoid cranial spread which may impair motor function to the hindlimbs (Goodrich and others 2002, Olbrich and Mosing 2003). Preservative free preparations of bupivacaine 0.5%, lidocaine 2% and mepivacaine 2% solutions (5-10mL) have been used by the author.

Transdermal patches containing 5% lidocaine are used to treat a range of chronic neuropathic and musculoskeletal pain in humans, with systemic uptake having been proven. Application of two 700mg patches to the limbs of horses for 12 hours failed to demonstrate systemic uptake in a study by Bidwell and others (2007). Doubling the number of patches for 24 hours gave variable systemic uptake (Andreoni and Giorgi 2009). If the skin was subjected to an alcohol scrub prior to patch placement there was a tendency for a more rapid and pronounced, but less sustained uptake. Antinociceptive effects assessed by pricking the skin under the patch at removal showed no difference in sensation between horses which had had a patch applied and control animals. This application therefore appears to be of little benefit.

Diffusion catheters (Fig 4) are another method of providing targeted pain relief. These are available commercially -(~~Fig 4~~Mila International Inc, Kentucky, USA) or can be improvised from narrow gauge plastic tubing or intravenous cannulae. The use of these for prolonged perineural administration of lidocaine, mepivacaine and bupivacaine to the palmar metacarpal nerves has been investigated experimentally in horses (Driessen and others 2008). Although regional anaesthesia was achieved, significant oedema developed, necessitating discontinuation of the infusions, limiting their clinical potential. Alternatively, catheter implantation during wound closure, allowing local anaesthetic to be instilled directly at the surgical site for post-operative pain management has been described in small animals (Abelson and others 2009) with no associated risk of wound complications and has been successfully used in horses at the author's hospital to provide analgesia for 48 hours following surgical resection of thoracolumbar ~~dorsal~~ spinous processes (Fig 5).

Prolonged intra-synovial administration of local anaesthetic agents in human patients has been associated with chondrolysis, with bupivacaine appearing to exhibit the greatest degree of chondrotoxicity. This effect appears to be dose and time dependent, being particularly pronounced with formulations containing adrenaline. Consequently a number of local anaesthetic agents have been tested in animal models and chondrocyte cultures, with mixed results; *in vitro* results not always supporting *in vivo* ones (Webb and Ghosh 2009; Dragoo and others 2010). An *in vitro* study of bupivacaine, lidocaine and mepivacaine on equine chondrocyte cultures showed mepivacaine to be the least chondrotoxic, with cell viability on exposure to this agent approaching that of the saline control (Park and others 2011). Single intra-synovial injection of local anaesthetic solution is performed regularly at the author's hospital to provide targeted pain relief following arthroscopic surgery, with no apparent problem.

Ketamine

Used at sub-anaesthetic doses, this NMDA receptor antagonist has potent analgesic properties and may counteract central sensitization, so making it potentially useful in the management of chronic as well as acute pain. Infusions of 0.4 and 0.8mg/kg/hour have been shown to be tolerated well in conscious horses, with excitement seen at 1.6mg/kg/hour, although no somatic analgesia was demonstrated (Fielding and others 2006). Peterbauer and others (2008) however, did demonstrate analgesic properties in conscious horses after 0.6mg/kg IV bolus followed by 20µg/kg/minute infusion. Analgesia is mainly somatic rather than visceral and is mediated by a number of mechanisms in addition to NMDA receptor activity. In addition to infusion administration, IM bolus dosing at 0.2-0.5mg/kg has been practiced by the author to manage acute episodes of pain, or acute-on-chronic episodes in cases of laminitis or following surgical intervention. Epidural administration (0.5, 1.0 and 2.0mg/kg) has been shown to provide analgesia lasting 30 to 75 minutes (De Segura and others 1998).

Tramadol

Tramadol is a synthetic analogue of codeine which has been used in the management of acute and chronic moderate to severe pain in humans. It is a centrally acting analgesic that has agonist activity at mu opioid receptors and also inhibits the reuptake of noradrenaline and serotonin. Although ~~N~~not licenced in the horse, ~~but~~ the pharmacokinetics and pharmacodynamics of intravenously, intramuscularly and orally administered tramadol ~~in horses~~ have been investigated in this species (Shilo and others 2007, Cox and others 2010, Dhanjal and others 2009, Knych and others 2013a 2013b, Giorgi and others 2007, Stewart and others 2011). ~~Tramadol is a synthetic analogue of codeine which has been used in the management of acute and chronic moderate to severe pain in humans. It is a centrally acting analgesic that has agonist activity at mu opioid receptors and also inhibits the reuptake of noradrenaline and serotonin.~~ Minimum plasma tramadol levels which provide analgesia in people vary greatly between 100 and 600ng/mL, with much of the analgesic effect of tramadol being attributed to the M1 metabolite (O-desmethyltramadol) which has 200 times the affinity for the mu opioid receptor than the parent drug. In people there is genetically predetermined variation in the ability to produce this metabolite, making some individuals poorly responsive to the drug. It is unknown whether this is also true in horses, although a large individual variation in plasma concentrations of MI (and several other metabolites) has been demonstrated (De Leo and others 2009, Knych and others 2013a, 2013b, Giorgi and others 2007). Oral bioavailability following a 5mg/kg dose has been reported as approximately 65% in fasted horses, increasing to approximately 85% in fed horses (Giorgi and others 2007), whilst Shilo and others (2007) reported only 3% following 2mg/kg administered to fasted horses. Knych and others (2013a) used doses of 3, 6 and 9mg/kg PO which showed a very wide variation in plasma levels, with only the 9mg/kg dose consistently achieving plasma concentrations within the human analgesic range. No adverse events were reported apart from mild signs of colic and increased pacing behaviour in 1 horse at the higher

dose. Intramuscular administration of 2mg/kg resulted in rapid and complete absorption with attainment of useful plasma concentrations and no adverse effects (Shilo and others 2007). Cox and others (2010) and Shilo and others (2007) reported side effects including ataxia, muscle twitching and sweating for 15 minutes after 2mg/kg IV and Giorgi and others (2007) reported confusion, agitation, tremor and tachycardia after 5mg/kg IV but not PO. Dhanjal and others (2009) reported side effects following 2mg/kg IV and were unable to demonstrate an antinociceptive effect using a noxious thermal stimulus. Guedes and others (2012) administered 5mg/kg PO twice daily to horses with chronic laminitic pain and showed only weak evidence of analgesia, whilst ketamine showed a much greater effect. Epidural administration of 1mg/kg tramadol produced analgesia after 30 minutes with effects lasting for 4 hours (Natalini and Robinson 2000).

Gabapentin

Originally used as an adjuvant anticonvulsant, ~~it~~ gabapentin was subsequently shown to be effective in treating a range of chronic pain syndromes in people. It is a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) but neither parent drug nor metabolites show affinity for, or activity at $GABA_A$ or $GABA_B$ receptors. The major mechanism of action is currently thought to be via voltage dependent calcium channels, thereby reducing neurotransmitter release (Kong and Irwin 2007). Pharmacokinetics of a single dose of 5mg/kg PO (Dirikolu and others 2008) and 20mg/kg PO and IV (Terry and others 2010) have been evaluated in horses. No adverse events were noted after either dose or route of administration although sedation was evident for 1 hour after the IV dose. Rapid but poor absorption (compared with humans, rats, dogs and monkeys) followed PO administration with a bioavailability of only 16% following the higher dose. ~~Not~~ Gabapentin is not licensed for veterinary species but there ~~is a~~are case reports of its use in horses. Davis and others (2007) describe its use in a heavily pregnant mare with suspected neuropathic pain ~~(Davis and others 2007)~~ at 2.5mg/kg PO every 8 hours, increasing dosing interval over 6 days, with apparent beneficial

effect and no detriment to the foetus. It is also reported as a component of a multimodal approach to provision of analgesia in the management of severe laminitis associated hoof pain, at doses between 3.3mg/kg every 8 hours and 2mg/kg every 12 hours PO (Dutton and others 2009).

Bisphosphonates

Bisphosphonates have been shown to reduce pain in human patients with osteoarthritis and cancer pain and improve joint mobility. These drugs inhibit osteoclast proton secretion, reducing the acidity of the microenvironment associated with bone resorption, so reducing activation of acid sensitive ion channels in sensory neurons. A direct anti-inflammatory effect is also demonstrated by inhibiting osteoblast secretion of vascular endothelial growth factor, reducing cytokine release from activated macrophages (Silvina and Barbara 2014). Tiludronic acid is licenced for treatment of inflammatory and degenerative joint disease in horses at a dose of 1mg/kg by intravenous infusion over 30 minutes. Improvement of lameness in horses suffering from bone spavin (Gough and others 2010) and navicular disease (Denoix and others 2003) has been demonstrated in tiludronate treated horses.

Isoxsuprine hydrochloride is licenced for the treatment of navicular disease in horses. Its action causes vasodilation, lowers blood viscosity and inhibits platelet aggregation, thereby potentially improving circulation in the affected area. Some, but inconsistent evidence of clinical efficacy has been shown (Rose and others 1983; Turner and Tucker 1989).

Conclusion

The World Health Organisation 'pain ladder' (Fig 6) describes a graded approach to administration of analgesic agents, combined with adjunctive therapies and provides a useful framework to follow for pain management. Originally designed to provide guidance managing cancer pain in people, is now much more widely applied. The number of drugs available for use in horses is limited, however by

understanding the action of what is available and adopting a multi-modal approach, additive or synergistic activities can be exploited to maximise effect whilst minimising the risk of side effects. Adjunctive therapies can equally be vital in achieving a successful outcome (Fig 7). These range from simple bandaging, hot and cold compresses or using ice, physiotherapy, acupuncture, corrective or remedial farriery up to surgical interventions such as hoof wall resection, and salvage procedures such as neurectomy (sometimes in conjunction with fasciotomy) and arthrodesis. Novel attributes of drugs used for other indications can also be exploited for good effect, for example the use of tricyclic antidepressants for chronic pain management in people and small animals. However evidence of safety and efficacy in the horse in this regard is often lacking.

Quiz

1. In addition to being a general anaesthetic agent, ketamine provides profound analgesia via its action at NMDA receptors. Which of the following drugs also has NMDA receptor activity?
    a) Gabapentin
    b) Methadone
    c) Paracetamol
    d) Tramadol

2. Which of the following statements is **true** of alpha 2 agonists?
    a) They provide reliable somatic analgesia
    b) The analgesia they provide lasts as long as the sedative effects
    c) They are all licensed for administration by the oral transmucosal route
    d) It is possible to achieve sedation by administering them into the epidural space

3. The following classes of drugs can effectively be administered epidurally, **except** for which one?

a) Alpha 2 agonists

b) Non-steroidal anti-inflammatories

c) Opioids

d) Local anaesthetics

4. Which of the following statements is **true** regarding intra-synovial administration of analgesic agents?

a) Local anaesthetics should never be used due to their chondrotoxic effects

b) There are no drugs licenced for use by this route in the horse

c) Total dose of corticosteroids should be restricted due to the potential for adverse systemic side effects

d) There are no opioid receptors present in synovial tissue therefore these drugs will not be effective by this route

Answers: 1 b), 2 d), 3 b), 4 c).

Contributorship

The author is the sole contributor to this article and accepts responsibility for its content.

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Further reading

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Figure 1.

Epidural injection (here shown being performed at the sacro-coccygeal/first inter-coccygeal space) is a useful technique for achieving more targeted drug delivery. It is important to observe good hygiene and where possible to use preservative free drugs.

Figure 2.

Epidural catheter placed at the sacro-coccygeal/first inter-coccygeal space. Note the bacterial filter and sterile dressing to maintain cleanliness. With appropriate care, these can be maintained for several days for extended pain management without the requirement for repeated needle puncture.

Figure 3.

Commercially available epidural catheter kits. Several makes are available and contain all the necessary components.

Figure 4.

Commercially available wound diffusion catheters. These are available with different diffusion lengths so can be chosen to suit the extent of the surgical field. Home-made ones can be constructed from long intravenous cannulae or dog urinary catheters.

Figure 5.

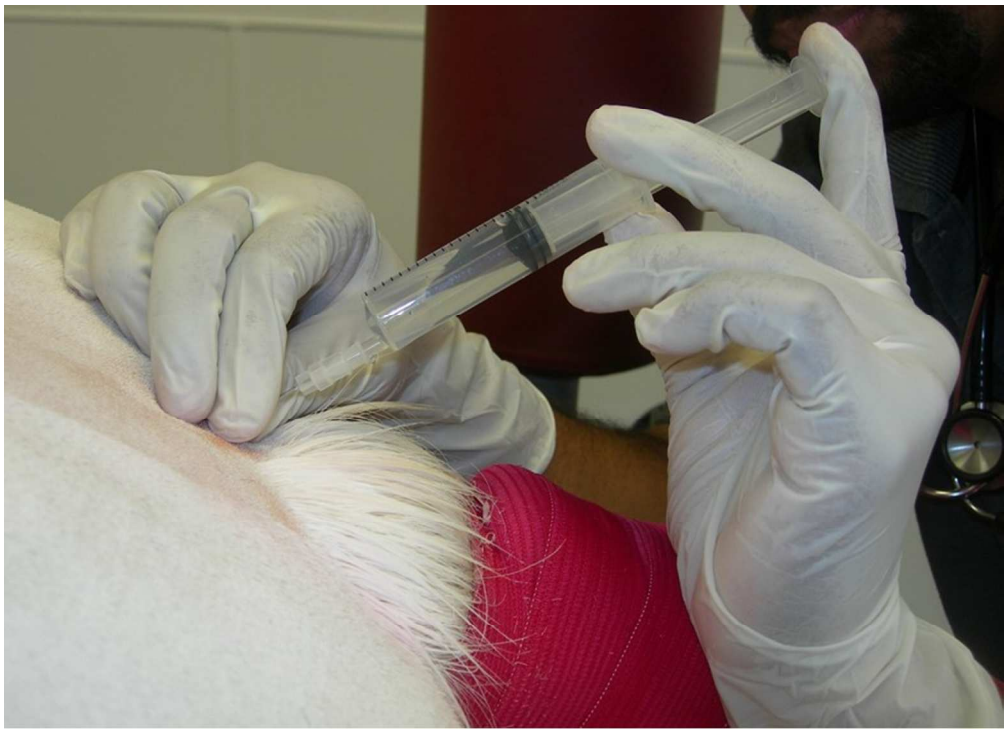
Commercial wound diffusion catheter in-situ following ~~dorsal~~ spinous process resection. The catheter is placed during wound closure and exited through a stab incision distant from the surgical site. Note the bacterial filter to preserve sterility of injected local anaesthetic agent.

Figure 6.

World Health Organisation 'Pain Ladder'. Originally designed for guidance in managing cancer pain in people, it describes a logical, progressive approach to provision of analgesic agents when managing many types of clinical pain.

Figure 7.

Severe case of laminitis. These cases can be extremely challenging to manage, often presenting with complex pain that is refractory to conventional analgesic protocols. Adjunctive approaches are as important as pharmacological therapy, with hoof wall resection and provision of adequate mechanical support illustrated here.



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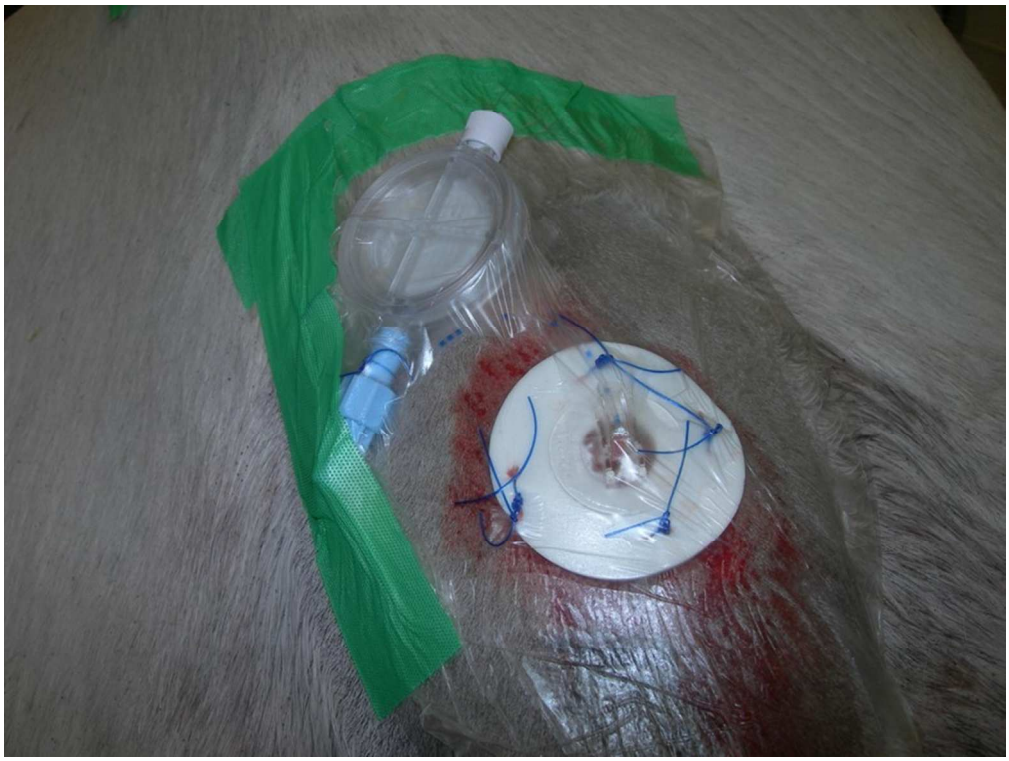

Epidural catheter placed at the sacro-coccygeal/first inter-coccygeal space. Note the bacterial filter and sterile dressing to maintain cleanliness. With appropriate care, these can be maintained for several days for extended pain management without the requirement for repeated needle puncture.

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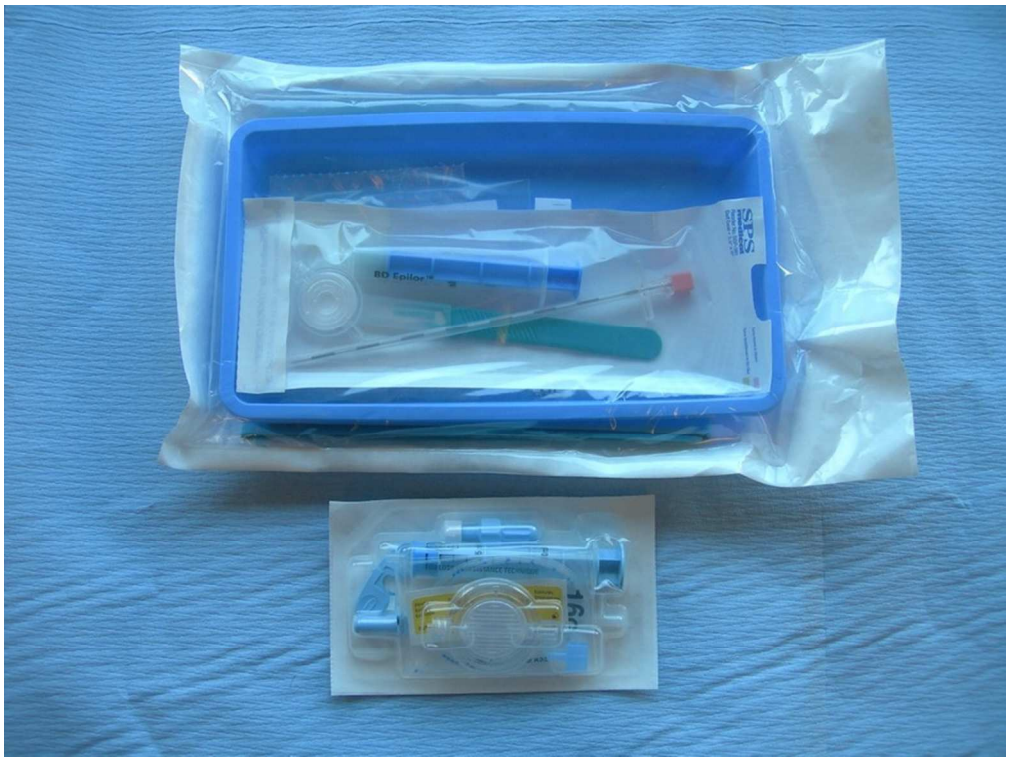

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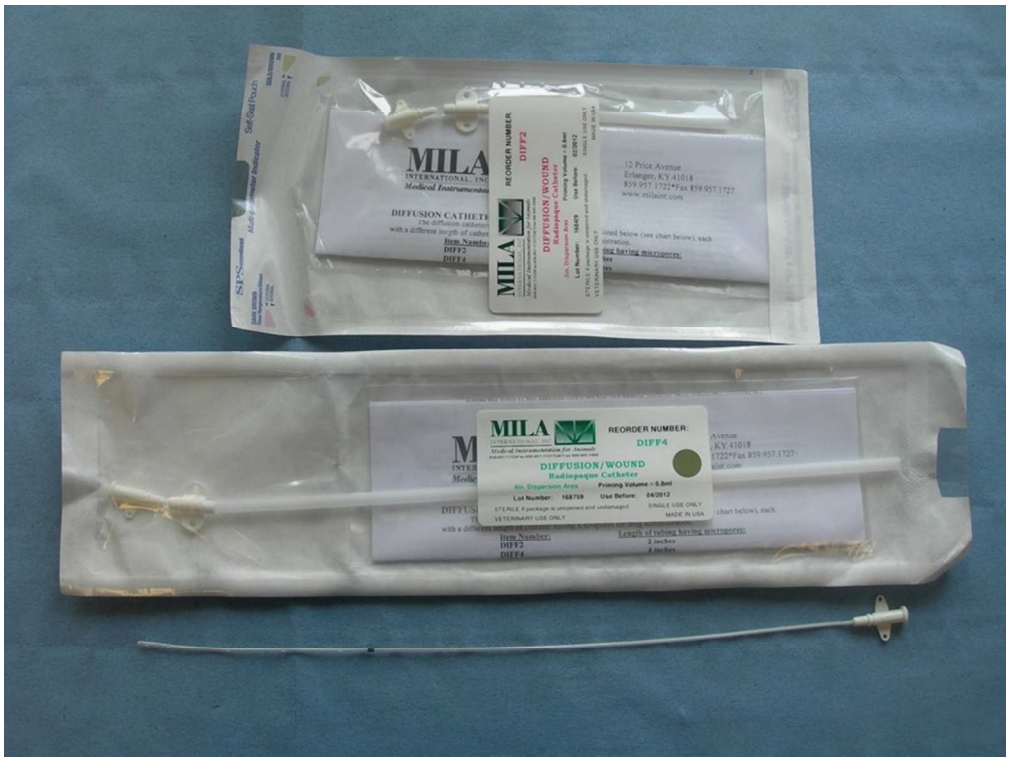

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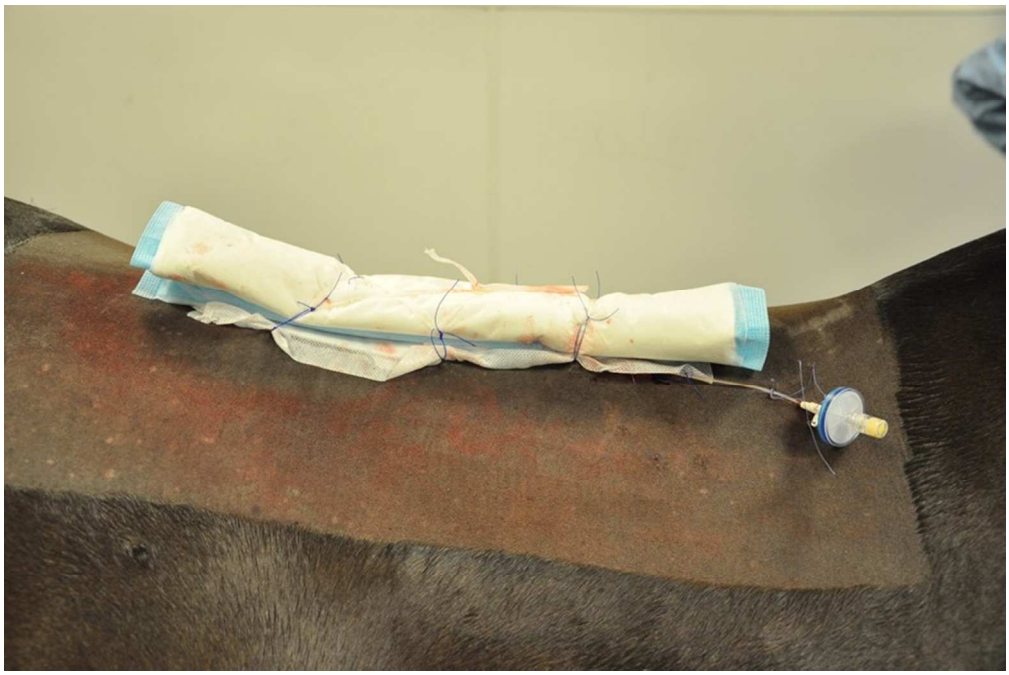

Commercial wound diffusion catheter in-situ following spinous process resection. The catheter is placed during wound closure and exited through a stab incision distant from the surgical site. Note the bacterial filter to preserve sterility of injected local anaesthetic agent.

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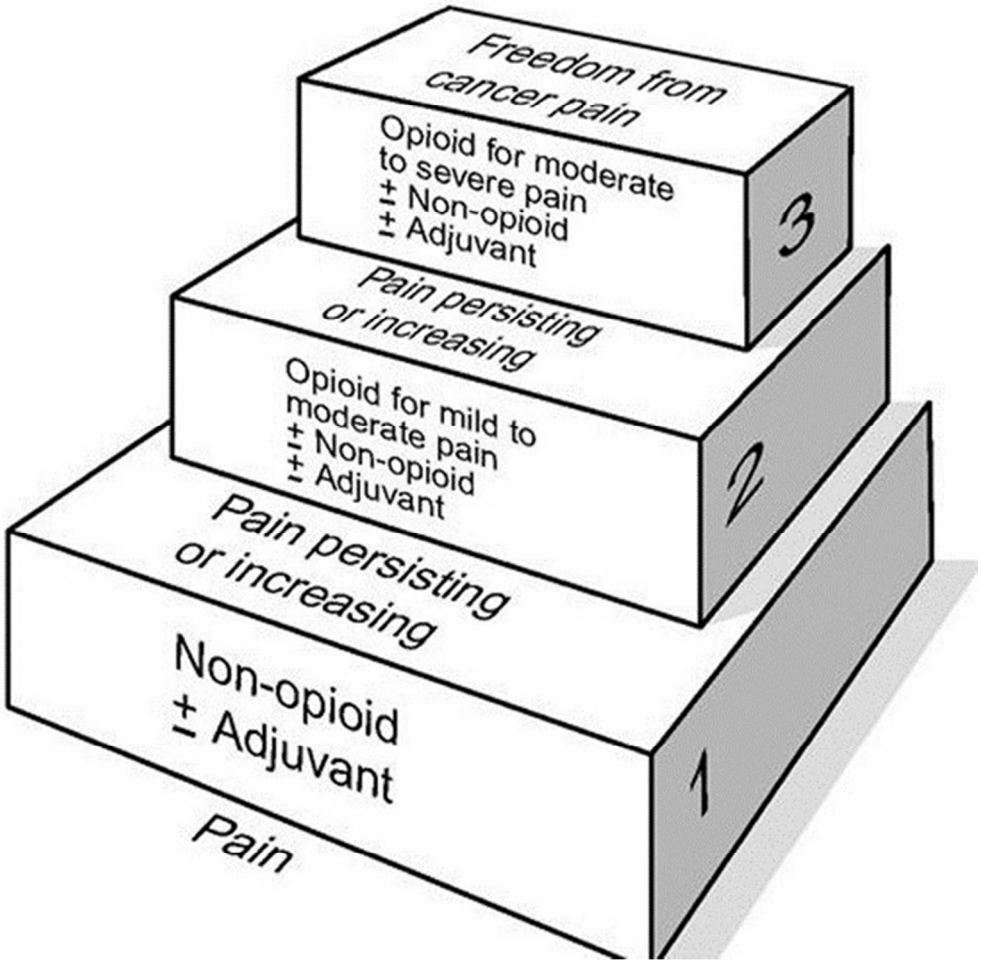

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109x104mm (150 x 150 DPI)

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