UPDATE ON NOVEL ANALGESIC FORMULATIONS
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Key Points
- Many novel analgesic formulations developed for human use are not practical or effective in veterinary patients
- Available or pipeline novel analgesic formulations for veterinary patients are targeted towards extended delivery or ease of administration
- Some novel analgesic formulations revolve around “old” analgesics (e.g. opioids) in a novel delivery matrix; however, while the drug may be effective, the delivery matrix may not have been tested in all species
- Care is advised in extrapolating data on effectiveness of novel formulations between species

The ideal analgesic formulation would be effective against a broad range of pain types; have a rapid onset and controllable duration; be free of undesirable side effects such as respiratory depression, sedation, etc.; lack clinically problematic metabolites; and be readily accessible and cost-effective. Perhaps most importantly in veterinary medicine, the “ideal” analgesic would also be easy and safe to administer, with a dosing interval that is extended enough to be convenient to the practitioner as well as to the owner at home. One of the barriers to finding the “ideal” analgesic is a current deficiency in drug delivery technology. Many of the currently available analgesics are effective, e.g. opioids, but are not formulated in delivery systems that provide steady-state analgesia or extended duration in veterinary patients. The pharmaceutical industry has made a focused effort to improve drug delivery systems by incorporating known analgesics, e.g. morphine, into novel delivery matrices. This focus has been largely driven by the human analgesic market, and many of these technologies are essentially variations on patient-controlled analgesia which is not practical in veterinary medicine. This lecture will summarize the most relevant novel analgesic formulations that have potential or current use in veterinary medicine.

Topical Drug Delivery Systems:
Topical analgesics deliver drug locally to underlying tissue when they are applied directly over the area of interest. In most cases, insignificant serum concentrations of drug are attained, making topical systems relatively free of side effects. Because these topical agents are designed for penetration of human skin, their efficacy in veterinary patients is uncertain and many products have yet to be tested or studied in the veterinary population.

One product that has received acceptance in veterinary medicine as a topical local anesthetic is EMLA cream. EMLA is a eutectic mixture of lidocaine and prilocaine. Application of EMLA cream to skin allows for a high concentration of the local anesthetic drugs at the site of catheter placement, without systemic absorption. EMLA has been shown to decrease the percentage of cats that require sedation for jugular catheter placement, without producing measurable serum concentrations of the local anesthetic. Application of EMLA to shaved skin of dogs, followed by a 20-30 minute period during which the area is covered with a simple occlusive dressing (e.g. tegaderm covered with vetwrap) in order to ensure continued contact of the EMLA with the skin, substantially reduces struggling during catheter placement in unsedated or lightly sedated animals.

The lidocaine patch also relies on drug being absorbed across the skin for local delivery to a painful area, with minimal systemic uptake or risk of toxic side effects. Lidocaine is a sodium channel blocker that is most effective against rapidly firing ectopic impulses that are generated from
injured neurons. The Lidoderm 5% patch® was recently approved by the FDA for treatment of post-herpetic neuralgia in humans. A recent Pubmed search could not identify any studies that have been performed in companion animals on analgesic efficacy of the lidocaine patch. One study demonstrated a lack of systemic absorption of lidocaine (as measured by ELISA) after 2 lidocaine 5% patches were placed on the carpi of healthy horses, but analgesia was not evaluated.

Many topical NSAIDs have been developed in human medicine, with the primary advantage being that peak plasma concentrations of the drug are < 10% of those that occur after oral intake of NSAIDs, therefore reducing the adverse side effect profile associated with this class of drugs. In veterinary medicine, the only commercially available topical NSAID is Surpass®. Surpass® is a 1% diclofenac cream that has been shown to be effective against pain in horses, secondary to osteoarthritis, when applied directly over the affected joint. Other studies have confirmed the analgesic efficacy of Surpass® in experimentally induced osteoarthritis and in horses with inflammation associated with regional limb perfusion. Application of Surpass® to skin does result in measurable urinary and serum concentrations of diclofenac for up to 10 days, thus its use should be undertaken with knowledge of the clearance times in horses that are in active competition and that may be tested for NSAID administration.

Capsaicin, derived from red chili peppers, has long been attributed to have analgesic properties. The mechanism by which topical capsaicin may provide analgesia is thought to be mediated via depletion of substance P stores in nerve endings. When applied topically capsaicin causes release of substance P from C fiber sensory afferents in that area; with repeated topical application, in theory, substance P stores within C fibers become depleted, thereby reducing nerve signaling from the sensory neuron. Capsaisin cream (Equiblok®) has recently gained some popularity for the treatment of localized osteoarthritis in horses, however, there is no evidence that the 0.2% capsaicin cream penetrates equine skin. Repeated topical application may cause skin irritation. Eye irritation can occur if the horse rubs its face near the area of application or if the person who applied the cream by hand rubs their eye afterward. There are no scientifically controlled published studies of the effectiveness of topical capsaicin cream for pain in horses with osteoarthritis.

Transdermal Delivery Systems:

Unlike topical drug delivery systems, transdermal drug delivery centers on systemic uptake of the drug to create its analgesic effects. Because of systemic uptake, dose-dependent side effects are of similar concern as for parenteral routes of administration. Transdermal formulations, however, offer the advantages of convenient “at home” catheter-free drug delivery, as well as an extended duration of effective use. The fentanyl patch is the most well-known transdermal analgesic formulation in veterinary medicine, and can no longer be considered novel, so will not be covered here.

The buprenorphine patch has been evaluated to a limited extent in veterinary patients. This patch (Purdue Pharma, Cranberry NJ) was recently approved by the FDA for the treatment of moderate to severe pain in people. The patch is commercially available in sizes that deliver 35, 52.5 or 70 mcg/hour. Like the fentanyl patch, the buprenorphine patch should deliver drug at a relatively constant rate in a convenient formulation without the risk of first-pass metabolism. In one study in cats, serum concentrations of drug were variable between individuals after placement of a 35 mcg/hour patch, but all cats had absorbed measureable buprenorphine concentrations by 6 hours after patch placement and some cats showed typical signs of opioid-induced euphoria. A recent study in dogs also reported variable serum drug concentrations after a 70 mcg/hour buprenorphine patch was placed, and some dogs were very low absorbers. From limited data available, it appears that the buprenorphine patch deserves further clinical investigation.
Transmucosal Drug Delivery:

Like transdermal formulations, transmucosal drug administration offers ease of use while achieving therapeutic serum concentrations of drug. Therefore, side effects of systemic drug administration pertain to transmucosal routes of delivery. Of available analgesics, buprenorphine and methadone have been studied in veterinary patients for transmucosal use.

Buprenorphine has been extensively studied in cats as a transmucosal analgesic, with limited studies being reported in dogs. Buprenorphine has close to 100% bioavailability when administered transmucosally to cats. Higher bioavailability in cats compared to other species is partially explained by differences in oral pH. Oral pH of cats has been reported to range from 8 to 9, whereas humans have an oral pH ranging from 5.4 to 7.5. Buprenorphine is a weak base with a pKa of 8.24. Therefore, a high percentage of the drug would exist in the unionized form in the feline oral cavity, enhancing its absorption. Reports of the analgesic efficacy of transmucosal buprenorphine in cats are variable, and likely relate to dose, the analgesic test, and other medications that may have been used. In dogs, transmucosal buprenorphine has very limited use. At doses of 0.12 mg/kg (3-10 times the parenteral dose), bioavailability is ~ 50%, with plasma concentrations being similar to an IV dose of 0.02 mg/kg. Given the relatively large volume of buprenorphine that would need to be administered to a dog to achieve a dose of 0.12 mg/kg transmucosally, and given the relatively low bioavailability reported in this study, oral transmucosal buprenorphine is probably not a practical or cost-effective analgesic option for dogs.

Methadone has physicochemical properties similar to buprenorphine, with a similar pK and therefore similar potential bioavailability when administered via the oral transmucosal route. One study recently reported that methadone was indeed bioavailable after transmucosal administration in cats: at doses of 0.6 mg/kg, peak plasma concentrations were attained 2 hours later with evidence of analgesia as measured by mechanical pressure. While these results are promising, further studies are needed to prove that clinical analgesia (i.e. post-ovariohysterectomy) is achieved.

Extended release oral opioids:

Many short and long acting formulations of oral opioids are available in human medicine; however, few have been studied for bioavailability or efficacy in veterinary patients. Although often prescribed for post-operative pain, the actual efficacy of these oral formulations is questionable. Several studies of MS Contin®, an oral sustained release morphine product, have documented minimal serum concentrations of drug after oral administration in dogs, most likely due to extensive first pass metabolism. Avinza® has both immediate release and sustained release granules containing morphine, but one study showed that dogs had variable absorption and the sustained release nature of this formulation did not apply in dogs, i.e. few dogs had measurable serum concentrations at 24 hours after dosing. It is possible that veterinary species other than dogs, with less first pass metabolism, may benefit from oral extended release opioid formulations, but studies are lacking.

Polymer gels:

A commercial sustained release preparation of buprenorphine is currently available and marketed directly for veterinary use (Buprenorphine SR®). This product is likely a variation on polymer gel technology, although the patent is still pending. According to the manufacturer, buprenorphine SR® can be administered subcutaneously every 72 hours to provide analgesia (Zoopharm Inc, buprenorphine SR package insert, January 2012). Limited studies have demonstrated early promise in the use of buprenorphine SR for mild to moderate pain. A study in rats demonstrated 2 – 3 days of analgesia after subcutaneous administration of buprenorphine SR®. A recent study showed that Buprenorphine SR®, at a one-time dose of -.012 mg/kg, was as analgesic as transmucosal buprenorphine at 0.02 mg/kg BID for pain after ovariohysterectomy. All cats were also administered meloxicam, so analgesia was not solely due to buprenorphine in either group. The
analgesic use of buprenorphine SR in dogs or other species has not been examined in a controlled non-biased published study, but its use warrants further investigation.

Liposome-encapsulated Opioids:

Encapsulation into liposomes is a method of preparing long-acting formulations of opioid drugs. Liposomes release their contents by release through passive efflux or release through liposome degradation in the biological milieu. In 2004 the FDA approved an extended-release liposome-encapsulated formulation of morphine for epidural use in people (Depodur®, EKR Therapeutics Inc, Cedar Knolls NJ). Depodur® provides up to 48 hours of analgesia after epidural administration without the need for an indwelling epidural catheter. While Depodur® obviates the need for an indwelling epidural catheter, there are some disadvantages to its use, including the current price of this product. In conversations with MD anesthesiologists, there is also concern about the inability to “reverse” the extended-release product once it is administered epidurally, in the event of an adverse reaction or a change in surgical planning.

The pharmacology laboratory at the University of Wisconsin has been working for a number of years on various types of liposome-encapsulated formulations of oxymorphone, hydromorphone, buprenorphine, and butorphanol for subcutaneous systemic administration to laboratory and companion animals for purposes of providing extended durations of analgesia. Depending on the lipid composition of the formulation, the amount of incorporated cholesterol, and the method of trapping the opioid within the liposome, we have developed formulations that release opioid anywhere from a 48-72 hour duration, up to 3 weeks. In dog studies, analgesia has been similar between the liposome-encapsulated hydromorphone formulation and a constant rate infusion of fentanyl, with expected side effects of nausea, vomiting and sedation that tend to dissipate after the 1st hour of administration. Systemic administration of liposome-encapsulated opioids has many theoretical advantages, including excellent bioavailability compared to extended release oral formulations of opioids, particularly in veterinary patients. Other advantages include the ease of administration, the lack of necessary IV access or long-term catheter placement, the established analgesic and safety profile of this class of drugs in veterinary medicine, and the inability of the injected liposome-encapsulated drug to be accessed by children or diverted for abuse. Some potential disadvantages include the long-acting nature of these formulations in the event that a patient has an adverse reaction to the drug. Additionally, cost of manufacture and the existence of patents that use similar technology but with different classes of drugs may limit the commercialization of these drug delivery systems.

References available upon request.