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SHORT COMMUNICATION

Pharmacokinetics of ammonium sulfate gradient loaded liposome-encapsulated oxymorphone and hydromorphone in healthy dogs

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Abstract

Objective To evaluate the pharmacokinetics, in dogs, of liposome-encapsulated oxymorphone and hydromorphone made by the ammonium sulfate gradient loading technique (ASG).

Animals Four healthy purpose-bred Beagles aged 9.5 ± 3.2 months and weighing 13.4 ± 2.3 kg.

Study design Randomized cross-over design.

Methods Each dog was given either 4.0 mg kg^{-1} of ASG-oxymorphone or 8.0 mg kg^{-1} of ASG-hydromorphone SC on separate occasions with a 3-month washout period. Blood was collected at baseline and at serial time points up to 1032 hours (43 days) after injection for determination of serum opioid concentrations. Serum opioid concentrations were measured with HPLC-MS and pharmacokinetic parameters were calculated using commercial software and non-compartmental methods.

Results Serum concentrations of oxymorphone remained above the limit of quantification for 21 days, while those for hydromorphone remained above the limit of quantification for 29 days. C_{max} for ASG-oxymorphone was 7.5 ng mL^{-1}; C_{max} for ASG-hydromorphone was 5.7 ng mL^{-1}.

Conclusions and clinical relevance Oxymorphone and hydromorphone, when encapsulated into liposomes using the ammonium sulfate gradient loading technique, result in measureable serum concentrations for between 3 to 4 weeks. This formulation may have promise in the convenient use of opioids for clinical treatment of chronically painful conditions in dogs.

Keywords dog, hydromorphone, opioids, oxymorphone, pain management.

Introduction

The mu agonist opioids, oxymorphone and hydromorphone, are commonly recommended for acute pain control in dogs (Hellyer 2002). Presently available formulations of extended release opioids prescribed for oral administration to humans undergo significant first pass effect in dogs and, thus, are not suitable for oral administration in this species. (Kukanich et al. 2005a; Aragon et al. 2009).

Oxymorphone is a mu opioid agonist that is approximately 10 times more potent than morphine (Prommer 2006; Papich 2011a). A pharmacokinetic study from our laboratory of the conventional formulation of oxymorphone in dogs has been published (KuKanich et al. 2008a). When administered either IV or SC, the conventional formulation

of oxymorphone, 0.1 mg kg^{-1}, has a short terminal half-life (0.8–1.0 hour) and short mean residence time (1.3 hours), and has a rapid clearance, exceeding hepatic blood flow, after IV administration (KuKanich et al. 2008a). The short terminal half-life and rapid clearance suggest the duration of effect is short, 2–4 hours, in dogs administered 0.1 mg kg^{-1} (KuKanich et al. 2008a; Papich 2011a).

Hydromorphone is a mu opioid agonist that is approximately seven times more potent than morphine (Hennies et al. 1988; Papich 2011b). Pharmacokinetic studies using conventional formulations of hydromorphone in dogs have also been previously reported (Guedes et al. 2008; KuKanich et al. 2008b). Despite different study conditions, analytical methods, and pharmacokinetic analyses, the pharmacokinetic results from these two different studies of hydromorphone were similar. The results show that hydromorphone had a short terminal half-life (<1 hour), rapid clearance exceeding hepatic blood flow, and short mean residence time (~ 1.3 hours) after IV administration of 0.1 mg kg^{-1} (KuKanich et al. 2008b; Guedes et al. 2008). These studies indicate a short duration of approximately 2 hours following 0.1 mg kg^{-1} due to the rapid clearance of hydromorphone (Guedes et al. 2008; KuKanich et al. 2008b; Papich 2011b).

The short terminal half-life and rapid clearance of oxymorphone and hydromorphone necessitate frequent administration, up to every 2 hours, to maintain targeted blood concentrations. The frequent administration is labor intensive and costly, produces large fluctuations in blood concentrations, and necessitates frequent and perhaps painful injections for the patient. Peaks in drug concentrations are associated with more adverse effects, such as sedation, nausea, or dysphoria. A strategy to overcome frequent administration and minimize fluctuations in plasma drug concentrations is to administer the drugs by constant rate IV infusion (CRI). However, a CRI requires hospitalization, maintenance of an IV catheter, is labor intensive in the form of constant supervision of the patient, and may result in phlebitis, catheter associated infections, and air embolisms as well as other adverse effects (Mathews et al. 1996; Walsh et al. 2005).

A different strategy to overcome the need for frequent administration is to incorporate the active drug into a repository or sustained release formulation. One approach is to encapsulate drug into liposomal membranes that release slowly over time. In previous work, our laboratory has developed liposome-encapsulated formulations of oxymorphone and hydromorphone that release drug over 3–4 days after subcutaneous administration (Smith et al. 2008; Krugner-Higby et al. 2011). These formulations were made using a freeze-thaw method and liposome membranes composed of dipalmatoylphosphatidylcholine (DPPC) and cholesterol. The release time of these formulations made them suitable for peri-operative pain control, but did not offer an extended duration longer than could be achieved with products such as the fentanyl patch (Kyles et al. 1996).

In the present study, we hypothesized that the use of an ammonium sulfate gradient loading method (ASG) would 'trap' the opioid inside of the liposome due to relative ion exchange across the liposome membrane, producing a formulation with a longer release time. We tested our hypothesis by measuring serum concentrations of opioid after subcutaneous injection of either ammonium sulfate gradient loaded oxymorphone (ASG-oxymorphone) or hydromorphone (ASG-hydromorphone) into healthy adult male Beagles. Serum opioid concentrations were used to calculate standard pharmacokinetic parameters using commercial software.

Materials and methods

Animals

The study was approved by the University of Wisconsin School of Veterinary Medicine Animal Care and Use Committee (Protocol # V1285) committee. Four healthy purpose-bred male neutered Beagle dogs (Ridgelan Laboratories, WI, USA) were used, with a mean ± SD age of 9.5 ± 3.2 months and body weight of 13.4 ± 2.3 kg. Normal health status was confirmed prior to entry into the study based upon the results of physical examination, complete blood count, and serum chemistry profile. Dogs were housed individually and fed commercial dog chow (Harlan Labs Dog Chow; Harlan Labs, WI, USA) and water *ad libitum*. Dogs were walked outside and socialized in the laboratory on a regular basis prior to testing. After arrival and acclimation, all dogs were anesthetized on one occasion only, for purposes of castration and insertion of a permanent vascular access port (VAP) (Norfolk Medical Products, IL, USA). Anesthesia consisted of 0.05 mg kg^{-1} acepromazine and 0.04 mg kg^{-1} buprenorphine IM, propofol IV to effect, and maintenance on isoflurane in oxygen. Post-operative pain was managed with