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RESEARCH PAPER

Pharmacokinetics of hydromorphone hydrochloride in healthy dogs

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Abstract

Objective To assess the pharmacokinetics of hydromorphone administered intravenously (IV) or subcutaneously (SC) to dogs.

Study design Randomized experimental trial.

Animals Seven healthy male neutered Beagles aged 12.13 ± 1.2 months and weighing 11.72 ± 1.10 kg.

Methods The study was a randomized Latin square block design. Dogs were randomly assigned to receive hydromorphone hydrochloride 0.1 mg kg^{-1} or 0.5 mg kg^{-1} IV (n = 4 dogs) or 0.1 mg kg^{-1} (n = 6) or 0.5 mg kg^{-1} (n = 5) SC on separate occasions with a minimum 14-day washout between experiments. Blood was sampled via a vascular access port at serial intervals after drug administration. Serum was analyzed by mass spectrometry. Pharmacokinetic parameters were determined with computer software.

Results Serum concentrations of hydromorphone decreased quickly after both routes of administration of either dose. The serum half-life, clearance, and volume of distribution after IV hydromorphone at 0.1 mg kg^{-1} were 0.57 hours (geometric mean), 106.28 mL $minute^{-1}$ kg^{-1}, and 5.35 L kg^{-1}, and at 0.5 mg kg^{-1} were 1.00 hour, 60.30 mL $minute^{-1}$ kg^{-1}, and 5.23 L kg^{-1}, respectively. The serum half-life after SC hydromorphone at 0.1 mg kg^{-1} and 0.5 mg kg^{-1} was 0.66 hours and 1.11 hours, respectively.

Conclusions and clinical relevance Hydromorphone has a short half-life, suggesting that frequent dosing intervals are needed. Based on pharmacokinetic parameters calculated in this study, 0.1 mg kg^{-1} IV or SC q 2 hours or a constant rate infusion of hydromorphone at 0.03 mg kg^{-1} $hour^{-1}$ are suggested for future studies to assess the analgesic effect of hydromorphone.

Keywords constant rate infusion, dog, hydromorphone, IV, pharmacokinetics, subcutaneous.

Introduction

Hydromorphone is an opioid agonist that primarily exerts its analgesic effects through its activity at the μ receptor (Hennies et al. 1988). In humans, hydromorphone is approximately seven times more potent than morphine, exhibits similar efficacy, produces a shorter duration of action, and at equianalgesic doses produces a similar adverse effect profile as morphine (Mahler & Forrest 1975; Coda et al. 1997).

A few studies have reported on the pharmacodynamics of hydromorphone in dogs. Hydromorphone [0.1 mg kg^{-1} intravenously (IV)] administered to

dogs significantly reduced the minimum alveolar concentration (MAC) of isoflurane for at least 4.5 hours (Machado et al. 2006). However, the relationship between decreased MAC and analgesia was not established. Previous studies have demonstrated acepromazine significantly decreases the MAC of halothane in dogs despite this drug's lack of analgesic properties (Heard et al. 1986). Hydromorphone [0.04–0.08 mg kg^{-1} intramuscularly (IM)] administered with acepromazine (0.04 mg kg^{-1} IM) resulted in a significant decrease in pupil size at 10 and 20 minutes post-administration (Stephan et al. 2003). Hydromorphone administered to dogs (0.22 mg kg^{-1} IM) resulted in rapid sedation (5.44 ± 0.86 minutes) that lasted at least 25 minutes, with no significant effect on systolic blood pressure or heart rate, and resulted in no significant change in serum histamine concentrations (Smith et al. 2001).

The pharmacokinetics and pharmacodynamics of hydromorphone administered to cats have been evaluated (Wegner et al. 2004). Hydromorphone exhibited a large volume of distribution (median 2.96 L kg^{-1}), a rapid clearance (median 24.6 mL $minute^{-1}$ kg^{-1}), and a short terminal half-life (1.7 hours) following administration of 0.1 mg kg^{-1} IV. Thermal thresholds were significantly increased for 5.75–7.5 hours post-injection (Lascelles & Robertson 2004; Wegner et al. 2004), but the relationship between thermal thresholds and clinical analgesia is unclear.

To the authors' knowledge no studies examining the pharmacokinetics of hydromorphone in dogs have been published. The purpose of this study was to investigate the pharmacokinetics of hydromorphone after IV and subcutaneous (SC) administration in healthy dogs.

Materials and methods

Animals

The Animal Care and Use Committee at the University of Wisconsin approved the study. Seven healthy male neutered Beagle dogs were used ranging in age from (mean ± SD) 12.13 ± 1.2 months and body weight 11.72 ± 1.10 kg. Normal health status was based on the results of physical examination, CBC, and serum chemistry profile. After arrival and acclimatisation, all dogs were anesthetized for castration and the insertion of a permanent vascular access port (Companion Port; Norfolk Medical, Skokie, IL, USA). Premedication consisted of 0.05 mg kg^{-1} acepromazine and 0.04 mg kg^{-1} buprenorphine IM. Anesthesia was induced with propofol IV to effect, and maintained with isoflurane in oxygen. Postoperative pain was managed with 0.04 mg kg^{-1} of buprenorphine IM at extubation and 4.0 mg kg^{-1} of carprofen PO once a day for 2 days after surgery. For purposes of implantation of the permanent vascular access ports, a cut-down incision was made over the right jugular vein with the dog in left lateral recumbency and approximately 7'' of the distal end of the silastic catheter was threaded into the jugular vein, using a needle introducer, to approximately the right atrium. A second incision was then made between the scapulae on the dorsal surface of the dog and a curved hemostat was used to tunnel SC to the proximal end of the catheter, which was then grasped and threaded over the receiving end of the vascular access port. The port was sutured to SC fascia using 2–0 absorbable suture at four symmetrical points around the disc-shaped port. The overlying SC layers and skin of both incisions were closed routinely. The port was flushed at surgery and daily for 3 days after surgery with 2 mL of 100 IU mL^{-1} heparinized saline. A 30-day recovery period was allowed before any dog participated in the study.

Drug dosing protocols

All SC drugs were administered in the loose skin caudal to the scapulae and at least 5 cm distal to the permanent vascular access port. All IV drug administration was into a cephalic or lateral saphenous vein by an experienced person (LJS). All drug treatments were administered via a 3 mL syringe attached to a 22-SWG 1'' needle. Dogs randomly received hydromorphone (Hydromorphone HCl; Elkins-Sinn, Cherry Hill, NJ, USA) at doses of 0.1 (equivalent to 0.089 mg kg^{-1} hydromorphone base) and 0.5 mg kg^{-1} (equivalent to 0.444 mg kg^{-1} hydromorphone base) both IV and SC on separate occasions. A 14- to 21-day washout period was observed between each drug administration. Initially five dogs per IV treatments and six dogs per SC treatments were included in the study. However, due to technical difficulties with sample collection only four dogs were included for both IV doses, and five dogs were included in the 0.5 mg kg^{-1} SC dose group.