PHARMACOKINETICS OF SINGLE-DOSE BUPRENORPHINE, BUTORPHANOL, AND HYDROMORPHONE IN THE DOMESTIC FERRET (*MUSTELA PUTORIUS FURO*)

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Abstract

The objective of this study was to establish the clinical pharmacokinetic profile of 4 different opioid drugs (buprenorphine, butorphanol, hydromorphone, and morphine) in the domestic ferret (*Mustela putorius furo*). Twenty-four, approximately 1-year-old, male neutered purpose-bred domestic ferrets were used for this study. The ferrets were divided into 4 groups of 6, with a different opioid drug used for each group. A preopioid venous blood sample was obtained via cranial vena cava venipuncture. Following the initial blood collection, a single injection of opioid (hydromorphone 0.1 mg/kg, buprenorphine 0.04 mg/kg, butorphanol 0.3 mg/kg, and morphine 1 mg/kg) was given to each ferret, dependent on assigned drug group, intramuscularly (buprenorphine) or subcutaneously (hydromorphone, butorphanol, and morphine). Intramuscular injections were administered in the semimembranosis and semitendinosis muscles, whereas the subcutaneous injections were delivered in the intrascapular subcutaneous space. A venous blood sample was obtained at 5, 15, 30, 60, 120, 240, 360, 480, and 720 minutes postinjection from the ferrets in the buprenorphine, butorphanol, and hydromorphone groups. Mass spectrometry and liquid chromatography was performed to obtain plasma concentrations of the administered drugs. The mean maximum concentration of buprenorphine was 6.96 ng/mL, butorphanol was 48.6 ng/mL, and hydromorphone was 17.3 ng/mL. Maximum concentrations were achieved at a mean of 9 minutes after administration for buprenorphine, 13.3 minutes for butorphanol, and 8.33 minutes for hydromorphone. The mean half-life of buprenorphine was 219.1 minutes, butorphanol was 91.1 minutes, and hydromorphone was 24.7 minutes. Owing to severe complications arising within the morphine group, including hypersalivation and vomiting, the morphine study was discontinued prior to blood sample collection. Intramuscular injections of buprenorphine and subcutaneous injections of butorphanol or hydromorphone appeared to be well tolerated by all ferrets. The pharmacokinetics of buprenorphine, butorphanol, and hydromorphone of a single equipotent dose of each drug have been established through this research investigation and may be useful for further studies.

Key words: ferret; analgesia; pharmacokinetics; butorphanol; buprenorphine; hydromorphone

The domestic ferret (*Mustela putorius furo*) is a popular pet, with an estimated 748,000 pet ferrets as of 2012, and accounts for the highest veterinary expenditures among companion exotic pets.[1] Currently, ferrets are legal in every state except California. The ferret has long been known for its tendency to develop disease conditions that require surgical intervention, from gastrointestinal obstructions to various neoplastic processes.[2-7] Despite the fact that ferrets frequently receive surgical diagnostics and treatment from veterinarians, very little is known about pain and its management in this particular species. Most of the clinical information regarding the use of

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opioids to manage pain in ferrets is extrapolated from information obtained from other mammalian species (e.g., canine and feline).[8-11] Dosages and information regarding the use of opioid drugs in ferrets extrapolated from other animal species may be problematic and potentially dangerous in the clinical setting, as ferrets are taxonomically, behaviorally, and physiologically unique among pet mammals.[8] Moreover, it has been reported that ferrets appear to become relatively more sedate than dogs and can suffer from severe respiratory suppression after administration of opioid agents.[9,12-14]

Butorphanol, buprenorphine, morphine, and hydromorphone are the most commonly recommended opioid drugs for providing analgesia in ferrets.[9,12-14] Currently, little data exist for the pharmacological or clinical profile of any of the drugs, listed earlier, for use in ferrets. Butorphanol is the best studied, with 4 publications describing anesthetic, sedative, and cardiorespiratory effects of this opioid in combination with other drugs.[15-18] In a combined (tiletamine, zolazepam, xylazine, and butorphanol) study, addition of butorphanol was shown to increase the duration of analgesia, ease endotracheal intubation, and increase time of dorsal recumbency, suggesting at least an increased analgesic and sedative effect. However, the addition of butorphanol to the combination also caused hypoxemia, prompting the author to conclude that supplemental oxygen should be provided to ferrets if butorphanol is included in the tiletamine, zolazepam, and xylazine cocktail.[15] In both a diazepam, acepromazine, xylazine, and butorphanol study, and a diazepam, ketamine, acepromazine, xylazine, and butorphanol study, statistically and clinically significant cardiorespiratory depression occurred in all ferret groups. However, owing to the presence of butorphanol in all of the cocktails and variance of other drugs, it is unclear how much effect butorphanol actually had regarding the cardiorespiratory suppression.[16,17] In a combination medetomidine, ketamine, and butorphanol study, the addition of butorphanol to the combination of drugs caused the most respiratory depression and significantly increased the duration of analgesia over the combinations that did not contain butorphanol.[18] Nevertheless, the combination of drugs used made evaluation of the effects of any single component very difficult. Therefore, clinical application to any anesthetic/sedative combination other than those described in these papers is clinically challenging.

There are no studies assessing the pharmacokinetics of morphine in ferrets; however, 1 study exists describing its epidural use in ferrets. In this double-blinded placebo controlled trial, ferrets treated with epidural morphine prior to surgical ovariohysterectomy and anal sacculectomy returned to function faster and exhibited less pain associated behaviors than placebo treated controls, suggesting that morphine administered epidurally may be an effective form of analgesia in ferrets.[19] At this time the authors of this article do not know if systemic morphine might also be an effective means of providing pain relief. In regard to hydromorphone, there are no studies of any kind relating to its use in ferrets, although it has been recommended based upon its less severe side effects in other species. An apparent benefit of using hydromorphone over other opioid drugs in ferrets would be that, anecdotally, ferrets appear to have problems with other systemically administered opioid agents.[10,13,20] There is also no published data regarding the use of buprenorphine in ferrets. However, it is used frequently in other mammalian species for pain control and sedative benefits.

In a pilot study assessing cardiorespiratory effects of butorphanol, buprenorphine, and hydromorphone in 5 ferrets, trends were found suggesting a drop in plasma pH, rise in arterial PaCO2, and concurrent drop in PaO2.[21] From this work, the need for a larger research investigation was apparent, to assess the significance of these findings, with one goal to be the establishment of pharmacokinetic parameters of opioid drugs in ferrets.

The purpose of the research investigation described in this article was to establish the single-dose pharmacokinetic profile of 4 different opioid drugs in domestic ferrets. These drugs include buprenorphine, butorphanol, hydromorphone, and morphine.

MATERIALS AND METHODS

Animals

Twenty-four, approximately 1-year-old, male neutered purpose-bred domestic ferrets weighing approximately 1 kg were housed in 4 groups of 6 and were acclimatized for a period of 5 days. When not used for the study, each ferret was given *ad libitum* water and food. The day of the study each ferret was housed separately, and held