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RESEARCH PAPER

Chloramphenicol significantly affects the pharmacokinetics of oral methadone in Greyhound dogs

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Abstract

Objective To assess the effects of cytochrome P450 (CYP) inhibitors (ketoconazole, chloramphenicol, trimethoprim, fluoxetine, cimetidine and medetomidine) in various combinations on the pharmacokinetics of oral methadone in Greyhound dogs to determine the specific effects of the different inhibitors and if a clinically relevant interaction occurs.

Study design Non-randomized, sequential design.

Animals Six healthy Greyhound dogs (three male, three female).

Methods Canine CYP inhibitors (ketoconazole, chloramphenicol, trimethoprim, fluoxetine, cimetidine and medetomidine) were administered in varying combinations prior to the administration of oral methadone. Plasma was obtained from each dog to enable the determination of methadone and CYP inhibitor drug concentrations using liquid chromatography with either mass spectrometry or ultraviolet detection.

Results Significant increases in the area under the curve (AUC) and maximum plasma concentrations (C_{MAX}) of methadone occurred in all groups administered chloramphenicol. The AUC (6 hours ng mL^{-1}) and C_{MAX} (6 ng mL^{-1}) of methadone significantly increased to 541 hours ng mL^{-1} and 47.8 ng mL^{-1}, respectively, when methadone was administered with chloramphenicol as a sole inhibitor. There were no significant effects of CYP inhibitors other than chloramphenicol on methadone pharmacokinetics, which suggests that chloramphenicol was primarily responsible for the pharmacokinetic interaction.

Conclusions and clinical relevance This study demonstrated significant effects of chloramphenicol on the pharmacokinetics of oral methadone. Further studies should investigate the effects of chloramphenicol on methadone pharmacokinetics in multiple dog breeds and examine whether oral methadone would be an effective analgesic in dogs. In addition, the safety of chloramphenicol and its effects on the pharmacokinetics of parenteral methadone warrant assessment.

Keywords CYP2B11, cytochrome P450, inhibitor, metabolism, methadone.

Introduction

Methadone is a μ-opioid agonist, but may be an analgesic of higher efficacy than other μ-opioid agonists as it also produces effects as an *N*-methyl-D-aspartate (NMDA) receptor antagonist and adrenergic α_2-agonist (Codd et al. 1995; Gorman et al. 1997). Methadone is a synthetic opioid marketed as a racemic mixture. It is available as an approved injectable formulation for use in dogs in some countries and is used in an extra-label manner in others. Both enantiomers exert pharmacologic effects, with the L-enantiomer more potent at the μ-opioid receptor (Kristensen et al. 1995), but both

enantiomers have effects on the NMDA and α_2-receptors (Matsui & Williams 2010).

Intravenous (IV) methadone pharmacokinetics in Beagles (Schmidt et al. 1994; Kukanich et al. 2005), Beagle and Beagle mix dogs (Ingvast-Larsson et al. 2010), and Greyhounds (KuKanich & Borum 2008) indicate that this drug has a high hepatic extraction ratio and as such is predicted to have low oral bioavailability. The pharmacokinetics of IV methadone across the different dog breeds were found to be similar. Reports of the pharmacokinetics of oral methadone in dogs support the hypothesis that methadone has low oral bioavailability in these animals. Methadone (2 mg kg^{-1}) administered orally to Beagle dogs did not result in plasma concentrations exceeding the analytical limit of detection (20 ng mL^{-1}) in any dog (Kukanich et al. 2005). However, concurrent administration of ketoconazole resulted in detectable concentrations in one of six dogs. The precise reason for the increased absorption of methadone in that dog but not in the other five dogs was not determined, but it was hypothesized to have arisen from either increased drug absorption or inhibited drug metabolism resulting in decreased first pass metabolism in that specific dog. Oral methadone administered to Greyhound dogs resulted in low plasma concentrations, whereby the mean area under the curve (AUC) after the oral administration of a dose of 2 mg kg^{-1} (Kukanich et al. 2011) was over 10 times lower (13.1 hours ng mL^{-1}) than the mean AUC after IV administration (150.76 hours ng mL^{-1}) of 0.5 mg kg^{-1} to Greyhounds (KuKanich & Borum 2008). This also suggests low oral bioavailability.

A study assessing the effects of cytochrome P450 (CYP) inhibitors demonstrated significant effects on the pharmacokinetics of oral methadone in Greyhound dogs (Kukanich et al. 2011). The mean AUC significantly increased (100-fold) and the maximum plasma concentration (C_{MAX}) was also significantly increased (15-fold) when methadone was administered concurrently with four CYP inhibitors (chloramphenicol, ketoconazole, trimethoprim and fluoxetine). The study results indicated that methadone is a CYP substrate and its metabolism is significantly affected by one or a combination of CYP inhibitors. However, the specific CYP inhibitor or combination of CYP inhibitors that produced significant effects on the pharmacokinetics of oral methadone were not evaluated. Pharmacologic effects which could be attributed to methadone were also observed in these dogs and included moderate to heavy sedation, bradycardia, hypothermia and vomiting, which suggests that the pharmacologic effects of methadone are clinically relevant when methadone is administered in combination with CYP inhibitors.

The activities of CYP inhibitors in dogs have been described. Chloramphenicol is a purported CYP2B11 inhibitor in dogs (Aidasani et al. 2008). Ketoconazole is a purported CYP3A inhibitor in dogs (Lu et al. 2005). Trimethoprim and fluoxetine are purported CYP2D15 inhibitors in dogs (Aidasani et al. 2008), and medetomidine is a purported CYP2B11 inhibitor in dogs (Baratta et al. 2010). Cimetidine is a weak CYP inhibitor in dogs (Aidasani et al. 2008), but higher doses may produce a more prominent effect (Ritschel et al. 1985).

The objective of this study was to evaluate the effects of canine CYP inhibitors and CYP inhibitor combinations on the pharmacokinetics of oral methadone in Greyhound dogs to determine if inhibition of methadone metabolism is caused by a single CYP inhibitor or combinations thereof. The hypothesis was that significant effects on the pharmacokinetics of methadone will occur when methadone is administered orally with CYP inhibitors.

Materials and methods

Six healthy Greyhounds, ranging in age from 3 to 5 years and weighing between 26 kg and 41 kg were enrolled in the study. These included three neutered males and three ovariohysterectomized females. The study was approved by the Institutional Animal Care and Use Committee at Kansas State University.

The study followed a non-randomized, non-blinded, sequential design with six treatment groups. Periods of at least 4 weeks were allowed between treatments (Table 1). Dogs were not fasted for the study and had free access to food and water for the duration of the study. Drugs administered included: methadone hydrochloride 10 mg tablets (Mallinckrodt Pharmaceuticals, Inc., MO, USA); ketoconazole 200 mg tablets (Taro Pharmaceutical Industries Ltd, NY, USA); chloramphenicol 500 mg tablets (Viceton; Bimeda, Inc., MN, USA); fluoxetine 20 mg capsules (Teva Pharmaceutical Industries, Inc., PA, USA), cimetidine 800 mg tablets (Apotex Corp., FL, USA), and medetomidine (Tocris Bioscience, Inc., MN, USA) administered as an aqueous solution (1 mg mL^{-1}).

In treatment 1, methadone (administered orally as whole tablets at a targeted dose of 1 mg kg^{-1} to the

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