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RESEARCH PAPER

Pharmacokinetics of intravenous and oral amitriptyline and its active metabolite nortriptyline in Greyhound dogs

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Abstract

Objective To evaluate the pharmacokinetics of amitriptyline and its active metabolite nortriptyline after intravenous (IV) and oral amitriptyline administration in healthy dogs.

Study design Prospective randomized experiment.

Animals Five healthy Greyhound dogs (three males and two females) aged 2–4 years and weighing 32.5–39.7 kg.

Methods After jugular vein catheterization, dogs were administered a single oral or IV dose of amitriptyline (4 mg kg^{-1}). Blood samples were collected at predetermined time points from baseline (0 hours) to 32 hours after administration and plasma concentrations of amitriptyline and nortriptyline were measured by liquid chromatography triple quadrupole mass spectrometry. Non-compartmental pharmacokinetic analyses were performed.

Results Orally administered amitriptyline was well tolerated, but adverse effects were noted after IV administration. The mean maximum plasma concentration (C_{MAX}) of amitriptyline was 27.4 ng mL^{-1} at 1 hour and its mean terminal half-life was 4.33 hours following oral amitriptyline. Bioavailability of oral amitriptyline was 6%. The mean C_{MAX} of nortriptyline was 14.4 ng mL^{-1} at 2.05 hours and its mean terminal half-life was 6.20 hours following oral amitriptyline.

Conclusions and clinical relevance Amitriptyline at 4 mg kg^{-1} administered orally produced low amitriptyline and nortriptyline plasma concentrations. This brings into question whether the currently recommended oral dose of amitriptyline (1–4 mg kg^{-1}) is appropriate in dogs.

Keywords amitriptyline, canine, nortriptyline, pharmacokinetics, tricyclic antidepressant.

Introduction

Antidepressants are widely used for the treatment of various chronic and neuropathic conditions in humans (Dharmshaktu et al. 2012). Amitriptyline is a tricyclic antidepressant (TCA) that is believed to provide analgesia by enhancing descending inhibitory action in the spinal cord predominantly as a serotonin–norepinephrine reuptake inhibitor, but also at other sites, including the *N*-methyl-D-aspartate (NMDA) receptor, μ and δ opioid receptors, the $GABA_B$ receptor, the adenosine A1 receptor, sodium, calcium and potassium channels, and as an anti-inflammatory by decreasing prostaglandin E_2 and tumor necrosis factor-α (TNF-α) production (Eschalier et al. 1981; Ogata et al. 1989; Antkiewicz-Michaluk et al. 1991; Cai & McCaslin 1992; Stein 1995; Skolnick et al. 1996; Micó et al. 1997; Gray et al. 1998, 1999; Yaron et al. 1999; Galeotti et al. 2001; Sawnyok et al. 2001; Yokogawa et al. 2002; Sudoh et al. 2003; Ignatowski et al. 2005; Sawynok et al. 2005; McCarson et al. 2006; Dharmshaktu et al. 2012). A recent case series published in the

veterinary literature suggested that amitriptyline may also be effective for the treatment of neuropathic and chronic pain in dogs (Cashmore et al. 2009). However, this was a small case series which did not include positive or negative controls and therefore conclusions on effectiveness should be made with caution.

In humans, amitriptyline is metabolized in part to the active metabolite nortriptyline, which, in addition to amitriptyline, appears to contribute to analgesic effects after amitriptyline administration at doses of 25–125 mg day^{-1} (Moore et al. 2012). In humans, steady-state plasma concentrations of amitriptyline plus nortriptyline in the range of 60–220 ng mL^{-1} and of nortriptyline at 60–140 ng mL^{-1} are associated with clinical antidepressant effects (Vandel et al. 1978). Few data are available on the pharmacokinetics of amitriptyline and its metabolites in dogs. One study reported the plasma concentrations of amitriptyline after oral administration to dogs, but did not give intravenous (IV) data or plasma concentrations of nortriptyline (Kukes et al. 2009). The purpose of this study was to evaluate the pharmacokinetics of amitriptyline and its metabolite nortriptyline after IV and oral administration in healthy Greyhound dogs.

Materials and methods

Animals

The study was approved by the Institutional Animal Care and Use Committee at Kansas State University College of Veterinary Medicine (protocol no. 3270). Five healthy Greyhound dogs, three male and two female, aged 2–4 years and weighing 32.5–39.7 kg were used.

Study design

The study consisted of a crossover design in which animals were randomized (STATA Version 10.2; StataCorp LP, TX, USA) to receive either IV amitriptyline first and oral amitriptyline second or oral amitriptyline first and IV amitriptyline second. At least 7 days were allowed between treatments. A complete physical examination, complete blood count and blood chemistry panel were performed in all dogs immediately before the start of the study. All dogs were found to be healthy with no signs of systemic disease.

Tablets containing either 10 mg amitriptyline (Qualitest Pharmaceuticals, AL, USA) or 25 mg amitriptyline (Sandoz, Inc., NJ, USA) were administered orally to non-fasted animals at a targeted dose of 4 mg kg^{-1} to the nearest whole tablet. Subjects were given a standard commercially available dry kibble dog food 2 hours prior to drug administration. Blood samples consisting of 9 mL whole blood were collected using an aseptically placed 16 gauge, polyurethane, extended-use jugular catheter (Venocath-16; Abbott Laboratories Ireland Ltd, Ireland) prior to drug administration and at 10, 20, 30 and 45 minutes and at 1, 2, 3, 4, 6, 8, 12, 24 and 32 hours after drug administration, and placed in tubes containing lithium heparin (BD Vacutainer; Becton Dickinson & Co., NJ, USA). Samples were stored on ice and plasma was immediately separated by centrifugation at 3000 ***g*** for 20 minutes and stored frozen at − 70 °C until analysis. The jugular catheters were flushed with 3 mL sterile 0.9% saline after each collection to maintain patency.

Amitriptyline for injection was not available as an approved drug at the time of the study; therefore, amitriptyline was compounded into sterile solution by dissolving amitriptyline hydrochloride in sterile 0.9% saline for injection to a concentration of 10 mg mL^{-1} and then filtering it through a 0.22 μmol L^{-1} filter (Fisher Scientific Co. LLC, PA, USA). Fresh amitriptyline injections were made on the day of drug administration. Amitriptyline was administered IV at 4 mg kg^{-1} over 5 minutes through an aseptically placed 20 gauge, 3.81 cm catheter (Terumo Medical Corp., NJ, USA) located in a cephalic vein, after which 9 mL sterile 0.9% saline was administered to flush the catheter. Blood samples (9 mL) were collected from an aseptically placed jugular catheter (Venocath-16) in the same fashion and at time intervals identical to those used after oral amitriptyline. Samples were handled and processed exactly as described for those obtained after oral amitriptyline. Subjects were observed continuously for the first 12 hours and then again at 24 and 32 hours for side effects.

Liquid chromatography/mass spectrometry

Amitriptyline and nortriptyline plasma concentrations were determined using liquid chromatography (LC) (Shimadzu Prominence; Shimadzu Scientific Instruments, Inc., MD, USA) with mass spectrometry (MS) (API 3000; Applied Biosystems, Inc., ON, Canada). Plasma samples were processed using a protein precipitation procedure. The internal standard solution consisted of 100 ng mL^{-1} of

