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RESEARCH PAPER

Population pharmacokinetics of methadone hydrochloride after a single intramuscular administration in adult Japanese sika deer (*Cervus nippon nippon*)

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Abstract

Objective To assess the population pharmacokinetics of methadone in deer.

Study design Prospective non-randomized experimental trial.

Animals Twelve healthy adult sika deer (nine males and three females).

Methods Deer received intramuscular administration of racemic methadone hydrochloride at 0.5 mg kg^{-1} or 1 mg kg^{-1}. Plasma methadone and its metabolite 2-Ethylidene-1,5-Dimethyl-3,3-Diphenyl-Pyrolidine (EDDP) concentrations were determined by validated liquid chromatography coupled to tandem mass spectrometry methods, at times 0, 30 minutes, 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours. Population pharmacokinetics analysis was undertaken using a non-linear mixed effects modelling (NONMEM).

Results A two-compartment linear disposition model best described observed time-concentration profiles of methadone and EDDP. Population parameter estimates of methadone were elimination clearance (17.3 L $hour^{-1}$), metabolic clearance (34.6 L $hour^{-1}$), volume of distribution of compartment 1 (216.0 L) and volume of distribution of compartment 2 (384.0 L). Population parameter estimates of EDDP were elimination clearance (121.0 L $hour^{-1}$), volume of distribution of compartment 3 (1.08 L) and volume of distribution of compartment 4 (499.5 L). The total clearance and total volume of distribution of methadone and EDDP were 51.9 L $hour^{-1}$, 121.0 L $hour^{-1}$, 600.0 L and 500.6 L, respectively. The methadone terminal elimination half-life was 8.19 hours. No adverse effects were observed after methadone administration.

Conclusions and Clinical relevance Following intramuscular injection, methadone was characterized by a large total volume of distribution, high systemic clearance and intermediate terminal half-life in sika deer.

Keywords *Cervus nippon nippon*, Japanese sika deer, methadone, opioid analgesia, population pharmacokinetics.

Introduction

Opioids bind to morphinic receptors in the nervous system, inhibiting release of excitatory neurotransmitters in the brain and spinal cord, thereby reducing the pain from a nociceptive stimulus without interfering with motor function (Steagall et al. 2006). In spite of some recognized side effects, such as vomiting, dysorexia, salivation and respiratory depression, opioids are used routinely in the perioperative period due to their analgesic, sedative, and anxiolytic effects (Garrido & Trocóniz 1999).

Methadone is a powerful analgesic (Ripamonti et al. 1997), and has recently received a marketing authorization for veterinary use in many European countries. It is considered to have the same analgesic potency as morphine in humans (Maiante et al. 2008), but has superior analgesic and sedation effects in dogs (He et al. 2009). Methadone is a synthetic opioid with basic (pKa 9.2) and lipophilic properties. It acts as a pure μ opiate receptor agonist, and is also a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist within the spinal cord, a norepinephrine and serotonin reuptake inhibitor and an alpha-2 adrenergic agonist (Garrido & Trocóniz 1999; Eap et al. 2002). Methadone has also a weak affinity for the δ and κ opioid receptors. The NMDA antagonist action might increase its analgesic effect (Monteiro et al. 2008), but some authors (Chizh et al. 2000) suggest that in the antinociceptive dose range, this does not significantly contribute to analgesic effects due to its low micromolar affinity to the NMDA receptors. Methadone is marketed most usually as a 50:50 racemic mixture (Eap et al. 2002), with (R)-methadone predominantly responsible for the opioid and mono-amine receptor effects (Garrido & Trocóniz 1999). Both enantiomers but mainly
(S)-methadone, have affinity for the NMDA receptor (Garrido & Trocóniz 1999).

Methadone analgesia has been demonstrated in dogs (Leibetseder et al. 2006), cats (Dobromylskyj 1993; Rohrer Bley et al. 2004; Steagall et al. 2006) and humans (Gourlay et al. 1986). Sedative effect has only been described in dogs (Monteiro et al. 2009). Analgesic effects are claimed to last for three to six hours in dogs and cats (Dobromylskyj 1993; Leibetseder et al. 2006) and administrations every 4 hours are recommended (Rohrer Bley et al. 2004).

Methadone has a large therapeutic index (Riviere & Papich 2009), but adverse effects have been reported with high dosages, including moderate respiratory function depression (hypoxemia) (Maiante et al. 2008; Raekallio et al. 2009), cardiovascular depression (hypotension due to bradycardia secondary to vagal stimulation) (Maiante et al. 2008), vomiting (direct action on the opioid receptors in the chemoreceptor trigger zone of the area postrema of the medulla oblongata) (Steagall et al. 2006; Monteiro et al. 2009) and hypothermia (interference with the hypothalamic thermoregulation) (Monteiro et al. 2008). These adverse effects are more potent with the intravenous route, but are generally less marked than with morphine (Maiante et al. 2008). Histamine release has been rarely described in humans after intravenous (IV) injection, but has not been studied in animals (Bowdle et al. 2004).

The purpose of this study was to assess the pharmacokinetic properties of a single intramuscular injection of methadone in healthy adult Japanese sika deer.

Materials and methods

Animals and study design

This study was approved by the Animal Care and Use Committee of Val de Loire (France). Twelve captive Japanese Sika deer (*Cervus nippon nippon*) were enrolled in the study, including nine males and three females. Deer were presumed healthy on the base of medical history and clinical examination. Animal's ages and weight ranged from 1.5 to 13 years and from 32.5 to 39.0 kg, respectively. Methadone HCl (Comfortan 10 mg mL^{-1}, Sogeval, 53022, France) was administered to ten deer at a dose of 1 mg kg^{-1} intramuscularly (IM), the injection being given in the right shoulder muscular mass. In a preliminary study, two deer received a dose of 0.5 mg kg^{-1}. Following disinfection with alcohol at the site, blood samples (4 mL) were collected from the jugular veins into sterile vacutainer lithium heparin collection tubes. Blood samples were collected just prior to methadone administration and at 30 minutes and 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours after drug administration. Whole blood was immediately stored frozen at −20 °C until analysis. Animals were restrained in a chute for methadone administration and blood collection. Water and grass hay were available at all time.

Further details of the methods of blood sample analysis, population pharmacokinetic analysis and