Some Pharmacokinetic Data for Danofloxacin in Healthy Goats

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ABSTRACT

The pharmacokinetics of danofloxacin was determined in five clinically normal adult female goats after intravenous (IV) or intramuscular (IM) doses of 1.25 mg/kg body weight. Blood and urine samples were collected from each animal at precise time intervals. Serum and urine concentrations were determined using microbiological assay methods and the data were subjected to kinetic analysis. After intravenous injection, the serum concentration–time curves of danofloxacin were characteristic of a two-compartment open model. The drug was rapidly distributed and eliminated with half-lives of 17.71 ± 1.38 min and 81.18 ± 3.70 min, respectively. The drug persisted in the central, highly perfused organs with a $K_{1,2}/K_{2,1}$ ratio of 0.67 ± 0.25. The mean volume of distribution at a steady state ($V_{ss}$) was 1.42 ± 0.15 L/kg. After intramuscular administration, the serum concentration peaked after 0.58 ± 0.04 h at approximately 0.33 ± 0.01 µg/ml. While danofloxacin could be detected in serum for 4 and 6 h, it was recovered in urine for up to 24 and 72 h after IV and IM administration, respectively. The systemic bioavailability after IM injection was 65.70% ± 10.28% and the serum protein-bound fraction was 13.55 ± 1.78%.

Keywords: bioavailability, danofloxacin, fluoroquinolones, goats, microbiological assay, pharmacokinetics

Abbreviations: $\alpha$, distribution rate constant; AUC, area under the curve from zero to infinity by the trapezoidal integral; AUMC, area under the first moment curve; $\beta$, elimination rate constant for IV route; $C_{max}$, peak drug concentration; $Cl_{tot}$, total body clearance; $Cl_{el}$, elimination for IM route; $F$, the systemic bioavailability; $K_{a,b}$, absorption rate constant; $K_{1,2}$ and $K_{2,1}$, first-order rate constants for drug distribution between the central and peripheral compartments; MRT, mean residence time; NA, not applicable; $t_{1/2,b}$, absorption half-life; $t_{1/2,b}$, elimination half-life for IV route; $t_{1/2,a}$, distribution half-life; $t_{1/2,h}$, elimination half-life for IM route; $T_{max}$, time to peak concentration; $V_{ss}$, volume of the central compartment; $V_{dss}$, volume of distribution at steady state

INTRODUCTION

The first antimicrobials based on the 4-quinolone ring were nalidixic acid and oxolinic acids, which are active in vitro against a wide range of Gram-negative bacteria. The problems associated with their application include a restricted spectrum of activity and the relatively rapid emergence of resistant mutants. This led to the discovery of the fluoroquinolones, one of which is danofloxacin. Danofloxacin (CP-76, 136; 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[(1S, 4S)-5-methyl-2,5-diazabicyclo-(2.2.1) hept-
2-yl]-3-quinolone carboxylic acid) has been recently introduced exclusively for use in veterinary medicine (Brown, 1996). As with other fluoroquinolones, danofloxacin achieves rapid bactericidal activity by inhibiting bacterial DNA gyrase (Neer, 1988; Chu and Fernandes, 1991). The drug possesses good in vitro activity against a variety of pathogens, including Gram-positive and Gram-negative bacteria and Mycoplasma. Danofloxacin shares with other fluoroquinolones (enrofloxacin, ciprofloxacin and marbofloxacin) a wide spectrum of activity, a large volume of distribution and activity at low concentrations (Van Custen et al., 1990; Spreng et al., 1995; Brown, 1996). The pharmacokinetic properties of danofloxacin in goats have not been reported but they have been evaluated in young calves and adult cattle (Grimsho et al., 1990; Giles et al., 1991b; Apley and Upson, 1993; Friis, 1993), lactating ewes (Shem-Tov et al., 1997a), lactating cows (Shem-Tov et al., 1998) and sheep (McKellar et al., 1998).

The importance of goats as food-producing animals, and the small amount of information regarding the pharmacokinetics of danofloxacin, led us to study its disposition in goats. Thus, the aim of the present study was to elucidate some of the pharmacokinetic parameters of danofloxacin in healthy goats following intravenous or intramuscular administration of a single dose, with a view to making recommendations on dosage.

MATERIALS AND METHODS

Experimental animals

Five healthy, nonlactating Egyptian goats weighing 28–32 kg (2 years old) were used. The goats were found to be healthy on physical examination. The body weight of each animal was recorded on the day prior to the start of the study. The animals were kept indoors under good hygienic conditions and fed on alfalfa hay, concentrate mixture in a pelleted form and water ad libitum. The study was conducted using a two-way crossover design, with one month interval between each experiment to ensure the complete absence of any residual drug.

Experimental design

Advocin injectable vial (Pfizer, Animal Health Division, Cairo, Egypt), is a clear, sterile aqueous solution containing 25 mg danofloxacin per ml. It was injected intravenously into the right jugular vein or intramuscularly into the lower third of the right cervical musculature at a dose of 1.25 mg/kg body weight. Blood samples of about 3 ml each were collected from the contralateral vein just before dosing and at 5, 10, 20, 30, 45 min and 1, 2, 4, 6, 8, 10, 12 and 24 h after drug administration by either route. The blood was allowed to clot at room temperature for 2 h, then the serum was separated by centrifugation at 3000g for 15 min. For urine samples, each goat was catheterized using a rubber balloon catheter (14 FR-30cc, Foletex Norta, Beijing, China). The bladder was emptied before the drug was administered. Urine samples