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Pharmacokinetics and bioavailability of furosemide in sheep

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Abstract

The pharmacokinetics and bioavailability of furosemide were determined following intravenous (IV), intramuscular (IM), and subcutaneous (SC) administrations at 2.5 mg/kg dose in sheep. The study was conducted on six healthy sheep in a three-way, three-period, crossover pharmacokinetic design with a 15-day washout period. In first period, furosemide was randomly administered via IV to 2 sheep, IM to 2 sheep and SC to 2 sheep. In second and third periods, each sheep received furosemide via different routes of administration with the 15-day washout period. Plasma concentrations were determined using a high-performance liquid chromatography assay and analyzed by noncompartmental method. The mean total clearance and volume of distribution at steady state following IV administration were 0.24 L h^{-1} kg^{-1} and 0.17 L/kg, respectively. The elimination half-life was similar for all administration routes. The mean peak plasma concentrations of IM and SC administration were 10.33 and 3.18 μg/ml at 0.33 and 0.42 hr, respectively. The mean bioavailability of IM and SC administration was 97.91% and 37.98%, respectively. The IM injection of furosemide may be the alternative routes in addition to IV. However, further research is required to determine the effect of dose and route of administration on the clinical efficacy of furosemide in sheep.

KEYWORDS

bioavailability, furosemide, pharmacokinetics, sheep

1 | INTRODUCTION

Furosemide is a sulfonamide derivative loop diuretic, which is widely used in human and veterinary medicine (CVMP, 1999). Mechanism of action of furosemide is by inhibiting the transport system of $Na^+/K^+/2Cl^-$ in the luminal membrane of ascending loop of Henle (Shankar & Brater, 2003). Because the 20%–30% of NaCl reabsorption occurs in ascending loop of Henle, the effect of furosemide is potent and is called as a high ceiling diuretic (Abbott & Kovacic, 2008; Pacifici, 2013; Roush et al., 2014). Furosemide increases urinary excretion of electrolytes such as sodium, chloride, potassium, magnesium, calcium, and ammonium by inhibiting the $Na^+/K^+/2Cl^-$ transport system (Abbott & Kovacic, 2008; Ho & Power, 2010). Furosemide also weakly inhibits the carbonic anhydrase enzyme and increases the urinary excretion of $HCO3^-$ and phosphate (Pacifici, 2013). Increased ion density in urine increases osmotic pressure, attracts water to itself, and increases the urine amount (CVMP, 1999). Furosemide stimulates the synthesis of vasodilator prostaglandin (PG) E_2 in the kidney, thus causing renal and extra-renal vascular effects (CVMP, 1999; Soma & Uboh, 1998). Furthermore, it has resulted in reduced inflammatory mediators such as leukotrienes and histamine in lung (CVMP, 1999; Kandasamy & Carlo, 2017).

Furosemide is approved for use in cattle and horses for the treatment of edema, fluid accumulation in body cavities, renal failure with oliguria, and intoxication (CVMP, 1999). Additionally, it has been reported that furosemide can be used for physiologic parturient edema and congestive heart failure in cattle (Constable et al., 2017; Shaikh et al., 2002), exercise-induced pulmonary hemorrhage, chronic obstructive pulmonary disease and congestive heart failure in horses

(Constable et al., 2017; Kochevar, 2009; Villarino et al., 2019) and edema of cardiac, hepatic and renal origin, renal failure, and intoxication in small animals (Kochevar, 2009). Furosemide can be used in sheep for indications like other animals. In addition, furosemide has been reported to treat edema in heartwater (cowdriosis) (Shakespeare et al., 1998) and to reverse tissue hypoxia in septic acute kidney injury (Iguchi et al., 2019) and to prevent postoperative pulmonary edema in cardiovascular surgeries in sheep (DiVincenti et al., 2014). The pharmacokinetics of furosemide was determined in horses (Dyke et al., 1996; Johansson et al., 2004), dog (Hirai et al., 1992), camel (Ali et al., 1998), piglets (Miceli et al., 1990), and cats (Sleeper et al., 2019). The studies have shown apparent differences in the effects and pharmacokinetics of furosemide for different routes of the administration among species (Ali et al., 1998; Johansson et al., 2004; Sleeper et al., 2019). We hypothesized that intramuscular (IM) and subcutaneous (SC) injections of furosemide would be used as an alternative route in sheep by the reach to similar total exposure (area under the curve) comparable to those achieved by intravenous (IV) administration. The aim of this study was to determine the pharmacokinetics and bioavailability of furosemide in sheep following the IV, IM, and SC administration.

2 | MATERIALS AND METHODS

2.1 | Chemicals

Furosemide (≥ 99%) analytic standard was purchased from Sigma-Aldrich (St. Louis, Mo., USA). Analytical-grade methanol, sodium acetate, acetic acid, and sodium hydroxide were supplied from Merck (Darmstadt, Germany). Parenteral formulation (Lasix, 20 mg/ml, Sanofi Aventis) of furosemide was used for IV, IM, and SC administrations to sheep.

2.2 | Animals

A convenience sample of six healthy Akkaraman female sheep (2.0 ± 0.3 years and 47 ± 4 kg of body weight) was used for the study. The animals were judged to be as healthy based on a clinical examination and biochemical, and hemogram parameters, and they had not received any other medications during the 1 month prior to the study. The sheep were housed in individual pens within 10 days before the study for acclimation period. The sheep were fed with drug-free commercial feed and alfalfa hay, and water was given ad libitum. The study procedures were approved by The Ethics Committee of the Faculty of Veterinary Medicine (University of Selcuk, Konya, Turkey).

2.3 | Experimental design

The study was conducted in a three-way, three-period, crossover pharmacokinetic design with a 15-day washout period between administrations. Furosemide was administered via IV (left jugular vein), IM (between the semitendinosus and the semimembranosus muscles), and SC (the axillary region) at a dose of 2.5 mg/kg. In the first period, furosemide was randomly administered via IV to 2 sheep, IM to 2 sheep, and SC to 2 sheep. In the second and third periods following the 15-day washout period, each sheep received furosemide via different routes of administration. From each sheep, a blood sample (2 ml) was obtained via the catheter (22 G, 0.9 × 25 mm, Bıcakcılar Medical Devices Industry and Trade Co., Istanbul, Turkey), which was inserted into the right jugular vein and fixed by covering the outer ends with an elastic bandage, before (0 min) and at 5, 10, 15, 20, 25, 30, and 45 min and 1, 1.5, 2, 3, 4, 5 and 6 hr after furosemide administration. Each blood sample was collected into a blood collection tube containing heparin as an anticoagulant and was centrifuged at 4,000 x *g* for 10 min within 1 hr after collection. The plasma was harvested and stored frozen at −80°C until analysis.

2.4 | HPLC and chromatographic conditions

Plasma furosemide concentrations were assayed using the high-performance liquid chromatography (HPLC)-UV system (Shimadzu, Tokyo, Japan) with the previously described method (Lin et al., 1979). Plasma samples taken from the deep freezer (at −80°C) were thawed to room temperature. A total of 200 µl plasma sample was transferred to micro-centrifuge tubes, and 400 µl of methanol was added. Then, the tubes were mixed by vortexing for 45 s and centrifuged at 10.000 x g for 15 min. The clear supernatant (200 µl) was transferred into autosampler vials, and 10 µl was injected into the HPLC-UV system. The HPLC system consisted of a pump (LC-20AT controlled by the CBM-20A), a degasser (DGU-20A), an autosampler (SIL 20A), column oven (CTO-10A), and an SPD-20A UV–Vis detector. Furosemide separation was performed using a Gemini C18 column (250 × 4.6 mm; internal diameter, 5 µm; Phenomenex, Torrance, CA, USA), and the wavelength was set at 280 nm. The column and autosampler temperatures were maintained at 40°C and 24°C, respectively. The mobile phase consisted of methanol (35%) and 0.01 M sodium acetate buffer (pH:5, 65%) was pumped using the HPLC system at the flow rate of 1 ml/min. Data analysis was performed using PC controlled LC solution software program (Shimadzu, Tokyo, Japan).

The stock solution of furosemide was prepared in methanol at a concentration of 100 µg/ml and stored at −80°C. Calibration standards and quality control samples were prepared by diluting the stock solution. The calibration standards (0.04–40 µg/ml) of furosemide prepared from blank sheep plasma were linear with correlation coefficient of >0.99. The lowest limit of quantification was 0.04 µg/ml with acceptable coefficient of variation (<20%) and bias (±15%). Quality control samples (0.4, 4, and 40 µg/ml) were used to determine the recovery, precision, and accuracy of the method. The recovery of furosemide was >95%. The coefficient of variation for intraday and interday precision was <6.36%. The intraday bias and interday bias of accuracy were ±5%.

2.5 | Pharmacokinetic calculations

Pharmacokinetic variables for each sheep of furosemide following IV, IM, and SC administration were analyzed by noncompartmental method (Gibaldi & Perrier, 1982) using WinNonlin 6.1.0.173 software program (Pharsight Corporation, Scientific Consulting Inc., North Carolina, USA). Pharmacokinetic parameters calculated included area under the concentration versus. time curve (AUC), terminal elimination half-life ($t_{1/2\lambda z}$), mean residence time (MRT), total clearance (Cl_T), and volume of distribution at steady state (V_{dss}). The AUC was estimated by the linear/log-method. The peak concentration (C_{max}) and the time to reach C_{max} (T_{max}) were determined directly from the plasma concentration–time curve. Bioavailability (F) after IM and SC administrations was calculated using the following formula: $F = (AUC_{IM,\,SC}/AUC_{IV}) \times 100$.

2.6 | Statistical analysis

All values were shown as the mean ± *SD*. Normality of data points was tested using the Shapiro–Wilk test. T_{max} data points were not normally distributed; therefore, Wilcoxon's rank-sum test was used. The $t_{1/2\lambda z}$, MRT, and AUC were analyzed using one-way analysis of variance (ANOVA) and post hoc Tukey tests. The C_{max} and F were evaluated using paired *t* test. All statistical analyses were performed using SPSS 22.0 program (IBM Corp, Armonk, NY). $p < .05$ was considered as statistically significant.

3 | RESULTS

The mean plasma concentration–time curves and pharmacokinetic parameters of furosemide (2.5 mg/kg) following IV, IM, and SC administrations to sheep are presented in Figure 1 and Table 1, respectively. Furosemide was detected in the plasma up to 5 hr following IV, IM, and SC administrations. The mean total clearance and volume of distribution at steady state following IV administration were 0.24 L h^{-1} kg^{-1} and 0.17 L/kg, respectively. The elimination half-life was similar for all administration routes ($p > .05$). The mean peak plasma concentrations of IM and SC administration were 10.33 and 3.18 μg/ml at 0.33 and 0.42 hr, respectively. The mean bioavailability of IM and SC administration was 97.91% and 37.98%, respectively.

4 | DISCUSSION

Furosemide is used in the wide range of dose in cattle (0.5–5 mg/kg), horses (0.5 to 1 mg/animal or 1 to 4 mg/kg), and pigs (2 to 5 mg/kg) for the treatment of conditions such as edema, intoxications, renal failure, and heart failure (Blaze & Glowaski, 2004; Constable et al., 2017; CVMP, 1999). In sheep, it has been also recommended for the same therapeutic effects at a dose range of 1 to 4 mg/kg (Blaze & Glowaski, 2004; Fajt & Pugh, 2012). In addition, the high doses of furosemide have been reported for the treatment (6 mg/kg) of the monensin toxicosis in sheep (Jones, 2001) and in experimental studies (5 to 10 mg/kg) on the lamb and sheep (Lush et al., 1983; Patel & Smith, 1997; Smith & Abraham, 1995). In this study, sheep received furosemide at 2.5 mg/kg dose within the recommended dose range (1–4 mg/kg, Blaze & Glowaski, 2004; Fajt & Pugh, 2012). However, cardiovascular, renal, and endocrine responses to furosemide in sheep vary depending on the dose (Lush et al., 1983; Patel & Smith, 1997; Smith & Abraham, 1995). The effects of furosemide vary for different routes of the administration because of the variable absorption (Ali et al., 1998; Johansson et al., 2004; Sleeper et al., 2019). In this study, the bioavailability of furosemide following IM, and SC injections, which are the widely preferred routes of drug administration in sheep, was determined. However, this study has some limitations that require determination of the effects of furosemide for the 2.5 mg/kg dose and according to the route of administration prior to its use in sheep.

The V_{dss} of furosemide after IV administration in sheep was 0.17 L/kg, which was lower than that previously reported in camel (0.43 L/kg, Ali et al., 1998), horse (0.25–0.65 L/kg, Dyke et al., 1996; Knych et al., 2018), dog (0.25 L/kg, Hirai et al., 1992), cat (0.23 L/kg, Sleeper et al., 2019), and piglet (0.20–0.62 L/kg, Miceli et al., 1990). In this study, the binding ratio of furosemide to the plasma proteins was not determined in sheep. The binding ratio of furosemide to the plasma proteins in horse, bovine, dog, and rabbit is 95, 98.1, 87, and 97.7%, respectively (Johansson et al., 2004; Prandota & Pruitt, 1991). In comparison between 3-day and 18-day piglets, the distribution volume of furosemide decreased from 0.62 L/kg to 0.2 L/kg due to the change in the binding ratio to the proteins (Miceli et al., 1990). The reason for low V_{dss} in sheep may be due to the fact that the binding ratio of furosemide to the plasma proteins varies between species. The Cl_T of furosemide in sheep was 0.24 L h^{-1} kg^{-1}, which was lower than that

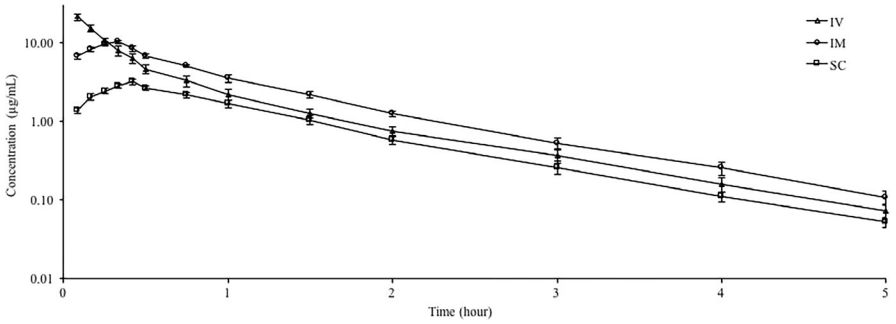

FIGURE 1 Semi-logarithmic plasma concentration–time curves of furosemide following intravenous (IV), intramuscular (IM), and subcutaneous (SC) administrations at a dose of 2.5 mg/kg in sheep ($n = 6$, mean ± *SD*)

TABLE 1 Plasma pharmacokinetic parameters of furosemide following intravenous (IV), intramuscular (IM), and subcutaneous (SC) administrations at a dose of 2.5 mg/kg in sheep ($n = 6$, mean ± *SD*)

Parameters	IV	IM	SC
$t_{1/2\lambda z}$ (h)	0.79 ± 0.04	0.80 ± 0.05	0.80 ± 0.02
$AUC_{0-\infty}$ (h*μg/mL)	10.49 ± 1.25[a]	10.18 ± 0.58[a]	3.95 ± 0.36[b]
$MRT_{0-\infty}$ (h)	0.70 ± 0.04[c]	1.07 ± 0.06[b]	1.24 ± 0.05[a]
Cl_T (L/h/kg)	0.24 ± 0.03	-	-
V_{dss} (L/kg)	0.17 ± 0.02	-	-
C_{max} (μg/mL)	-	10.33 ± 0.63	3.18 ± 0.24*
T_{max} (h) (M)	-	0.33	0.42*
F (%)	-	97.91 ± 10.44	37.98 ± 4.75*

Note: [a,b,c]Varied characters in the same row are statistically different ($p < .05$). $t_{1/2\lambda z}$; elimination half-life, AUC; area under the plasma concentration–time curve, MRT; mean residence time, Cl_T; total clearance, V_{dss}; volume of distribution at steady state, C_{max}; peak concentration, T_{max}; time to reach peak concentration, M; median.

*Value is statistically different than that in IM administration ($p < .05$).

previously reported in camel (0.32 L h^{-1} kg^{-1}, Ali et al., 1998), horse (0.44–0.78 L h^{-1} kg^{-1}, Dyke et al., 1996; Johansson et al., 2004), dog (0.44–0.67 L h^{-1} kg^{-1}, Hirai et al., 1992; Miyazaki et al., 1990), and piglet (0.78–0.9 L h^{-1} kg^{-1}, Miceli et al., 1990) and higher than that reported in cat (0.15 L h^{-1} kg^{-1}, Sleeper et al., 2019). The renal and fecal excretion ratios of furosemide, that differs significantly between species including cattle, horse, dog, and rat, ranged from 16% to 89.1%, and from 5.4% to 54%, respectively (CVMP, 1999; Hirai et al., 1992; Villarino et al., 2019). While the 85% of furosemide metabolized in the liver and kidney was excreted unchanged with urine in dogs and monkeys, this ratio was 75%–80% in pig and 50%–60% in horses (CVMP, 1999; Miceli et al., 1990; Villarino et al., 2019). The variability of Cl_T between species may be due to the difference in the elimination of furosemide from the body. In sheep, the $t_{1/2\lambda z}$ of furosemide was 0.79 hr, which was similar to that reported in dog (0.51–0.93 hr; Hirai et al., 1992; Miyazaki et al., 1990), and shorter than that reported in camel (1.97 hr, Ali et al., 1998) and horse (2.27–3.42 hr, Johansson et al., 2004). The difference in $t_{1/2\lambda z}$ may be due to changes in the volume of distribution and elimination of furosemide among the species.

The $t_{1/2\lambda z}$ (0.80 hr), obtained after IM and SC administration of furosemide in sheep, was similar to IV (0.79 hr) ($p > .05$). It has been noted that the $t_{1/2\lambda z}$ following the IM (1.82 hr) and IV (1.96 hr) administration of furosemide in camels did not show significant difference (Ali et al., 1998). However, there is no information about $t_{1/2\lambda z}$ of furosemide following the SC administration in ruminants. In this study, the C_{max} of furosemide following the IM and SC administration at 2.5 mg/kg dose was 10.33, and 3.18 μg/ml at 0.33 hr, and 0.42 hr, respectively. In camel, it was stated that the C_{max} and T_{max} of furosemide were 2.1 μg/ml and 0.25 hr, respectively, after the IM administration at the 1.5 mg/kg dose (Ali et al., 1998). The bioavailability of furosemide after IM and SC administration was 97.91% and 37.98%, respectively. The IM bioavailability of furosemide in camels has been reported as 71% (Ali et al., 1998).

The effect of furosemide is dose dependent in sheep (Lush et al., 1983; Patel & Smith, 1997; Smith & Abraham, 1995). In the present study, the pharmacokinetic/pharmacodynamics relationship of furosemide following the administration at 2.5 mg/kg dose in sheep was not determined. However, the plasma concentration required to show half maximum diuretic effect of furosemide has been reported to be 1 μg/ml in human and 1.5 μg/ml in dog (Hirai et al., 1992; Miyazaki et al., 1990). Additionally, while the diuretic effect of furosemide decreases in the plasma concentration of >10 μg/ml (CVMP, 1999; Hirai et al., 1992), the plasma concentration of >25 μg/ml increases the risk of ototoxicity (Kandasamy & Carlo, 2017). In the present study, the plasma concentrations of furosemide at the first (0.08 hr) and last (5 hr) sampling times were 6.68 μg/ml and 0.11 μg/ml for IM administration, respectively, and 1.38 μg/ml and 0.05 μg/ml for SC administration, respectively. Following the IV, IM, and SC administration of furosemide at 2.5 mg/kg dose in sheep, the plasma concentration was >1 μg/ml up to 1.5, 2, and 1.5 hr, respectively. The plasma concentration of furosemide after IV administration was 21.40 μg/ml at the initial sampling time (0.08 hr) and remained > 10 μg/ml at 0.25 hr. These data showed that IV, IM, and SC administration of furosemide at 2.5 mg/kg dose may provide the plasma concentration necessary for diuretic effect. However, the effect of high plasma concentration occurred after IV administration at 2.5 mg/kg dose should be assessed in terms of adverse effects.

In conclusion, furosemide in sheep showed fast elimination and small distribution of volume. The IM injection of furosemide with good bioavailability may be the alternative route in addition to IV. Despite low bioavailability, the SC route of furosemide at 2.5 mg/kg dose also provided the pharmacodynamics value (≥1 μg/ml) reported for the diuretic effect. However, further research is required to determine the effect of dose and route of administration on the clinical efficacy of furosemide prior to use in sheep.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

AUTHORS' CONTRIBUTION

DDC, OC, and KU contributed to the conception, design, analysis, and acquisition; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. OA, GC, and AC contributed to design and analysis and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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