Absorption and Disposition of a Selective Aldosterone Receptor Antagonist, Eplerenone, in the Dog

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Purpose. The present study was conducted to characterize the pharmacokinetics of eplerenone (EP), a selective aldosterone receptor antagonist, and its open lactone ring form in the dog.

Methods. Pharmacokinetic studies of EP were conducted in dogs following i.v., oral, and rectal dosing (15 mg/kg) and following intragastric, intraduodenal, intrajejunal, and intracolonic dosing (7.5 mg/kg).

Results. After oral administration, the systemic availability of EP was 79.2%. Systemic availabilities following administration via other routes were similar to that following oral administration. The half-life and plasma clearance of EP were 2.21 hr and 0.329 l/kg/hr, respectively. Plasma concentrations of the open lactone ring form were lower than EP concentrations regardless of the route of administration. The C-14 AUC in red blood cells was approximately 64% and 68% of the plasma AUC for i.v. and oral doses. Percentages of the dose excreted as total radioactivity in urine and feces were 54.2% and 40.6%, respectively, after i.v. administration, and 40.7% and 52.3%, respectively, after oral administration. The percentages of the dose excreted in urine and feces as EP were 13.7% and 2.5%, respectively, after i.v. administration, and 2.1% and 4.6% after oral administration, respectively. Approximately 11% and 15% of the doses were excreted as the open form following i.v. and oral doses.

Conclusions. EP was rapidly and efficiently absorbed throughout the gastrointestinal tract, resulting in a good systemic availability. The drug did not preferentially accumulate in red blood cells. EP was extensively metabolized; however, first-pass metabolism after oral and rectal administration was minimal. EP and its metabolites appear to be highly excreted in the bile.

KEY WORDS: eplerenone; selective aldosterone receptor antagonist; dog; pharmacokinetics, absorption.

INTRODUCTION

Eplerenone (SC-66110; EP) is the first highly selective aldosterone receptor antagonist (SARA) to effectively block aldosterone at receptor sites in tissues throughout the body (1). The presence of the stable 9,11-epoxide group in the steroid molecule of EP (Fig. 1) reduces the progestational and antiandrogenic actions associated with spironolactone, while maintaining its beneficial aldosterone-blocking properties. Clinical and preclinical studies have linked aldosterone to high blood pressure, cardiac hypertrophy, cardiac and vascular fibrosis, renal injury, magnesium loss, baroreceptor sensitivity, ventricular arrhythmias, and increased mortality in patients with heart failure (2). Although angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists reduce aldosterone levels, several studies have shown that aldosterone escape occurs in the majority of patients following chronic treatment (3,4). Furthermore, these drugs are less effective in salt-sensitive hypertensive patients. EP is expected to provide important clinical benefits to patients suffering from hypertension and chronic heart failure.

EP (Fig. 1) is a steroid nucleus-based antimineralocorticoid that is chemically and enzymatically interconvertible with an open form of the lactone ring of EP. SC-70303 is a potassium salt of the open lactone ring of EP. Under basic conditions, EP is converted to the open form, SC-70303 acid, whereas under acidic conditions SC-70303 acid is converted to the closed form, EP. The purpose of the present investigation was to characterize the pharmacokinetics of EP and SC-70303 acid in the dog, one of the major species for toxicity testing of these drugs.

MATERIALS AND METHODS

Test Compounds

The following compounds were supplied from G. D. Searle and Co. (Skokie, IL): nonradiolabeled EP (Lot No. RCT 9967) and radiolabeled [^{14}C]EP (Lot No. GDS 8181-13A). Nonradiolabeled material was stored at room temperature on desiccant and protected from light. Radiolabeled material was stored at approximately –70°C and protected from light. The purity of both test compounds was greater than 96%.

Animals

The study adhered to the "Principles of Laboratory Animal Care" (NIH publication #85-23. Revised 1985). A total of 12 purebred beagles, four dogs from each of the following sites, HSD/Ridglan Farms, Inc., Laboratory Animal Resources, and Hazleton Research Products, were obtained. Dogs were 6 to 13 months old and weighed 7 to 13 kg. During the study, the animals were housed at controlled room temperature (18° to 29°C) in individual, stainless steel cages, modified for the separation and collection of urine and feces. Dogs were fasted prior to dosing and fed ad libitum 4 hours after dose administration. All dogs were provided free access to water.

Study Designs

Intravenous and Oral Pharmacokinetics

Two male and two female beagles were fasted overnight prior to dosing. The animals received i.v. and oral doses of [^{14}C]EP in a crossover manner as an aqueous solution at a dose of 15 mg/kg with a dose volume of 2 ml/kg. The solution for both i.v. and oral doses was prepared by dissolving [^{14}C]EP in 15% sulfobutyl-β-cyclodextrin in 0.07 M sodium phosphate buffer (pH 7.4) and contained 0.5% the NaCl. A washout period of approximately 2 weeks was allowed between treatments. Blood, urine, and fecal samples were collected at specified time intervals.

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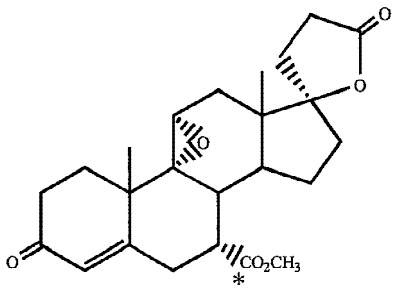
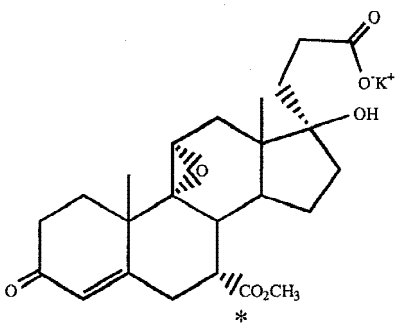


SC-66110



SC-70303

Fig. 1. Chemical structures of [^{14}C]EP and [^{14}C]SC-70303. Asterisks indicate the position of the labeled carbon atom.

Site Absorption

Four female beagles had chronic intestinal access ports (CIAP) implanted in the upper duodenum, jejunum, and colon. The animals with CIAP received EP solution at a dose of 7.5 mg/kg (dose volume of 1 ml/kg) intragastrically (IG) by a gastric tube or intraduodenally (ID), intrajejunally (IJ), and intracolonically (IC) via the CIAP. Blood samples were collected at specified time intervals.

Rectal Absorption

Four male beagles received [^{14}C]EP orally and rectally in a crossover manner at a dose of 15 mg/kg (dose volume of 2 ml/kg). Blood, urine, and fecal samples were collected at specified time intervals.

Sample Analysis

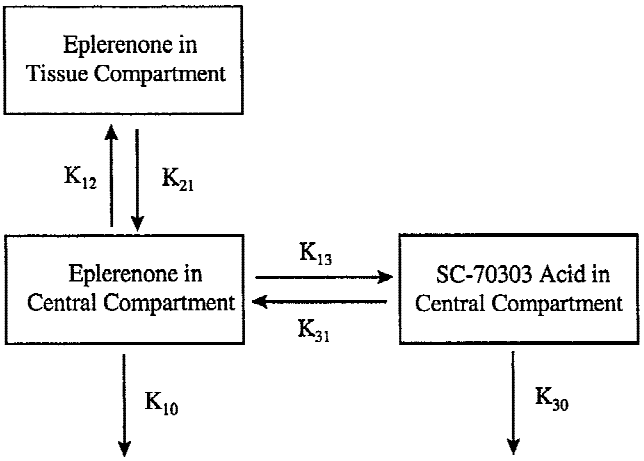
Concentrations of EP and SC-70303 acid in unacidified plasma were analyzed at CEDRA Corporation (Austin, TX) by a liquid chromatographic/tandem mass spectrometric (LC-MS/MS) assay. In addition, concentrations of total EP in acidified plasma (pH ~1.0) also were analyzed by a separate LC-MS/MS procedure. The assay sensitivity was 10 ng/ml for EP and SC-70303 acid and 50 ng/ml for total EP. Urinary and fecal concentrations of EP were determined by high-performance liquid chromatography (HPLC) without acidification, and the concentrations of total EP were determined after acidification of the samples.

LC-MS/MS Procedure

Concentrations of EP and SC-70303 acid were determined by an LC-MS/MS procedure using [D_3, $^{13}C_1$]EP and [D_3, $^{13}C_1$]SC-70303 acid, respectively, as internal standards. The plasma samples were extracted with a C18 Bond Elut solid phase column that was preconditioned with acetonitrile and water. After washing the column with water, the analytes were eluted from the column with 0.25 ml acetonitrile. To the eluates, 0.15 ml of 20 mM ammonium acetate in water was added, and the sample mixture was injected onto a reverse phase Zorbax column (Hewlett Packard, Newport, DEL).

Pharmacokinetic Analysis

EP curves and SC-70303 acid curves after i.v. administration of EP were simultaneously fit according to the following pharmacokinetic model using the SAAM II (SAAM Inst., Seattle WA) computer program.



Plasma concentrations of EP (C_{ep}) and SC-70303 acid (C_{sc}) can be described by the following tri-exponential equations:

$$C_{ep} = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \quad (1)$$

$$C_{sc} = De^{-\alpha t} + Ee^{-\beta t} + Fe^{-\gamma t} \quad (2)$$

where

$$A = \frac{X_0(\alpha\text{-}K_{21})\,(\alpha\text{-}K_{30}\text{-}K_{31})}{V_1(\alpha\text{-}\beta)\,(\alpha\text{-}\gamma)}$$

$$B = \frac{X_0(\beta\text{-}K_{21})\,(\beta\text{-}K_{30}\text{-}K_{31})}{V_1(\beta\text{-}\alpha)\,(\beta\text{-}\gamma)}$$

$$C = \frac{X_0(\gamma\text{-}K_{21})\,(\gamma\text{-}K_{30}\text{-}K_{31})}{V_1(\gamma\text{-}\alpha)\,(\gamma\text{-}\beta)}$$

$$D = \frac{X_0K_{13}\,(K_{21}\text{-}\alpha)}{V_3(\alpha\text{-}\beta)\,(\alpha\text{-}\gamma)}$$

$$E = \frac{X_0K_{13}\,(K_{21}\text{-}\beta)}{V_3(\beta\text{-}\alpha)\,(\beta\text{-}\gamma)}$$

$$F = \frac{X_0K_{13}\,(K_{21}\text{-}\gamma)}{V_3(\gamma\text{-}\alpha)\,(\gamma\text{-}\beta)}$$

and

$$\alpha + \beta + \gamma = K_{10} + K_{12} + K_{13} + K_{21} + K_{30} + K_{31}$$

$$\alpha\beta + \beta\gamma + \gamma\alpha = K_{10}K_{21} + K_{10}K_{30} + K_{10}K_{31} + K_{12}K_{30}K_{12}K_{31} + K_{13}K_{21} + K_{13}K_{30} + K_{21}K_{30} + K_{21}K_{31}$$

$$\alpha\beta\gamma = K_{10}K_{21}K_{30} + K_{10}K_{21}K_{31} + K_{13}K_{21}K_{30}$$

X_0 is the dose administered, and V_1 and V_3 are volumes of distribution for EP and SC-70303 acid, respectively.

Plasma concentration-time curves of total EP after i.v. administration were analyzed according to a bi-exponential equation using the WinNonlin computer program (Phasight Corp., Mountain View, CA).

RESULTS

Intravenous Pharmacokinetics

Figure 2 shows the mean plasma concentrations (± SEM) of total radioactivity, EP, and SC-70303 acid in plasma after i.v. administration of [^{14}C]EP. The mean initial concentration (± SD) of total radioactivity in male and female dogs was 33.9 ± 3.0 μg eq/ml 2 mins following i.v. dose administration. The half-life of total radioactivity of the terminal phase was 4.0 ± 0.2 hr, and the mean $AUC_{0-\infty}$ was 130 ± 15.7 μg eq · hr/ml.

Concentrations of total radioactivity in red blood cells (RBC) were lower than those in plasma. The RBC concentration of total radioactivity at 2 mins was 14.7 ± 2.4 μg eq/ml, and the $AUC_{0-\infty}$ in RBC was 82.6 ± 12.5 μg eq · hr/ml (approximately 64% of plasma AUC).

EP and SC-70303 acid concentration-time curves after i.v. administration of EP were simultaneously fit according to the pharmacokinetic model presented previously. The rate constants obtained are given in Table I. Although EP was rapidly converted to the open form, the conversion rate constant (K_{13}) of EP to SC-70303 acid was much smaller than the conversion rate constant (K_{31}) of SC-70303 acid to EP, resulting in high concentrations of EP. The mean elimination half-life of EP for the terminal phase (γ) was 2.1 hr. The mean plasma clearance of EP was 0.329 ± 0.086 l/kg/hr, and the mean $AUC_{0-\infty}$ was 47.8 ± 11.4 μg · hr/ml. The AUC of EP was approximately 36% of the AUC of total radioactivity, indicating extensive metabolism.

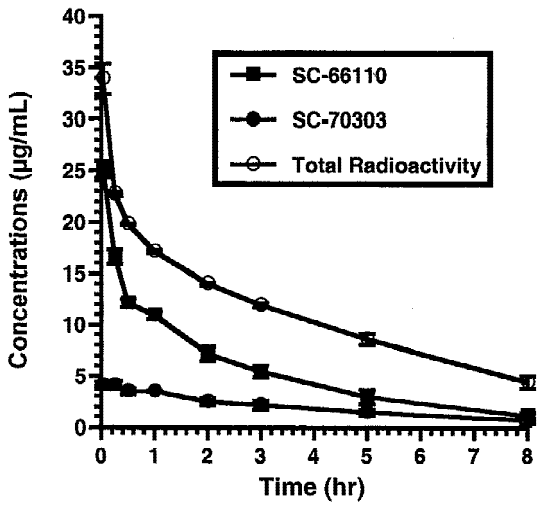


Fig. 2. Mean plasma concentration-time curves following i.v. dosing.

Table I. Pharmacokinetic Parameters of EP Obtained from Simultaneous Fit of EP and SC-70303 Acid

Parameters[a]	Dog 1	Dog 2	Dog 3	Dog 4	Mean	SD
α (hr^{-1})	33.2	26.6	26.6	23.8	27.6	4.0
β (hr^{-1})	6.35	19.8	12.2	6.82	11.3	6.3
γ (hr^{-1})	0.346	0.294	0.454	0.219	0.328	0.098
K_{10} (hr^{-1})	0.704	0.647	1.10	0.456	0.727	0.270
K_{12} (hr^{-1})	2.84	12.7	13.0	2.80	7.84	5.80
K_{13} (hr^{-1})	0.846	1.45	2.70	0.835	1.46	0.88
K_{21} (hr^{-1})	3.64	11.2	10.9	3.24	7.25	4.40
K_{30} (hr^{-1})	0.295	0.295	0.319	0.293	0.301	0.012
K_{31} (hr^{-1})	27.6	20.4	11.2	23.2	20.6	7.0
V_1 (l/kg)	0.497	0.428	0.376	0.574	0.469	0.0086
V_3 (l/kg)	0.0530	0.106	0.275	0.0500	0.121	0.106

[a] The rate constants are defined in the calculation and pharmacokinetic analysis section in the text. V_1 = volume of distribution for EP. V_3 = volume of distribution for SC-70303 acid.

Plasma concentrations of SC-70303 acid were lower than EP concentrations at all timepoints after i.v. administration. The mean C_{max} of SC-70303 acid was 4.21 ± 0.72 μg/ml, and the mean T_{max} was 0.20 ± 0.22 hr. These results indicate rapid conversion of EP to the open form after i.v. administration. The mean $AUC_{0-\infty}$ of SC-70303 acid was approximately 39% of the $AUC_{0-\infty}$ of EP.

At 2 mins, the mean concentration of total EP after i.v. administration was 28.9 μg/ml. When the concentration-time curves were analyzed according to a bi-exponential equation (Table II), the half-life of the terminal phase (β) of total EP was 2.67 hr. The mean Vd of total EP was 0.893 l/kg, and the mean clearance was 0.249 l/kg/hr. The mean $AUC_{0-\infty}$ was 64.0 μg · hr/ml. This value is approximately 49% of the $AUC_{0-\infty}$ values of total radioactivity.

Absorption

Oral Absorption

Figure 3 shows the mean (± SEM) plasma concentrations of total radioactivity, EP, and SC-70303 acid in plasma after oral administration of [^{14}C]EP. The mean (± SD) of total radioactivity in plasma was 14.4 ± 0.54 μg eq/ml, and the T_{max} was 1.0 ± 0.0 hr. The mean $AUC_{0-\infty}$ was 123 ± 22 μg eq · hr/ml, and the elimination half-life was 4 hr. The systemic availability of total radioactivity was 94.5 ± 6.6%, indicating good absorption of [^{14}C]EP in the dog. As observed in the i.v. data, RBC concentrations of total radioactivity were lower than plasma concentrations. The RBC C_{max} was 9.57 ± 0.6 μg eq/ml, and the AUC was 84.5 ± 15.9 μg eq · hr/ml, which was approximately 68% of plasma AUC for total radioactivity.

After oral administration, the mean C_{max} of EP was achieved within 1 hr, indicating rapid absorption (Table III). The systemic availability of EP was 79.2%, and the $AUC_{0-\infty}$ of EP was approximately 31% of the AUC value of total radioactivity. The plasma concentrations of SC-70303 acid were lower than EP concentrations after oral administration. The mean C_{max} of SC-70303 acid was 3.78 ± 1.02 μg/ml, and the mean T_{max} of SC-70303 acid was 0.75 ± 0.28 hr. The apparent terminal half-life of SC-70303 acid was 3.77 ± 1.16 hr, and the

Table II. Pharmacokinetic Parameters of Total EP Following the I.V. Dosing of EP

Parameters	Dog 1	Dog 2	Dog 3	Dog 4	Mean	SD
A (μg/ml)	16.4	13,3	24.2	10.6	16.1	5.8
α (hr^{-1})	5.69	6.91	11.1	3.08	6.70	3.34
α $t_{1/2}$ (hr)	0.122	0.100	0.0625	0.225	0.127	0.070
B (μg/ml)	15.7	15.8	17.9	15.4	16.2	1.2
β (hr^{-1})	0.304	0.234	0.412	0.184	0.284	0.098
β $t_{1/2}$ (hr)	2.28	2.96	1.68	3.77	2.67	0.90
V_1 (l/kg)	0.468	0.516	0.357	0.577	0.480	0.094
V_d (l/kg)	0.907	0.925	0.800	0.938	0.893	0.062
V_{ss} (l/kg)	0.862	0.900	0.763	0.903	0.857	0.066
CL (l/kg/hr)	0.276	0.216	0.329	0.173	0.249	0.068
AUC (μg · hr/ml)	54.4	69.3	45.5	86.9	64.0	18.2

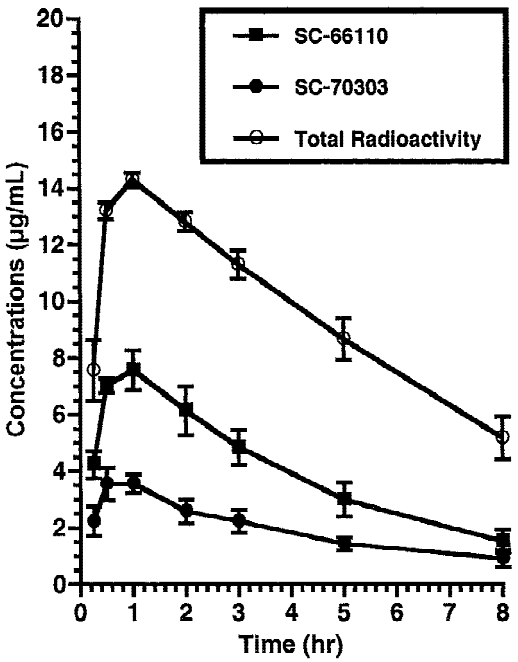


Fig. 3. Mean plasma concentration-time curves following oral dosing.

mean AUC was 21.2 ± 10.1 μg · hr/ml, which is approximately 55% of the $AUC_{0-\infty}$ value of EP. The mean C_{max} of total EP (10.4 μg/ml) was achieved at 0.75 hr, indicating rapid absorption (see Table III). The apparent terminal half-life of total EP in plasma was 3.24 hr, and the mean $AUC_{0-\infty}$ of total EP was 58.4 μg · hr/ml, which was approximately 47% of the mean AUC value of total radioactivity. The mean systemic availability of total EP was 90.0%, indicating good absorption of EP.

Site Absorption

Table IV summarizes the pharmacokinetic parameters of EP, SC-70303 acid, and total EP after IG, ID, IJ and IC administration. The T_{max} values for both EP and total EP increased in the following order: IJ < IG, ID < IC. The AUC values for EP or total EP after IG, ID, and IJ administration were similar. However, the drug was more slowly absorbed in the colon and the AUC values after IC administration were approximately 88% of that after IG administration.

Table III. Pharmacokinetic Parameters of EP, SC-70303 Acid and Total EP Following the Oral Dose of [^{14}C]EP

Parameters	Dog 1	Dog 2	Dog 3	Dog 4	Mean	SD
EP						
C_{max} (μg/ml)	7.63	9.51	7.15	7.63	7.98	1.04
T_{max} (hr)	1	1.0	0.5	0.5	0.75	0.28
$T_{1/2}$ (hr)	2.18	2.57	1.97	4.14	2.72	0.98
AUC (μg · hr/ml)	30.5	48.9	25.0	48.9	38.3	12.4
BA (%)	68.7	90.7	74.6	82.6	79.2	9.6
SC-70303 Acid						
C_{max} (μg/ml)	3.27	3.54	3.02	5.29	3.78	1.02
T_{max} (hr)	1	1	0.5	0.5	0.75	0.28
$T_{1/2}$ (hr)	3.40	4.29	2.35	5.05	3.77	1.16
AUC (μg · hr/ml)	15.3	22.6	12.0	34.7	21.2	10.1
Total EP						
C_{max} (μg/ml)	8.43	11.7	9.15	12.2	10.4	1.8
T_{max} (hr)	1	1	0.5	0.5	0.75	0.28
$T_{1/2}$ (hr)	3.01	3.59	2.35	4.00	3.24	0.72
AUC (μg · hr/ml)	46.2	73.4	36.3	77.6	58.4	20.2
BA (%)	84.9	106	79.8	89.3	90.0	11.4

Rectal Absorption

After rectal administration, the C_{max} values of total radioactivity, EP, SC-70303 free acid, and total EP were 7.32 ± 0.070, 4.35 ± 0.44, 0.916 ± 0.152 and 5.12 ± 0.54 μg/ml, respectively. The corresponding values after oral administration to the same dogs were 12.8 ± 1.2, 9.11 ± 1.74, 1.09 ± 0.10, and 10.1 ± 2.0 μg/ml, respectively. The T_{max} values ranged from 3.5 hrs to 5.3 hrs after rectal administration and from 1.0 hr to 1.5 hrs after oral administration. The AUC values of total radioactivity, EP, SC-70303 free acid, and total EP were 99.5 ± 15.0, 45.5 ± 7.8, 12.5 ± 2.4 and 57.5 ± 9.8 μg · hr/ml, respectively, after rectal administration, and 106 ± 14, 54.3 ± 9.0, 10.9 ± 1.6 and 64.7 ± 10.4 μg · hr/ml, respectively, after oral administration. Similarity of AUC values after rectal and oral administration indicates good absorption of EP in the rectum.

Metabolic Profiles

In plasma, the parent drug was the single major radioactive peak regardless of the route of administration (Fig. 4). In addition to the parent drug peaks, two major metabolite peaks (6β-OH and 21-OH) were observed. In both urine and feces, many metabolites were observed after i.v. and oral administration, indicating extensive metabolism of EP in the dog. The mean percentages of urinary radioactivity associated

Table IV. Mean Pharmacokinetic Parameters of EP After Gastric, Duodenum, Jejunum, and Colon Administration of EP

Route	Analyte	Mean (± SD) of Pharmacokinetic Parameters		
		C_{max} (μg/ml)	T_{max} (hr)	AUC (μg · hr/ml)
Stomach	EP	4.91 ± 0.80	0.56 ± 0.32	13.6 ± 1.2
	SC-70303	0.450 ± 0.034	0.75 ± 0.28	1.67 ± 0.10
	Total EP	5.31 ± 0.82	0.56 ± 0.32	15.2 ± 1.2
Duodenum	EP	4.88 ± 0.78	0.63 ± 0.26	14.4 ± 1.8
	SC-70303	0.472 ± 0.080	0.75 ± 0.28	1.94 ± 0.36
	Total EP	5.33 ± 0.82	0.63 ± 0.26	16.3 ± 2.0
Jejunum	EP	6.48 ± 1.12	0.25 ± 0.00	15.4 ± 2.2
	SC-70303	0.811 ± 0.140	0.38 ± 0.14	2.15 ± 0.40
	Total EP	7.22 ± 1.30	0.25 ± 0.00	17.4 ± 2.6
Colon	EP	1.70 ± 0.24	1.8 ± 0.8	11.6 ± 4.4
	SC-70303	0.233 ± 0.034	1.8 ± 0.6	1.85 ± 0.76
	Total EP	1.91 ± 0.26	1.5 ± 0.4	13.4 ± 5.0

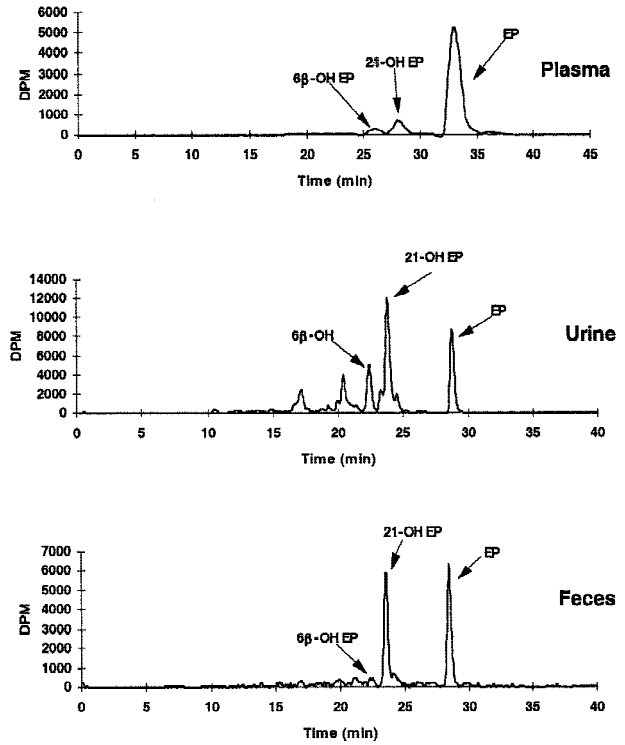


Fig. 4. Metabolic profiles of plasma (1 hr), urine and feces after oral administration.

with total EP were approximately 36.5 ± 7.3% and 21.6 ± 7.5% after i.v. and oral administration, respectively. The corresponding values for fecal radioactivity were approximately 20.4 ± 8.0% and 25.7 ± 5.3%, respectively.

Excretion

The mean percentages of the dose excreted as total radioactivity in the urine and feces were 54.2 ± 9.3% and 40.6 ± 2.7%, respectively, after i.v. administration. The corresponding values after oral administration were 40.7 ± 2.9% and 52.3 ± 3.7%, respectively. After rectal administration, urinary excretion of total radioactivity was similar to that following oral administration, indicating good absorption of the drug from the rectum. Urinary radioactivity excretion was maximal within the first 24 hours, indicating rapid elimination of the compound and metabolites. The total recovery of the radioactive dose in urine and feces was 96.7 ± 9.9% and 96.9 ± 0.4% after i.v. and oral administration, respectively. The mean percentage of the dose excreted in 0- to 48-hr urine as EP and total EP was 13.7 ± 3.8% and 19.6 ± 6.0%, respectively, after i.v. administration. The corresponding values after oral administration were 2.1 ± 1.8% and 8.6 ± 3.6%, respectively. The mean percentage of the dose excreted in feces as EP and total EP was 2.5 ± 0.8% and 7.9 ± 2.6% after i.v. administration. The corresponding values after oral administration were 4.6 ± 1.0% and 12.9 ± 1.8%, respectively.

DISCUSSION

Following an i.v. dose, EP was rapidly converted to its open form, reaching the C_{max} of SC-70303 acid in 0.2 hr. However, conversion to the closed form was more rapid as demonstrated by greater values for K_{31} than K_{13}. These conversion rates led to maintenance of higher EP concentrations compared with the acid concentrations. Thus, based on this analysis, alternative administration of SC-70303 would result in rapid conversion of the open lactone ring form to produce a comparable plasma concentration of EP.

EP is highly lipophilic with aqueous solubility of less than 5 mg/ml. However, the drug was rapidly and quantitatively absorbed after oral administration to the dog. EP was also well absorbed in humans (absorption greater that 70%) and increase in the AUC was approximately proportional to dose over the clinically relevant dose range (50 mg to 300 mg) (5). Thus, the dog is a good animal model for a study of absorption of EP. Quantitative absorption of EP was the result of good absorption of the drug throughout the gastrointestinal tract. The site absorption study demonstrated that the systemic availability of EP following ID, IJ, and rectal administration were similar to that of oral administration. However, absorption of EP was most rapid in the jejunum and slowest in the colon. Although colon absorption was slowest, the systemic availability of the drug following IC dose administration was 88% of that following oral dosing. Thus, the drug was well absorbed in the colon, which appeared to be due to the

longer residence time of the drug in the colon, with relatively good permeable characteristics compared with the other parts of the gastrointestinal tract. Based on these results, EP is expected to be a good candidate for an extended formulation to sustain blood levels for a longer time period if necessary.

Concentrations of total radioactivity in RBC were lower than those in the plasma, regardless of the route of administration selected. The majority of plasma radioactivity was due to the parent drug. Thus, EP did not preferentially accumulate in RBC in the dog.

EP was extensively metabolized, and approximately 17% and 7% of the dose after i.v. and oral administration, respectively, were excreted as the parent drug in both the urine and feces. Approximately 11% and 15% of i.v. and oral doses, respectively, were excreted as the SC-70303 acid. Therefore, the extensive metabolism accounted for the short half-life of the drug in the dog. However, the systemic availability of EP and total EP was good, and was approximately 80% and 90%, respectively, following oral dose administration. Furthermore, AUC ratios of EP or total EP to total radioactivity were similar following i.v. and oral administration. These results, as a whole, indicate that unlike other extensively metabolized drugs (e.g., propranolol, verapamil), the first-pass metabolism of EP was minimal after oral administration. Both propranolol and verapamil are completely absorbed (6). However, due to extensive first-pass metabolism, the systemic availabilities of the parent drug are only about 30% and 22%, respectively (7). As expected, the first-pass metabolism after rectal administration also was minimal.

Metabolites were eliminated by renal and fecal excretion, both of which are of similar importance. The relatively high proportion of fecal excretion suggests extensive biliary excretion of the metabolites and possibly, some intestinal secretion.

In conclusion, EP was rapidly and efficiently absorbed throughout the gastrointestinal tract. Preferential accumulation of the drug in RBC did not occur. The metabolism of EP was extensive; however, first pass metabolism after oral and rectal administration was minimal. The urinary and biliary excretion of EP and its metabolites are almost equally important routes of elimination.

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