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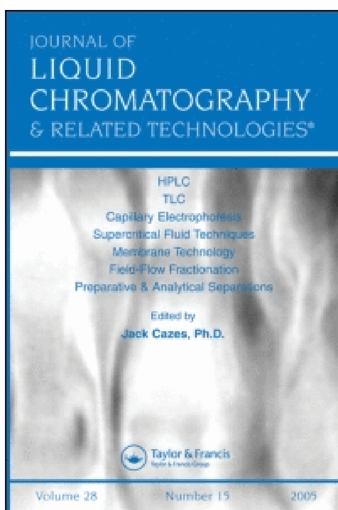

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
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To cite this Article Khetarpal, V. K. , Cariola, C. M. , Collina, S. J. and Ziemniak, J. A.(1994) 'Assay of RP 69698, a Novel LTB4-Antagonist, in Plasma by HPLC and its Application for Characterizing Pharmacokinetics of the Drug in Dogs', Journal of Liquid Chromatography & Related Technologies, 17: 2, 329 — 346
To link to this Article: DOI: 10.1080/10826079408013355
URL: http://dx.doi.org/10.1080/10826079408013355

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JOURNAL OF LIQUID CHROMATOGRAPHY, 17(2), 329-346 (1994)

ASSAY OF RP 69698, A NOVEL LTB4-ANTAGONIST, IN PLASMA BY HPLC AND ITS APPLICATION FOR CHARACTERIZING PHARMACOKINETICS OF THE DRUG IN DOGS

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ABSTRACT

To support the preclinical development of RP 69698, a novel antagonist of LTB4, a high-performance liquid chromatographic (HPLC) procedure was developed for its determination in plasma. The method involves extraction of RP 69698 from deproteinized plasma with hexane:ethyl acetate under acidic conditions followed by reversed-phase HPLC with detection at 258 nm. The method is rapid, simple, and is applicable to dog, rat, and monkey plasma. Validation studies using dog plasma showed that the values obtained for parameters of linearity, precision, and accuracy were within acceptable limits. Based on analysis of 0.5 ml of plasma, the lower limit of quantitation was determined to be 25 ng/ml. The method has been successfully applied to determine the pharmacokinetic parameters of RP 69698 in the dog following intravenous and intragastric administration. The results of the dog study indicated rapid clearance of the drug from plasma (0.4 L/hr/kg) and limited distribution (volume of distribution at steady state =0.24 L/kg). When given intragastrically as a solution in PEG 400, absolute bioavailability of the drug was 59% but when given as an aqueous suspension in 0.5% methylcellulose, the drug was poorly absorbed with absolute bioavailability estimated to be about 6%.

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INTRODUCTION

Leukotriene B4 (LTB4) has been shown to play a critical role in the onset of late-phase asthma by promoting the migration of eosinophils into respiratory tissues (1). RP 69698, 2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenylpyridine, is a specific inhibitor of LTB4 binding to polymorphonuclear leukocytes (PMNs) with IC50 ranging from 2.2 nM to 14.5 nM depending upon the species from which the PMNs were obtained (2). RP 69698 is undergoing evaluation as a potential therapeutic agent for the treatment of asthma. To support preclinical development of the drug, a method was developed to analyze RP 69698 in the plasma. This report describes the method and its validation using dog plasma. In addition, applicability of the method is shown in a pharmacokinetic study conducted in dogs following intravenous and intragastric administration of the drug.

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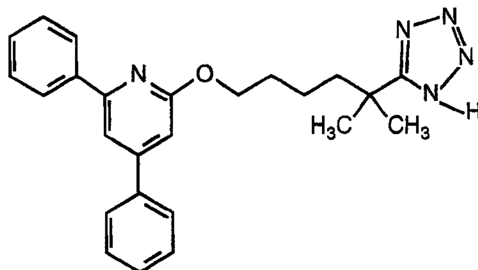
MATERIALS AND METHODS

Materials

The test compound, RP 69698, was synthesized at Rhône-Poulenc Rorer (Collegeville, PA). RP 69698 has a molecular weight of 413.5. The internal standard (I.S.) used was 5,7-dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)-furo[3,4,-e]-1,2,4-triazine, and was obtained from Aldrich Chemical Co., Milwaukee, Wisconsin. The structures of RP 69698 and I.S. are shown in Figure 1.

HPLC grade ethyl acetate, hexane, acetonitrile and sodium acetate were obtained from Fisher Scientific Co. (Pittsburgh, PA).

RP 69698



2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenylpyridine

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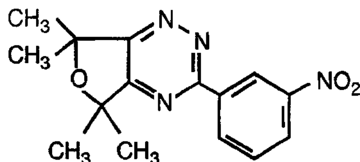
INTERNAL STANDARD



5,7-Dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)furo[3,4-*e*]-1,2,4-triazine

FIGURE 1. Structures of RP 69698 and internal standard (I.S.).

Acetic acid (analytical grade) and polyethylene glycol (PEG) 400 (certified grade) were also obtained from Fisher Scientific Co. Methylcellulose (viscosity of a 2% solution at 25°C: 400 cps) was obtained from Sigma Chemical Co. (St. Louis, MO). Deionized water was produced by a Milli-Q reagent water system (Millipore Corp., Bedford, MA). Control dog plasma (heparinized) was obtained from

either in-house supply or from Lampire Biological Laboratories (Pipersville, PA).

Preparation of Standards

Stock solutions of RP 69698 were prepared in acetonitrile at concentrations of 2.5 mg/ml or 1.0 mg/ml. The I.S. stock solution was prepared in acetonitrile at a concentration of 1.0 mg/ml. The working solutions of RP 69698 and I.S. were prepared by diluting stock solutions with HPLC mobile phase. Stock and working solutions were stored at room temperature in amber-colored volumetric flasks. Plasma standards, in the range of 25 ng/ml to 50 μg/ml, were prepared by aliquoting appropriate volumes of a stock or working solution of RP 69698 and adjusting to 5 ml with blank (drug free) plasma. Reference control concentrations (75, 250, and 750 ng/ml and 2.5 and 12.5 μg/ml) were similarly prepared for monitoring the performance of the assay during each run. Plasma standards and controls were stored at $-20^{\circ}C$ until used or up to a maximum of 1 month.

Buffer Solutions

Two sodium acetate buffer solutions, one adjusted to pH 5.0 and the other adjusted to pH 6.1, were used during the analytical procedure. The pH 5.0, 0.1M sodium acetate buffer was prepared by mixing 14.8 ml of 0.2M acetic acid and 352 ml of 0.2M sodium acetate and then bringing the volume to 1 liter with deionized water. The pH 6.1, 0.1M sodium acetate buffer was prepared by combining 15 ml of 0.2M acetic acid with 485 ml of 0.2M sodium acetate and then bringing the volume to 1 liter with deionized water. The buffer solutions were stored at room temperature for up to a week.

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HPLC Instrumentation and Operating Conditions

The chromatographic analyses were performed using a Waters (Milford, MA) HPLC system consisting of a model 510 pump, model 484 UV detector and a model 712 autosampler (WISP). The system was controlled by a 840 data control station. The HPLC peaks were identified by retention time with reference to standard compounds and quantitated using peak area ratio of RP 69698 to I.S. Analog data were collected, digitized and stored using chromatography software (version 4.1) obtained from Perkin Elmer Nelson systems (Cupertino, CA). The chromatographic conditions were as follows:

Column:	Partisil 10 (particle size 10μm), ODS-3 (25cm x 4.5mm I.D.) analytical column (Whatman, Clifton, N.J.)
Guard Column:	C18 RCSS Guard Pak-C18 precolumn module (Waters Assoc., Milford, MA.)
Temperature:	30°C
Mobile Phase:	48% Acetonitrile and 52% 0.1M sodium acetate (pH 6.1) buffer
Flow Rate:	2 ml/min
Run Time:	35 min
Detection:	Absorbance at 258 nm
Retention Time:	RP 69698 - approximately 10 min I.S. - approximately 14.5 min

Extraction Procedure

For sample preparation, frozen plasma was thawed at room temperature and a 0.5 ml aliquot was transferred to a 2.2 ml

polypropylene tube. To this, 50 μl of I.S. solution of appropriate conentration (2 μg/ml for low concentration range curve and 50 μg/ml for the high concentration range curve) was added and mixed. The plasma was deproteinized by adding 0.5 ml of acetonitrile followed by centrifugation at 6000 g for 10 min in an Eppendorf microcentrifuge (Brinkmann Instruments, Westbury, NY). The supernatant was transferred to a 16 x 150 mm disposable glass tube and acidified by adding 1 ml of 0.1M sodium acetate buffer adjusted to a pH of 5.0. RP 69698 and I.S. were extracted from the buffered matrix by mixing with 4 ml of hexane/ethyl acetate (3/1;v/v) and vortexing the mixture for 30 s. The organic (upper) layer was aspirated and transferred to a 15 ml conical centrifuge tube. The extract was evaporated to dryness under a stream of nitrogen at room temperature and the residue was reconstituted in 200 μl of HPLC mobile phase. After mixing, either 20 μl (high concentration range curve) or 100 μl (low concentration range curve) of the reconstituted extract was injected onto the HPLC column.

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Validation Studies

The recoveries of RP 69698 and I.S. were estimated in the range of 50 ng/ml to 5 μg/ml by comparing detector response to pure authentic standards with the response obtained from equivalent amounts added to and recovered from plasma with correction made for the fraction of reconstituted sample injected onto the column. Since a broad range of concentrations was expected to be analyzed by this method, to achieve better performance, standard curves were prepared in two concentration

ranges. A low concentration standard curve ranged from 25 ng/ml to 1000 ng/ml and a high concentration curve ranged from 1 μg/ml to 50 μg/ml. The linearity of the method was based on evaluation of correlation coefficient and variability of slope for within-day and day-to-day analyses. The precision of the method was based on determination of the coefficient of variation (CV) for within-day and day-to-day analyses. The accuracy of the method was determined from percentage difference between extrapolated values and nominal (spiked) values for reference controls. The lower limit of quantitation (LOQ) was defined as the concentration which could be quantified with acceptable accuracy (difference <15%) and precision (CV <15%). The stability of RP 69698 in plasma was determined under the conditions of storage (-20°C).

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Dog Pharmacokinetic Study

Six male beagle dogs, weighing about 8 to 10 kg, were obtained from White Eagle Laboratories (Doylestown, PA). After 2 weeks of acclimatization period, the dogs were given each of the following three treatments according to a 3-way crossover design during the three-week study period. Treatment 1 and 2 consisted of intravenous (I.V.) and intragastric (I.G.) administration, respectively, of RP 69698 given as a solution in PEG 400 at a dose of 2.5 mg/kg. Treatment 3 consisted of I.G. administration of the drug given as a suspension in 0.5% methylcellulose suspension. Blood samples were withdrawn from the cephalic vein into heparinized syringes (Sarstedt, Princeton, NJ) at 0 (pre-dose), 2 (I.V. only), 5, 10, 20, 30, and 45 min and at 1, 1.5, 2, 4, 6, 8, and 24 hr following each treatment. The samples were centrifuged

at 600 g for 10 min and plasma was separated and stored at -20°C until analyzed.

Sample Analysis

On the day of analysis, plasma samples were thawed, and an aliquot (0.5 ml) was removed. Based on the results of exploratory studies, the sample was analyzed by using either low concentration range curve (50 µl of 2 µg/ml I.S.) or high concentration range curve (50 µl of 50 µg/ml I.S.). When using the low concentration range curve, if the extrapolated value exceeded the upper limit of the curve (1 µg/ml), the sample was reanalyzed using the high concentration range curve. Similarly, when utilizing the high concentration range curve for extrapolation, if the sample concentration was below 1 µg/ml, the sample was reanalyzed using the low concentration curve.

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Data Analysis

The plasma concentration data were analyzed using the SIPHAR computer program (SIMED, Cedex-France) to provide the following pharmacokinetic parameters whenever appropriate: maximum observed plasma concentration (Cmax), time when Cmax was observed (tmax), the area under the curve from time zero to the time when the concentration was last quantifiable (AUC_{0-t}), the area from time zero to infinity ($AUC_{0-\infty}$), systemic clearance (CL), the volume of distribution at steady state (Vdss), and elimination half-life ($t_{1/2}$) values for the α- and β-phases. Absolute bioavailability (F) was determined from the ratio of dose normalized AUCs obtained for I.G. vs. I.V. administered drug.

RESULTS AND DISCUSSION

Chromatography

Initial development of the method indicated that, by using acetonitrile and 0.01M sodium acetate buffer as mobile phase, RP 69698 eluted as a symmetrical peak using a C18 column. The optimal mobile phase for separation of RP 69698 and I.S. was established by varying the pH of the buffer, to which the elution of the drug but not of the I.S., was found to be highly susceptible. Under the HPLC operating conditions described in the Materials and Methods section, the retention times of RP 69698 and I.S. were found to be 10 ($\pm$0.5) and 14.5 ($\pm$0.5) min, respectively. The seemingly large variability in retention times was mainly due to slight differences in the pH of the mobile phase. With any given mobile phase, however, the retention times remained unchanged during the course of an analytical run.

Preliminary studies established that RP 69698, which has an octanol/water partition coefficient of 3045 (log P= 3.48), could be extracted from deproteinized plasma under slightly acidic conditions with a relatively non-polar solvent. Further studies led to the selection of hexane/ethyl acetate (75/25; v/v) as the most suitable solvent for extraction. The choice of the I.S. was based on matching of physico-chemical properties and chromatographic behavior of RP 69698 with materials available in our library of compounds.

Blank plasma obtained from several species including dog, rat, monkey, and humans were tested and found to show no significant endogenous peak that would interfere with the analysis of RP 69698. Although the method has also been used for sample

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analysis obtained from studies in rats and monkeys, the validation studies reported here were performed with dog plasma. Typical chromatograms of blank dog plasma and dog plasma spiked with RP 69698 and an appropriate amount of I.S. are shown in Figure 2.

Assay Validation

The recoveries of RP 69698 and I.S. were determined for three representative concentrations of 50, 500, and 5000 ng/ml. As shown in Table 1, the mean recoveries were ≥79% at all concentrations for both compounds. The recoveries were quite reproducible (CV<10%) and there was no evidence for concentration-dependence within the tested range of 50 ng/ml to 50 μg/ml. By using non-weighted least square regression analysis, the standard curves were found to be linear in the range of 25 ng/ml to 1000 ng/ml and 1 μg/ml to 50 μg/ml. The correlation coefficients were >0.992 for all curves. The slopes were quite reproducible with CV values determined to be <2% for both within-day and day-to-day analysis. The results of within-day and day-to-day precision for both the low and high concentration range curves are shown in Table 2. The CV was <10% at all concentrations except at 1 μg/ml, where the day-to-day precision was about 15.8%. The accuracy of the assay appeared to be quite good as determined from % difference of extrapolated values from the nominal (spiked) concentrations (Table 3); at all levels the mean difference was <15%. A concentration of 25 ng/ml was established as the LOQ based on acceptable estimates obtained for precision (CV<15%) and accuracy (%difference <15%) at this level. Based on reanalysis of spiked standards stored at -20°C, it was found that the drug was stable in dog plasma for at least three months.

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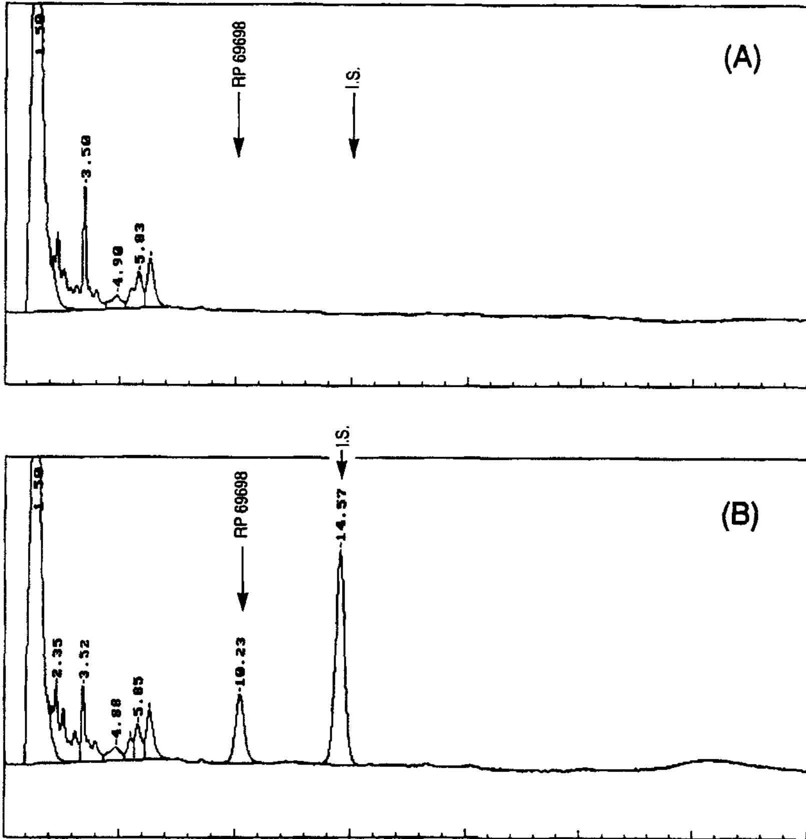

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FIGURE 2. Typical chromatograms obtained following analysis of blank dog plasma (A) and plasma spiked with 100 ng/ml RP 69698 and 200 ng/ml of I.S. (B).

Pharmacokinetic Characteristics of RP 69698 in the Dog

The plasma concentration data obtained following various treatments of RP 69698 are summarized in Table 4 and the results of pharmacokinetic analysis of these data are shown in Table 5. The plasma concentrations of RP 69698 in samples taken at 6, 8 and 24 hr post-treatment were generally below LOQ.

TABLE 1

Extraction Recoveries of RP 69698 and I.S. from Dog Plasma

Compound	Concentration (ng/ml)	% Recovery (Mean ± S.D.)(n=3)
RP 69698	50	89±6
	500	79±2
	5000	80±3
I.S.	50	82±1
	500	86±2
	5000	83±3

TABLE 2

Within-day and Day-to-Day Precision of the Analytical Procedure

RP 69698 Spiked Conc.	Within-Day Analysis (Mean±S.D.)(n=3) Conc. Measured	Day-to-Day Analysis (Mean±S.D.)(n=3) Conc. Measured
Low Concentration Range Curve		
(ng/ml)	(ng/ml)	(ng/ml)
25	22.4±1.7	26.7±1.8
50	44.7±3.2	50.9±1.8
100	100.6±2.7	103.2±4.6
200	193.5±1.3	198.0±5.8
400	420.5±5.0	393.9±4.2
1000	993.4±1.9	1002.5±1.3
High Concentration Range Curve		
(μg/ml)	(μg/ml)	(μg/ml)
1	1.1±0.1	1.2±0.2
5	5.1±0.0	5.3±0.3
10	10.1±0.1	10.3±0.2
25	24.1±0.2	23.4±1.3
50	50.4±0.1	50.7±0.6

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TABLE 3

Within-day and Day-to-Day Accuracy of the Analytical Procedure

RP 69698 Nominal Conc.	Within-Day Analysis (Mean±S.D.)(n=3) Conc. Measured	% Diff.	Day-to-Day Analysis (Mean±S.D.)(n=3) Conc. Measured	% Diff.
Low Concentration Range Curve				
(ng/ml)	(ng/ml)		(ng/ml)	
75	76.9±2.0	-2.5±2.6	78.8±4.2	-5.0±5.6
250	251.6±8.9	-0.6±3.5	254.7±12.0	2.0±5.9
750	749.0±7.3	0.1±1.0	759.0±5.8	1.2±2.9
High Concentration Range Curve				
(μg/ml)	(μg/ml)		(μg/ml)	
2.5	2.7±0.1	-2.7±10.1	2.4±0.4	6.7±6.1
12.5	12.2±0.0	2.7±0.5	10.1±2.1	10.0±14.9

TABLE 4

Plasma Concentrations of the Unchanged Drug in Dogs Following Treatment with RP 69698 Administered Either as a Solution in polyethylene glycol (PEG) 400 or as a Suspension in 0.5% Methylcellulose (MC).

		RP 69698 Plasma Conc. (Mean±S.D.)(n=6) (μg/ml)		
Time Post-dose (min)	Route Vehicle Dose	I.V. PEG 400 2.5 mg/kg	I.G. PEG 400 2.5 mg/kg	I.G. 0.5% MC 5.0 mg/kg
2		15.51±2.04	NS	NS
5		10.20±2.01	0.02±0.03	BQL
10		8.08±1.75	0.54±0.39	BQL
20		5.62±1.45	1.74±0.91	BQL
30		4.07±1.34	2.02±1.09	BQL
45		2.43±1.10	2.12±0.82	0.04±0.03
60		1.28±0.82	1.74±0.89	0.07±0.07
90		0.91±0.99	1.26±1.12	0.13±0.17
120		0.28±0.16	0.58±0.22	0.30±0.22
240		0.03±0.03	0.07±0.05	0.14±0.11
360		BQL	0.03±0.06	BQL
480		BQL	BQL	BQL

NS = No sample taken at this sampling time
BQL = Below Quantitation Limit (0.025 μg/ml)

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TABLE 5

A Summary of the Pharmacokinetic Parameters of RP 69698 Determined in Dogs Following Intravenous and Intragastric Administration of the Drug

TREATMENT			PHARMACOKINETIC PARAMETER*							
ROUTE	VEHICLE	DOSE (mg/kg)	Cmax (μg/ml)	tmax (hr)	Abs. Rate ($t_{½}$; hr)	$t_{½}\alpha$ (hr)	$t_{½}\beta$ (hr)	CL (L/hr/kg)	Vdss (L/kg)	F (%)
I.V.	PEG 400	2.50	15.51[1] ±2.04	0.03[2]	-	0.19 ±0.12	0.53 ±0.13	0.39 ±0.09	0.24 0.07	-
I.G.	PEG 400	2.50	2.32 ±0.84	0.67 ±0.13	0.25 ±0.08	NC	0.54 ±0.16	-	-	59.03 ±33.06
I.G.	0.5% Methyl-cellulose	5.00	0.31 ±0.21	2.67 ±1.03	NC	NC	NC	-	-	5.68 ±4.58

* Values given are Mean±S.D. for n=6
1 Mean concentration at the earliest sampling time
2 Earliest sampling time (2 min)
NC = Not calculated due to inadequate data

Following an I.V. dose, CL of the drug occurred relatively rapidly at a rate of 0.39 L/hr/kg. The Vdss was estimated to be about 0.24 L/kg, suggesting limited distribution and providing evidence for the lack of extensive tissue binding. The plasma concentration data was best described by a biexponential curve. A typical best-fit of the data is shown in Fig. 3. The average $t_{1/2}$ value for the α-phase, which most likely represents the distribution phase, was estimated to be about 0.19 hr. The average $t_{1/2}$ for the β-phase was about 0.59 hr which seems to indicate that the drug is rapidly eliminated from the central compartment.

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When administered I.G. as a solution in PEG 400 at a dose of 2.5 mg/kg, Cmax averaged about 2.32 μg/ml. In the individual dogs, the tmax was either 30 min or 45 min with an average value estimated to be about 0.67 hr. The plasma concentration data was best described by either a biexponential (Fig. 3) or a triexponential curve. The first exponent described the absorption phase, whereas the other exponent(s) described the elimination phases(s). Due to a somewhat slower absorption rate ($t_{1/2}$=0.25 hr), the α-phase was not discernible. The average $t_{1/2}$ for the β-phase was estimated to be about 0.54 hr, which is similar to that determined after I.V. administration. In two of the six dogs, an additional elimination phase with $t_{1/2}$ of about 1.16 hr and 3.85 hr was also apparent.

When RP 69698 was given as a suspension in 0.5% methylcellulose at a dose of 5 mg/kg, the concentrations attained in plasma were quite low. The average value for Cmax was

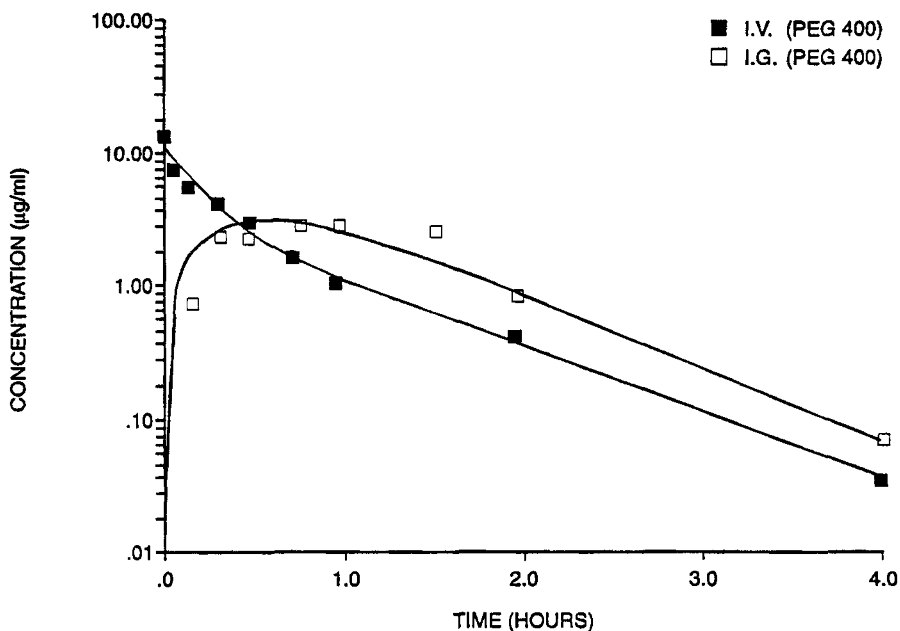

FIGURE 3. A representation of the best fit of the plasma concentration data obtained in a dog following I.V. and I.G. treatment with 2.5 mg/kg RP 69698 given as a solution in PEG 400.

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estimated to be 0.31 µg/ml which was attained at about 2.67 hr (tmax). A plot of the data indicated no clear pattern of decline and, therefore, no effort was made to calculate the elimination $t_{1/2}$(s).

Based on ratio of AUCs obtained following I.G. vs. I.V. administered drug, the bioavailability of RP 69698 was estimated to be about 59% when given as a solution but only 6% when given as a suspension in 0.5% methylcellulose. These data indicate that solubility of the drug apparently becomes the limiting factor for absorption of the drug when given as a suspension.

CONCLUSIONS

The method described in this report for the assay of RP 69698 in plasma was developed to obtain pharmacokinetic characteristics of the drug and to perform toxicokinetic studies. The method is simple, specific and adaptable to plasma from several species. Validation studies, performed with dog plasma as the matrix, showed that by utilizing low and high concentration range standard curves, concentrations of 25 ng/ml or higher can be quantitated with satisfactory precision and accuracy. RP 69698 was found to be stable in dog plasma when stored at -20°C up to about 3 months. The suitability of the method was demonstrated by analyzing plasma samples from a pharmacokinetic study of the drug in dogs. The results of this study indicated rapid clearance of the drug from plasma and limited distribution. The plasma elimination of the drug was characterized as biphasic with $t_{1/2}$s of about 11 min and 35 min for the distribution (α) and elimination (β) phases respectively. Also, the study showed poor bioavailability of the drug from suspension relative to the solution, thus, indicating that the dissolution of the drug in gastrointestinal tract limits the absorption of the drug. Availability of the analytical method helped in identifying the critical issues related to the development of the drug.

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REFERENCES

1. F.F. Sun, B.M. Taylor, N.J. Crittendon, C.I. Czuk, J.A. Oostreen and I.M. Richards, "Leukotrienes and Prostenoids in Health and Disease", in New Trends in Lipid Mediators Research, Vol. 3, U. Zor, Z. Naor, and A. Danon, eds., Basel, Karger, 1989, pp 84-88.

2. C. Sutherland, L. Mitchell, R. Galemmo, J. Travis, D. Sweeney, L. Beale, W. Chan, F. Huang, L. Labaudiniere and B. Terlain, "Evidence for Species Specific variation in High Affinity Leukotriene B4 (LTB4) Receptor Conformation: Relative Activities of Structurally Diverse LTB4 Antagonists in Several LTB4 Receptor Binding Assays" (Abstract) Sixth International Conference, Inflammation Research Association, White Haven, PA, USA.

Received: April 10, 1993
Accepted: June 30, 1993

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