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Report

Pharmacokinetics of Furegrelate After Oral Administration to Normal Humans

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Furegrelate sodium is a thromboxane synthetase inhibitor with potential for the treatment of various diseases including hypertension, thrombosis, and renal disorders. The absorption and disposition of the parent drug in normal male volunteers have been studied after single- and multiple-dose oral administration. The results from the single-dose study indicate that furegrelate is rapidly absorbed, with a T_{max} of 1.0–1.7 hr, has an apparent terminal disposition rate constant of 0.12–0.17 hr^{-1}, and is eliminated primarily by the kidney, with 62–78% of the dose excreted as parent drug. After multiple-dose oral administration for 4.5 days using a b.i.d. dosing regimen, no apparent change in the absorption, disposition, and elimination kinetics is detected and only a slight potential for drug accumulation is observed.

KEY WORDS: thromboxane synthetase inhibitor; human pharmacokinetics; single and multiple oral doses; high-performance liquid chromatography–ultraviolet (HPLC-UV).

INTRODUCTION

Furegrelate, the sodium salt of 5-(3′-pyridinylmethyl)-benzofuran-2-carboxylic acid (Fig. 1), is a thromboxane synthetase inhibitor with activity *in vivo* (1). The drug inhibits the biosynthesis of thromboxane A2, a naturally occurring eicosanoid formed by the metabolism of arachidonic acid (2). Thromboxane A2 stimulates platelet aggregation and has vasoconstrictive effects (3–5). Thus, furegrelate sodium has potential in the treatment of various diseases including hypertension, thrombosis, and renal disease.

Pharmacokinetic evaluations of furegrelate in the dog (6) have shown the drug to be well absorbed and rapidly eliminated, with an apparent terminal disposition half-life of 2–3 hr in fasted animals. The primary route of elimination was renal with about 70% of the administered dose excreted in the urine as parent drug. The absolute bioavailability of furegrelate in the dog was 75–80% by area under the serum concentration–time (AUC) comparison and over 90% by cumulative urinary excretion results for intravenous and oral doses.

This report presents results for drug concentrations in physiological fluid samples obtained following single- and multiple-dose oral administration of furegrelate sodium to normal male volunteers. The high-performance liquid chromatographic (HPLC) methods employed to analyze human serum and urine specimens for furegrelate were described earlier (6). Pharmacokinetic evaluation of the data was performed using noncompartmental techniques (7).

MATERIALS AND METHODS

A total of 89 normal male volunteers participated in the single- and multiple-dose studies. Informed consent was obtained from each individual. All subjects were evaluated by medical history, physical examination, electrocardiogram, and laboratory tests (hematology, serum chemistry, urinalysis) prior to dosing. The volunteers ranged in age from 18 to 50 years and were within 20% of their ideal weights.

In the single-dose study, 36 volunteers received furegrelate sodium administered orally as compressed tablets. Four subjects were evaluated at each of the following dose levels: 100, 200, 400, 800, 1000, 2450, 3150, 4900, and 6300 mg. Blood samples (10 ml) were collected from each individual at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hr. The blood was allowed to clot; the serum was harvested by centrifugation at 2000 rpm for 15 min, transferred to a storage vial, frozen, and maintained at −30°C or lower until analysis. Urine collection intervals were predose (−24 to 0 hr), 0–4, 4–8, 8–12, and 12–24 hr. Urine specimens were collected in flasks during the interval, and after mixing, the volume was measured and an aliquot (10–15 ml) transferred

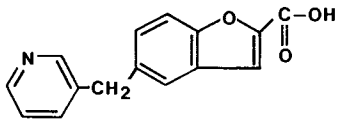

Fig. 1. Chemical structure of the free acid of furegrelate sodium.

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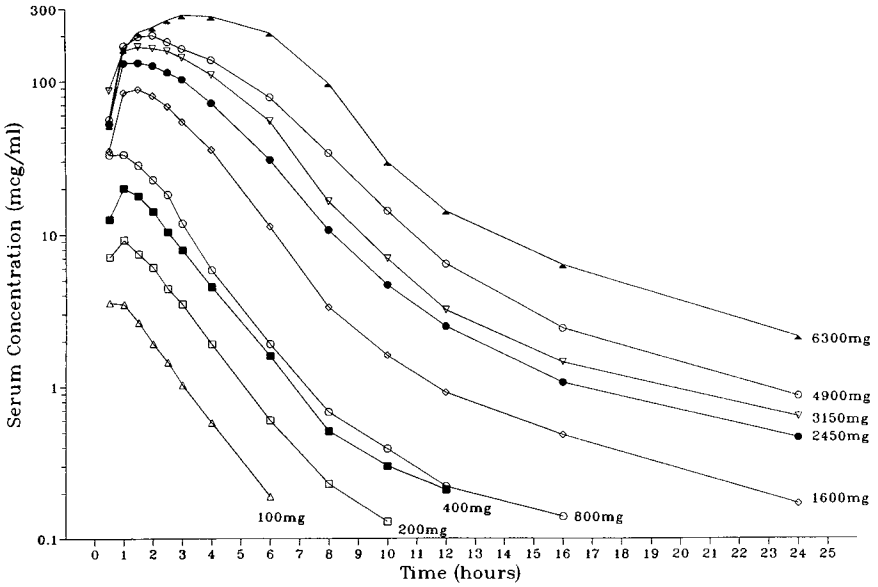

Fig. 2. Average serum concentrations of furegrelate in humans receiving single oral tablets. Dose level: 100 mg, open triangle; 200 mg, open square; 400 mg, filled square; 800 mg, open hexagon; 1600 mg, open diamond; 2450 mg, filled circle; 3150 mg, open inverted triangle; 4900 mg, open circle; 6300 mg, filled triangle.

to a storage vial, frozen, and maintained at −30°C or lower unitl analysis.

In the multiple-dose study, 18 volunteers received furegrelate sodium and were divided into four treatment groups. Five volunteers were in the 200- and 400-mg groups, and four in the 800- and 1600-mg groups. Each group was administered drug as compressed tablets twice a day (b.i.d.) for 4.5 days (a total of nine doses per volunteer). Blood samples were collected on day 1 and day 5 at −1, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 11, and 13 hr after the morning dose. The −1-hr sample on day 1 was a predose sample. Urine collection intervals were 0–6, 6–12, and 12–24 hr for days 1 and 5 and 24–48 hr after the day 5 dose. Thus, the 0- to 6- and 6- to 12-hr intervals represented one dose and the 12- to 24-hr interval the second dose for day 1. All the intervals for day 5 were for a single dose. The serum and urine collection and storage procedures were as described for the single-dose study.

Analytical Methods

The analytical methods employed for the quantitative determination of furegrelate in serum and urine specimens have been previously defined (6). For serum, the linear range for analysis of furegrelate was 0.1 to 50 μg/ml, the precision

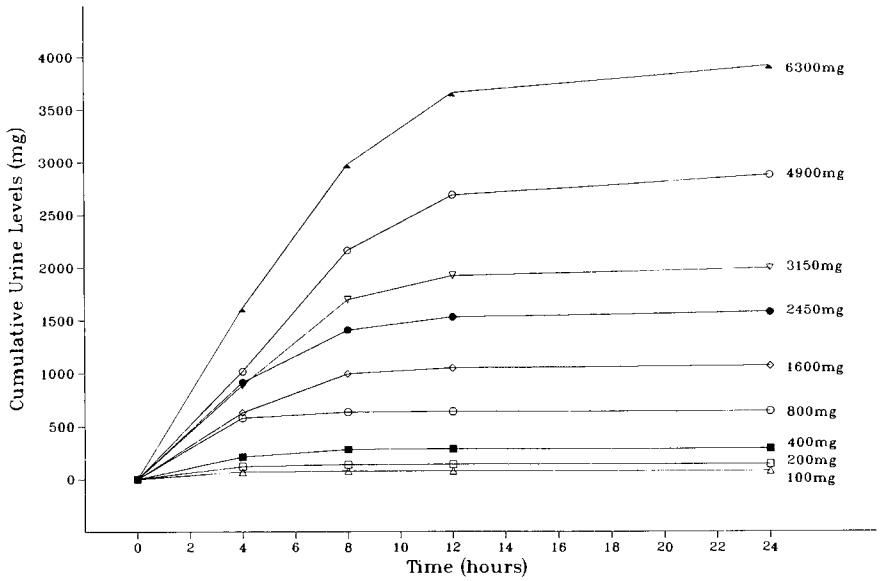

Fig. 3. Average cumulative urine levels of furegrelate in humans receiving single-dose oral tablets. For dose level–symbol relationship, see the legend to Fig. 2.

Table I. Pharmacokinetic Parameters for Furegrelate After Single-Dose Oral Administration to Normal Volunteers[a]

Dose (mg)	Pharmacokinetic parameter average and SD							
	C_{max} (μg/ml)	T_{max} (hr)	β (hr^{-1})	AUC (μg × ml/hr)	V_A/F (liters)	Cl_T/F (ml/min)	U_T (mg)	Cl_R (ml/min)
100	4.3	1.0	0.576	8.7	20.4	196	71.9	142
SD (±)	1.9	0.4	0.084	1.7	1.2	32	7.1	32
200	10.8	1.1	0.381	24.8	21.8	137	134.1	92
SD (±)	3.5	0.6	0.026	3.8	4.7	25	3.7	15
400	22.7	1.1	0.167	57.2	46.4	128	281.9	91
SD (±)	4.5	0.5	0.049	19.3	12.6	26	26.2	36
800	39.3	1.0	0.214	92.8	45.5	152	625.4	121
SD (±)	14.6	0.7	0.077	25.1	17.9	42	114.5	52
1600	92.2	1.3	0.137	311.4	41.6	95	1,060	62
SD (±)	37.7	0.5	0.002	118.2	14.8	35	131	19
2450	140.3	1.4	0.120	573.1	44.3	82	1,570	53
SD (±)	27.4	0.5	0.026	247.1	23.9	33	120	24
3150	185.1	1.6	0.127	821.4	31.3	65	1,983	41
SD (±)	20.6	0.5	0.017	123.9	8.3	9	212	10
4900	208.8	1.7	0.152	1,025	29.8	82	2,864	48
SD (±)	47.8	0.3	0.055	191	14.1	19	608	16
6300	288.6	3.1	0.163	1,830	25.9	65	3,903	40
SD (±)	35.9	1.2	0.035	115	13.2	16	510	10

[a] Number per dose group: 4.

(from the relative standard deviation of standards analyzed with each sample set) was 1.3 ± 0.8% (N = 24), the detection limit was 0.020 μg/ml, and the recovery through the sample preparation was quantitative (95–105%) over the linear range. The linear range for furegrelate in urine was 20 to 2000 μg/ml, the precision of analysis was 2.0 ± 1.0% (N = 23), and the detection limit was 0.4 μg/ml. Reference solutions and a fortification series of furegrelate in serum and urine over the linear range were run with each sample set and were used in the calculation of drug concentrations in the physiological matrices.

Pharmacokinetic Evaluation

The serum and urine concentrations of furegrelate from the single- and multiple-dose oral studies were subjected to pharmacokinetic evaluation by noncompartmental techniques (7). The pharmacokinetic parameters evaluated included the maximum serum concentration (C_{max}), the time to reach C_{max} (T_{max}), the apparent terminal disposition rate constant (β) calculated from the slope of the least-squares linear regression analysis of the linear portion of the log serum concentration–time plot, the area under the serum concentration–time curve from time zero to infinity (AUC) using the trapezoidal rule from time zero to the last quantifiable serum concentration [$C(t)$] and $C(t)/\beta$ for the remaining area to infinity, the volume of distribution of the fraction absorbed (V_A/F) from the dose divided by AUC · β, the total-body clearance of the fraction of the dose absorbed (Cl_T/F) from the dose divided by AUC, the cumulative urinary excretion of furegrelate (U_T), and the renal clearance of the fraction of the dose absorbed (Cl_R/F) from U_T divided by AUC.

RESULTS AND DISCUSSION

Serum concentration–time profiles and cumulative urinary excretion profiles for the volunteers receiving single oral furegrelate sodium doses of 100 to 6300 mg are presented in Figs. 2 and 3, respectively. Each curve is the average of four individuals receiving a dose level; the average curve was representative of the individual serum concentration–time curves and the cumulative urinary excretion level curves. Table I summarizes the average (SD) (N = 4) pharmacokinetic parameter estimates of C_{max}, T_{max}, β, AUC, V_A/F, Cl_T/F, U_T, and Cl_R/F for the nine dose groups in the single-dose study. With increasing doses, the average values for C_{max}, AUC, and U_T increased, suggesting a linear relationship between the drug dose and the serum and urine profiles of the parent drug. When the values were normalized for dose, the overall average (SD) (N = 36) and range were 5.2 (1.5) μg/ml/(100-mg dose) and 4.3–5.9 μg/ml/(100-mg dose) for C_{max} and 66.8 (9.4) mg/(100-mg dose) and 58.4–78.2 mg/(100-mg dose) for U_T, indicating uniform absorption (C_{max}) and excretion (U_T) over the evaluated dose range. T_{max}, with the exception of the 6300-mg

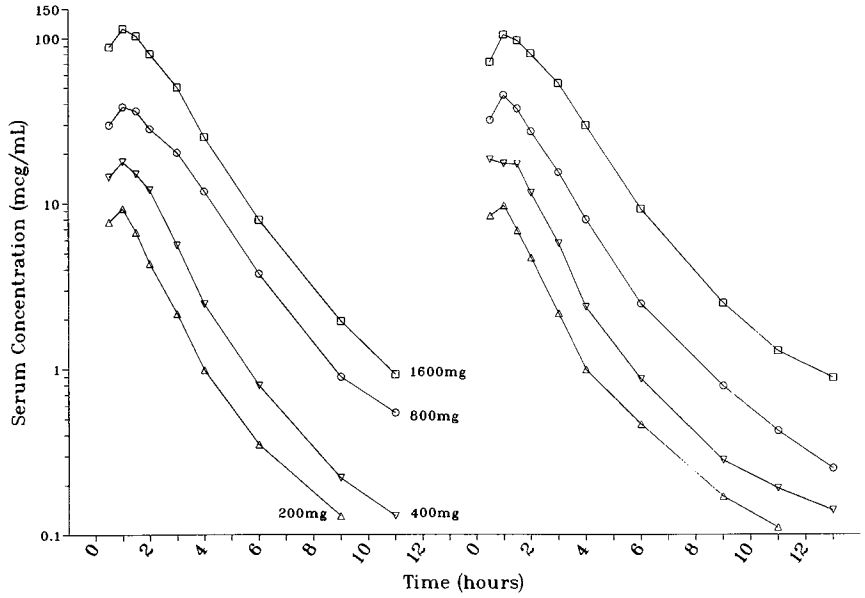

Fig. 4. Average serum concentrations of furegrelate after the first dose on days 1 and 5 from humans receiving b.i.d. oral dose tablets. Dose level: 200 mg, triangle; 400 mg, inverted triangle; 800 mg, circle; 1600 mg, square.

dose, was consistent and ranged from 1 to 1.7 hr. AUC and β appeared to fall into two groups. For β, the group averages above the 400-mg dose were similar and suggested a disposition half-life for furegrelate of 4.2–5.8 hr. For the two groups below the 400-mg dose, the terminal phase was not observed for the serum concentrations measured and the values reported are most likely a combination of the distribution and disposition phases. The increase in AUC with increasing doses was not uniform over the dose range. When the AUC averages were normalized for dose, the dose groups above and below 1600 mg had similar AUCs, with the lower-dose groups having AUC values about 50% those of the higher-dose groups. This apparent difference may be attributed, in part, to the more reliable determination of the terminal phase at the higher doses, which allowed better extrapolation of AUC to infinity. Other possible explanations for the apparent larger values of AUC for the higher doses include a change in the total-body clearance caused by saturation of the metabolic and/or elimination pathway(s), increased absorption at higher doses, and an increased volume of distribution, i.e., tissue accumulation. Since dose-normalized C_{max}, U_T, and T_{max} are relatively uniform over

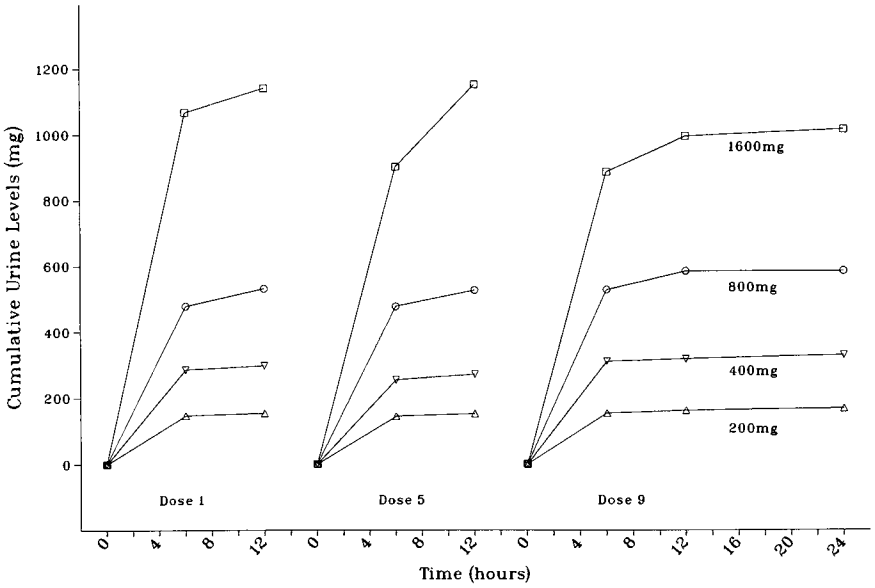

Fig. 5. Average cumulative urinary levels of furegrelate after the first dose on days 1 and 5 from humans receiving b.i.d. oral dose tablets. For dose level–symbol relationship, see the legend to Fig. 4.

Table II. Pharmacokinetic Parameters for Furegrelate After Multiple-Dose Oral Administration to Normal Volunteers

Dose (mg)	Day of dosing	Pharmacokinetic parameter average and SD				
		C_{max} (μg/ml)	T_{max} (hr)	β (hr^{-1})	AUC (μg × ml/hr)	U_T (mg)
200 (N = 5)	1	10.1	1.0	0.343	20.3	153.2
	SD (±)	2.8	0.4	0.081	4.1	11.4
	5	11.0	0.8	0.311	21.5	173.8
	SD (±)	2.8	0.3	0.094	3.0	25.0
400 (N = 5)	1	18.7	0.9	0.430	44.8	297.2
	SD (±)	4.1	0.4	0.052	6.1	36.4
	5	21.0	1.0	0.334	47.4	336.8
	SD (±)	1.5	0.5	0.054	5.2	37.6
800 (N = 4)	1	41.7	1.7	0.451	123.7	531.2
	SD (±)	12.0	1.0	0.041	31.2	27.2
	5	45.2	0.9	0.337	113.0	582.4
	SD (±)	11.3	0.3	0.062	32.4	103.2
1600 (N = 4)	1	114.0	1.0	0.470	327.5	1,140.8
	SD (±)	6.6	0.0	0.027	35.6	299.2
	5	103.9	1.0	0.378	323.1	947.2
	SD (±)	13.9	0.4	0.078	81.2	114.0

the dose range, the rate and extent of absorption appear to be independent of the dose. V_A/F values are also fairly uniform, suggesting similar volumes of distribution over the dose range. Cl_T/F and Cl_R/F averages are divided into two distinct groups, with doses of 800 mg furegrelate sodium or less in one group and doses of 1600 mg or greater in the other. These observations support the possible change in the rate of clearance of furegrelate with increased doses. Additional pharmacokinetic evaluations of furegrelate in humans are necessary to define better the absorption, disposition, and elimination characteristics of furegrelate sodium after oral administration and to evaluate further the possible change in the rate of clearance with larger doses.

The serum concentration–time and cumulative urinary excretion profiles of furegrelate in normal humans receiving b.i.d. doses of drug for 4.5 days are shown in Figs. 4 and 5, respectively. The average curves (N = 4 or 5) after the first and last drug doses levels of 200, 400, 800, and 1600 mg are presented. The similarity of the curves for each dose level suggests no apparent change in the absorption, disposition, and elimination profiles of furegrelate over the evaluated multiple-dose range. The averages (SD) of various pharmacokinetic parameter estimates for day 1 and day 5 results are given in Table II. The average values for C_{max}, T_{max}, AUC, and U_T for the four dose levels in the multiple-dose study were similar for doses on day 1 and day 5 and to the corresponding values obtained after single-dose administration. The average values of β were also similar for day 1 and day 5 doses and were fairly consistent for the four dose groups. However, with the exception of the 200-mg dose, the average β values were larger in the multiple-dose study than observed for the corresponding dose in the single-dose study, suggesting that the terminal disposition phase was not well defined after b.i.d. dosing. The 24-hr serum samples obtained after the last drug dose contained trace (0.02 to 0.1 μg/ml) or nondetectable (less than 0.02 μg/ml) concentrations of furegrelate for each individual at the four dose levels. The 24- to 48-hr urine collections for the volunteers had trace (less than 20 μg/ml) levels of furegrelate. These data suggest that little or no bioaccumulation of furegrelate occurred after b.i.d. dosing for 4.5 days. HPLC-UV chromatograms of urine samples did not contain chromatographic peaks which could be attributed to metabolites of furegrelate for either the single- or the multiple-dose regimens.

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