Pharmacokinetics of Rosoxacin in Human Volunteers

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Abstract □ Reversed-phase liquid chromatography was used to determine plasma rosoxacin concentrations in normal, healthy males, each of whom received one 300 mg capsule of rosoxacin. The plasma data for each subject were described by an open one-compartment body model with first-order absorption, and the pharmacokinetic parameters were determined. The mean (±*SE*) apparent first-order terminal elimination rate constant was 0.203 ± 0.015 hr^{-1} (N = 16), the mean apparent volume of distribution was 0.644 ± 0.050 liters/kg, and the mean apparent plasma clearance was 2.08 ± 0.15 ml/min/kg.

Keyphrases □ Rosoxacin—pharmacokinetics, normal, healthy males □ Pharmacokinetics—rosoxacin, one-compartment body model, oral absorption, normal, healthy males □ Absorption—first-order with open one-compartment body model, pharmacokinetics of rosoxacin, normal, healthy males

Rosoxacin[1], 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)-3-quinolinecarboxylic acid, is a member of the class of orally active antimicrobial agents which includes nalidixic acid. The metabolic fate and assay methods for this class of compounds has been reviewed (1).

Rosoxacin is effective *in vitro* against a variety of microorganisms (2–5) and has been used clinically for the treatment of gonorrhea (6). Concentrations of rosoxacin, which were higher than the minimum inhibitory concentrations for most Enterobacteriaceae, were found in renal hilar lymph, renal interstitial fluid, prostatic interstitial fluid, prostatic secretion, vaginal and urethral secretions, and cerebrospinal fluid from dogs treated with this compound (7, 8).

The present report describes the results of a pharmacokinetic study in a group of normal, male, human subjects receiving 300 mg of rosoxacin.

EXPERIMENTAL

Human Volunteers—Appropriate institutional review and approval were obtained from the subjects, none of whom had clinical or laboratory findings indicative of renal, hepatic, or cardiac dysfunction. The mean (±*SE*) age of these volunteers was 29.4 ± 1.9 yr; the mean weight was 71.7 ± 1.6 kg and the mean height was 174 ± 1.7 cm. Each of the 16 volunteers received a single 300-mg capsule of rosoxacin. Blood samples were collected before medication and 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10, 12, 15, and 24 hr after treatment. The blood was centrifuged, and the plasma was separated and frozen until assayed.

Assay Procedure—Plasma samples were analyzed by a high-performance liquid chromatographic (HPLC) method developed previously (9). Plasma standards, prepared in control human plasma, were extracted and analyzed with each set of plasma samples from the volunteers. Plasma rosoxacin concentrations were determined by inverse prediction on the linear regression of peak height ratios obtained from plasma and internal standards. The minimum quantifiable level of the assay was estimated as the concentration whose lower 80% confidence limit just encompassed zero[2], and was ~0.13 μg of rosoxacin/ml of plasma.

Three separate modular HPLC systems were used for the analyses. Each consisted of an automatic injector, a pump, a column[3], and a UV detector monitoring the column effluent at 280 nm.

Pharmacokinetic Calculations—The data obtained from the analysis of the human plasma samples were described by a one-compartment open model with first-order absorption by means of an unweighted nonlinear regression procedure (10). This model is described by the equation:

$$C = A[e^{-k_e(t-t_0)} - e^{-k_a(t-t_0)}] \quad \text{(Eq. 1)}$$

where C is the plasma concentration at time t, t_0 is the lag time (before absorption begins), A is a constant, and k_a and k_e are apparent first-order rate constants for absorption and elimination, respectively. The volume of distribution of rosoxacin, V, was calculated by:

$$V = \frac{FDk_a}{A(k_a - k_e)} \quad \text{(Eq. 2)}$$

where F is the fraction of the administered dose (D) which is available to the systemic circulation; the other terms are as defined previously. The total area under the plasma concentration *versus* time curve [AUC_0^∞], time to maximum concentration (t_{max}), maximum concentration (C_{max}), and plasma clearance (Cl_p) for each subject were calculated from:

$$t_{max} = t_0 + \frac{\ln(k_a/k_e)}{k_a - k_e} \quad \text{(Eq. 3)}$$

$$C_{max} = A[e^{-k_e(t_{max}-t_0)} - e^{-k_a(t_{max}-t_0)}] \quad \text{(Eq. 4)}$$

$$AUC_0^\infty = \frac{A(k_a - k_e)}{k_a k_e} \quad \text{(Eq. 5)}$$

$$Cl_p = \frac{FD}{AUC_0^\infty} \quad \text{(Eq. 6)}$$

In addition to the regression-dependent parameters defined previously, the plasma concentration data were analyzed with respect to the following model-independent parameters: the maximum observed plasma concentration (C_{max}^{obs}), the time at which the maximum plasma concentration was observed (t_{max}^{obs}), and the area under the plasma concentration *versus* time curve, 0–24 hr, AUC_0^{24}. The latter was calculated by trapezoidal rule, using all data for the 24-hr study period.

RESULTS AND DISCUSSION

The mean observed plasma rosoxacin concentration data are shown in Fig. 1. Plasma levels declined exponentially with time suggesting a one-compartment body model. Pharmacokinetic parameters for each subject were estimated after computer-fitting of the data by an iterative nonlinear least-squares regression technique (10). For subjects 1 and 6 it was necessary to adjust the lag time such that it corresponded to the

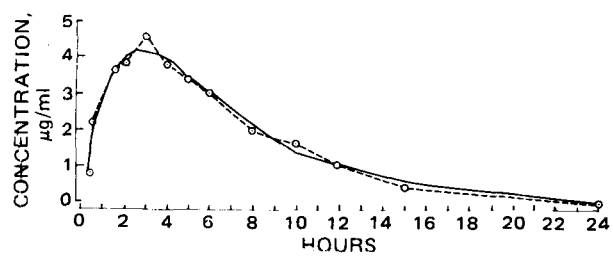

Figure 1—*Plasma concentrations of rosoxacin in human volunteers after oral administration of a single capsule containing 300 mg of rosoxacin. Mean plasma concentration observed in 16 subjects (dotted line) and concentration predicted by the open one-compartment model with oral absorption (solid line).*

[1] Eradicil, Sterling Drug Inc., New York, N.Y.

[2] R. W. Ross and H. Stander, "Some Statistical Problems in Drug Metabolism," paper presented at the Princeton Conference on Applied Statistics, December, 1975.

[3] Partisil-PXS 10/25 PAC column, Whatman, Clifton, N.J.

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Table I—Pharmacokinetic Parameters Derived from Rosoxacin Plasma Data

	Model-Independent			Regression-Dependent									
Subject Number	t_{max}^{obs}, hr	C_{max}^{obs}, μg/ml	AUC_0^{24}, μg hr/ml	A, μg/ml	k_a, hr^{-1}	k_e, hr^{-1}	t_0, hr	t_{max}, hr	C_{max}, μg/ml	AUC_0^{∞}, μg hr/ml	$t_{1/2}$, hr	$\frac{V}{F}$, liters/kg	$\frac{Cl_p}{F}$, ml/min/kg
1	4.0	6.32	48.1	10.2	1.25	0.176	1.00[a]	3.90	6.38	49.8	3.94	0.458	1.34
2	1.5	4.30	24.6	6.77	1.76	0.241	0.21	1.52	4.26	24.2	2.88	0.740	2.98
3	2.5	3.29	20.8	5.61	1.19	0.225	0.00	1.72	3.09	20.3	3.08	0.877	3.28
4	3.0	5.91	42.4	8.91	1.24	0.171	0.27	2.12	5.60	44.8	4.05	0.603	1.73
5	2.5	5.61	31.2	20.6	0.66	0.328	0.51	2.62	5.15	31.4	2.11	0.380	2.08
6	4.0	3.56	26.6	6.48	1.16	0.214	1.00[a]	4.21	3.60	24.7	3.24	0.866	3.08
7	2.5	3.58	27.1	7.26	0.73	0.200	0.65	3.09	3.24	26.3	3.47	0.732	2.45
8	3.0	6.57	51.4	10.1	1.18	0.160	0.17	2.13	6.37	54.4	4.33	0.539	1.44
9	3.0	5.60	47.8	12.6	0.77	0.195	0.26	2.65	5.91	48.3	3.55	0.425	1.39
10	4.0	4.88	50.3	21.0	0.37	0.195	0.32	3.97	4.89	51.1	3.55	0.492	1.60
11	1.5	5.83	33.3	9.36	1.51	0.235	0.29	1.75	5.62	33.7	2.95	0.466	1.82
12	1.5	4.18	29.6	6.91	1.18	0.196	0.26	2.08	4.03	29.3	3.54	0.697	2.29
13	3.0	2.85	32.4	4.91	0.65	0.115	0.53	3.76	2.79	35.2	6.03	1.016	1.95
14	2.0	4.86	35.0	6.18	1.95	0.154	0.62	2.03	4.58	37.0	4.50	0.858	2.20
15	1.5	4.28	39.4	5.23	3.12	0.117	0.22	1.31	4.43	43.0	5.92	0.758	1.48
16	3.0	5.56	32.6	25.8	0.53	0.325	0.31	2.68	4.68	31.1	2.13	0.393	2.13
Mean	2.66	4.89	35.8	10.5	1.20	0.203	0.41	2.60	4.66	36.5	—	0.644	2.08
SE	0.22	0.30	2.42	1.59	0.17	0.015	0.071	0.23	0.28	2.69	—	0.050	0.15

[a] No meaningful value; the lag time is that time at which the observed plasma concentration first exceeded the minimum quantifiable level.

first time point with measurable rosoxacin concentration, to obtain a reasonable fit of the data. In the other 14 subjects, no adjustment was necessary (Table I). Using the mean parameters, the plasma rosoxacin concentration, C (μg/ml) at time t (hr), is given by:

$$C = 10.5\,[e^{-0.203(t-0.41)} - e^{-1.20(t-0.41)}] \qquad \text{(Eq. 7)}$$

The mean apparent first-order terminal elimination half-life for rosoxacin was ~3.4 hr.

The mean observed concentration data were also described by the model, and a comparison of the observed and predicted concentrations is shown in Fig. 1. The observed, model-independent, parameters are in reasonable agreement with those calculated from the open one-compartment body model with oral absorption, Table I.

The mean apparent volume of distribution was 0.644 liters/kg. This suggests that rosoxacin is distributed into the total body water, which may be responsible for the membrane permeability and relatively high levels of rosoxacin found in tissues (7, 8). This hypothesis will be tested in future studies.

An earlier study of the pharmacokinetics of rosoxacin in the dog (9) reported an apparent first-order terminal elimination half-life of 2 hr and a plasma clearance, corrected for body weight, of 8.6 ml/min/kg. In humans the elimination half-life is longer, ~3.4 hr, and the plasma clearance of rosoxacin, corrected for weight, is slower, 2.08 ml/min/kg.

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