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Disposition of Roxithromycin in Patients with Normal and Severely Impaired Renal Function

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The disposition of roxithromycin, an investigational macrolide antibiotic, was evaluated in 20 subjects, 10 with normal renal function (creatinine clearance [CL_{CR}] of 116 ± 17 ml/min [mean ± standard deviation]) and 10 with severely impaired renal function (CL_{CR} of 10.2 ± 2.6 ml/min) after a single 300-mg oral dose. Plasma concentration-time data were analyzed in terms of a one- or two-compartment oral absorption model utilizing nonlinear regression analysis. The terminal elimination half-life was significantly prolonged in the group with severely impaired renal function (15.5 ± 4.7 h) compared with that of the group with normal renal function (7.9 ± 2.5 h). Apparent total body clearance was significantly reduced in the renally impaired (25.3 ± 10.5 ml/min) in relation to the group with normal renal function (48.8 ± 11.1 ml/min). The first-order absorption rate constants and apparent volumes of distribution did not differ between the two groups. These data indicate that the disposition of roxithromycin is significantly delayed in subjects with CL_{CR}s of <15 ml/min and suggest that the roxithromycin dosing interval be doubled for these patients.

Roxithromycin is an investigational macrolide antibiotic which is similar to erythromycin in chemical structure and antimicrobial spectrum of activity (1, 5, 10). Preliminary data for animals and humans suggest that oral roxithromycin administration attains concentrations in plasma higher than those of erythromycin because of acid stability and thus better absorption (13). Furthermore, the terminal elimination half-life ($t_{1/2\beta}$) is 7 to 10 h in subjects with normal renal function compared with about 2 h for erythromycin (13). Although only 15% of roxithromycin is eliminated renally unchanged, recent data with other compounds have demonstrated marked alterations in nonrenal disposition in the presence of decreased renal function (2). Therefore, this study was designed to evaluate and compare the dispositions of roxithromycin in subjects with normal and severely impaired renal function.

MATERIAL AND METHODS

Twenty subjects 18 years of age or older participated in the study after granting written informed consent. The study was approved by our Institutional Review Board. Ten subjects had normal renal function (24-h ambulatory creatinine clearance [CL_{CR}] of ≥90 ml/min), and ten subjects had chronic renal failure, with CL_{CR}s of <15 ml/min, but were not yet receiving dialysis therapy.

Prior to study entry, each participant underwent a complete medical history, physical examination, hematological and biochemical screening profile, 24-h ambulatory CL_{CR} determination, urinalysis, electrocardiogram, and chest X ray.

Patients with a history of gastrointestinal, cerebrovascular, respiratory, or hepatic disease or a known allergy to macrolide antibiotics were excluded from the study. None of the participants had received an investigational drug or antibiotic therapy during the month prior to the start of the study. Concurrent drug therapy was permitted for the subjects with chronic renal failure. Therapy included drugs for the treatment of hypertension, diabetes, and hyperparathyroidism. All such concurrent therapy was continued unchanged for 2 weeks prior to the study and during the course of the investigation.

All participants were admitted to the Clinical Research Unit 12 h prior to drug administration. Ten hours prior to drug administration a standard light snack was served, after which the subjects fasted until 4 h after roxithromycin administration. No concomitant medications were ingested during the 10-h period prior to or for 4 h after roxithromycin administration. Each subject received a single 300-mg oral dose of roxithromycin (lot RP 409; Hoechst-Roussel Pharmaceuticals, Inc.) administered with 240 ml of water.

Blood samples (10 ml) were collected in heparinized VACUTAINER tubes immediately before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 48 h following roxithromycin administration. Blood samples were immediately centrifuged, and the resultant plasma was frozen at −20°C until assayed.

Urine was collected immediately prior to and during the following periods after drug administration: 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 24, 24 to 36, and 36 to 48 h. After the total volume and pH of the fresh urine collections were measured, a sample was obtained and frozen at −20°C until assayed.

Chemical assays. Roxithromycin concentrations in plasma and urine samples were measured by a microbiological assay (on file at Hoechst-Roussel Pharmaceuticals, Inc.), using *Micrococcus luteus* ATCC 9341. This assay procedure had lower levels of sensitivity of 1.0 and 0.25 μg/ml in plasma and urine, respectively. The intra-assay coefficients of variation were 7.6 and 12.1% at roxithromycin plasma concentrations of 6 and 2 μg/ml, respectively. The intra-assay coefficients of variation were 10.9 and 11% at roxithromycin urine concentrations of 10 and 25 μg/ml, respectively.

Data analysis. The maximum roxithromycin concentration in plasma (C_{max}) and time to maximum concentration in

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TABLE 1. Subject demographics[a]

Subject	Sex	Age (yr)	Wt (kg)	Ht (cm)	BSA (m^2)	CL_{CR} (ml/min)
Group 1 (normal)						
1	M	58	91.4	182.9	1.93	122
2	M	55	91.4	180.3	1.91	124.4
3	M	69	81.4	177.8	1.80	90.3
4	M	46	80.4	182.9	1.82	119
5	M	30	71.8	188.0	1.77	115
6	M	28	64.6	172.7	1.60	90
7	M	26	90.9	182.9	1.92	123.6
8	F	26	61.8	162.6	1.50	123.5
9	M	32	90.4	177.8	1.88	145.3
10	M	32	67.7	182.9	1.70	108
Mean ± SD		40.2 ± 15.6	79.2 ± 11.9	179 ± 7	1.78 ± 0.14	116.1 ± 16.6
Group 2 (ESRD)						
11	M	40	80.4	182.9	1.82	11
12	F	31	64.1	154.4	1.46	9.9
13	M	79	73.6	177.8	1.72	4
14	F	57	77.7	162.6	1.65	12
15	M	42	102.3	172.7	1.94	11.1
16	M	58	80.4	190.5	1.88	8.1
17	M	40	90.4	180.3	1.90	10.3
18	M	25	72.7	167.6	1.64	13
19	M	46	53.2	167.6	1.44	10.1
20	M	61	103.2	180.3	2.01	12.7
Mean ± SD		47.9 ± 16	79.8 ± 15.7	173 ± 11	1.75 ± 0.20	10.2 ± 2.6
P value		NS	NS	NS	NS	<0.05

[a] BSA, Body surface area; M, male; F, female; ESRD, end-stage renal disease; NS, not significant.

plasma (T_{max}) were determined by visual inspection of the plasma concentration-time curves. Analysis of the plasma concentration-time profile for roxithromycin was performed using nonlinear regression analysis in terms of a one- or two-compartment first-order oral absorption model with and without a time lag (9). The optimal pharmacokinetic model was selected on the basis of visual inspection, minimization of the residual sum of squares, and Akaike criteria (14). Roxithromycin concentrations in plasma were weighted as their reciprocal. Pharmacokinetic parameters derived included the absorption rate constant (K_a) and terminal elimination rate constant (β). The area under the plasma concentration-time curve from 0 h to the last measurable sampling time (AUC_{0-t}) was calculated by linear trapezoidal estimation. The $AUC_{0-\infty}$ was estimated as $AUC_{0-t} + (C_P/\beta)$, where C_P represents the last measured concentration in plasma. The $t_{1/2\beta}$ was calculated as 0.693/β. The apparent total body clearance (CL_P/F) of roxithromycin was calculated as dose/$AUC_{0-\infty}$. The apparent volume of distribution (V/F) of roxithromycin was calculated as $(CL_P/F)/\beta$. The renal clearance (CL_R) of roxithromycin was calculated as the quotient of the amount of roxithromycin recovered in the urine during the period $t1$ to $t2$ divided by the AUC for that same time interval (AUC_{t1-t2}). The apparent nonrenal clearance of roxithromycin (CL_{NR}) was calculated as the difference between CL_P/F and CL_R.

Statistical differences in clinical characteristics and the pharmacokinetic parameters of roxithromycin in the two subject groups were assessed by using an independent Student t test. Statistical significance was assessed at the $P < 0.05$ level. Data are expressed as means ± standard deviations.

RESULTS

There were no significant differences in any demographic parameters other than renal function between the two treatment groups (Table 1). The decline in the postabsorptive roxithromycin plasma concentration for the subjects with normal renal function was best described in all cases by a one-compartment first-order oral absorption model (Fig. 1). An absorption lag time of 0.21 ± 0.035 h (range, 0.15 to 0.23 h) was apparent in 5 of the 10 subjects.

The decline in the postabsorptive roxithromycin plasma

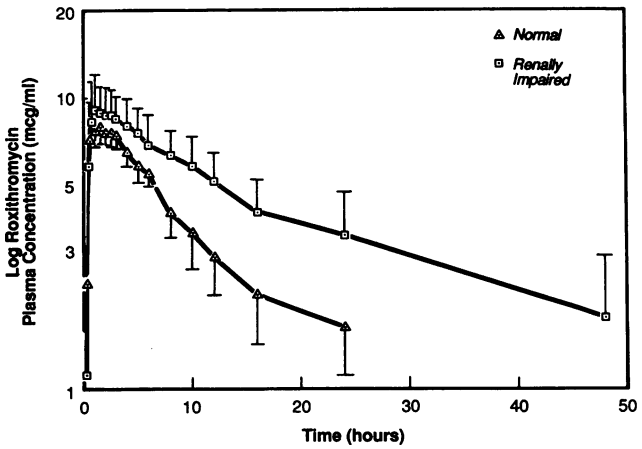

FIG. 1. Mean (± standard deviation) plasma concentration-time curves of roxithromycin following administration of a 300-mg oral dose to normal volunteers and volunteers with severe renal impairment (CL_{CR}, <15 ml/min).

TABLE 2. Roxithromycin pharmacokinetic parameters[a]

Patient	C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (μg · h/ml)	V/F (liter/kg)	K_a (h^{-1})	$t_{1/2\beta}$ (h)	CL_P/F (ml/min)	CL_R (ml/min)	CL_{NR} (ml/min)
Group 1 (normal)									
1	8.67	3.00	105.13	0.39	5.37	8.74	47.28	5.11	42.17
2	8.67	0.48	179.39	0.39	5.67	13.93	27.69	4.95	22.74
3	8.67	2.50	138.54	0.40	2.74	9.04	40.76	4.26	36.50
4	8.59	0.75	78.47	0.39	5.53	5.15	71.02	5.01	66.01
5	9.09	1.50	108.64	0.39	5.28	6.44	55.05	3.84	51.21
6	9.49	1.50	109.00	0.46	3.25	6.75	47.72	5.54	42.18
7	8.66	2.00	124.00	0.47	1.62	7.8	47.33	5.55	41.78
8	6.98	0.75	103.06	0.67	6.29	8.4	48.52	8.24	40.28
9	9.30	0.75	113.72	0.34	4.88	6.85	46.14	6.01	40.13
10	8.84	0.78	92.45	0.48	8.97	6.09	56.64	7.05	49.60
Mean ± SD	8.7 ± 0.7	1.4 ± 0.9	115.33 ± 27.81	0.44 ± 0.1	4.96 ± 2.05	7.9 ± 2.5	48.8 ± 11.1	5.5 ± 1.3	43.3 ± 11.1
Group 2 (ESRD)									
11	12.15	1.00	329.12	0.36	14.77	19.82	15.76	0.67	15.09
12	11.95	1.03	282.18	0.40	7.04	15.68	17.79	0.36	17.43
13	8.76	3.00	371.70	0.48	1.59	19.65	19.02	0.08	18.94
14	10.52	4.02	293.23	0.36	1.91	17.12	16.96	0.41	16.55
15	8.00	3.02	245.93	0.39	2.86	21.29	20.40	0.11	20.29
16	11.31	1.00	178.88	0.50	2.22	16.59	28.0	0.30	27.70
17	5.21	2.50	93.03	0.63	3.13	12.62	47.47	0.08	47.39
18	12.48	2.50	148.47	0.29	0.97	6.62	35.04	0.83	34.21
19	10.11	2.48	265.27	0.58	3.06	15.64	18.98	0.22	18.76
20	11.17	1.00	212.94	0.29	4.10	10.23	33.93	0.50	33.43
Mean ± SD	10.2 ± 2.3	2.2 ± 1.1	242.07 ± 84.97	0.43 ± 0.12	4.17 ± 4.09	15.5 ± 4.66	25.3 ± 10.5	0.36 ± 0.25	25.0 ± 10.5
P value	NS	NS	<0.05	NS	NS	<0.05	<0.05	<0.05	<0.05

[a] ESRD, End-stage renal disease; NS, not significant.

concentration for the renally impaired subjects was best described for 9 of the 10 subjects by a one-compartment first-order oral absorption model and for 1 subject by a two-compartment first-order oral absorption model (patient 11). An average absorption time lag of 0.31 ± 0.23 h (range, 0.17 to 0.67 h) was observed for 4 of the 10 renally impaired subjects.

No significant differences in C_{max}, T_{max}, V/F, and K_a were observed between the two study groups (Table 2). The $t_{1/2\beta}$ of roxithromycin was significantly prolonged in the renally impaired subjects, 15.5 ± 4.7 h compared with 7.9 ± 2.5 h in the subjects with normal renal function. The CL_P/F of roxithromycin was significantly lower in the renally impaired, 25.3 ± 10.5 ml/min compared with that in the subjects with normal renal function, 48.8 ± 11.1 ml/min. Both CL_R and CL_{NR} were significantly lower in the renally impaired subjects.

The mean cumulative urinary excretion of roxithromycin over 48 h in both study groups is depicted in Fig. 2. Approximately 40 mg of roxithromycin, or 13% of the administered dose, was recovered in the urine of the subjects with normal renal function, compared with about 5 mg, or 2% of the administered dose, in the urine of the renally impaired subjects.

All subjects tolerated the single-oral-dose administration of roxithromycin without adverse clinical effects or clinically important changes in laboratory tests or physical examination.

DISCUSSION

This study characterized the pharmacokinetics of roxithromycin in subjects with severely impaired renal function and subjects with normal renal function after the administration of a single oral dose. No significant difference in K_a, C_{max}, or T_{max} was observed between the two groups of subjects, suggesting that renal insufficiency does not change the absorption of roxithromycin. While plasma protein binding studies were not done, protein binding has been reported to be about 90%, mostly to α_1-acid glycoprotein (13). Patients with chronic renal failure have been shown to have elevated levels of this protein; thus, there may be greater plasma protein binding of roxithromycin in this patient group (3). However, the V/Fs for both groups were not different, indicating that the CL_P/F of roxithromycin did not change because of a change in drug distribution. In the group of

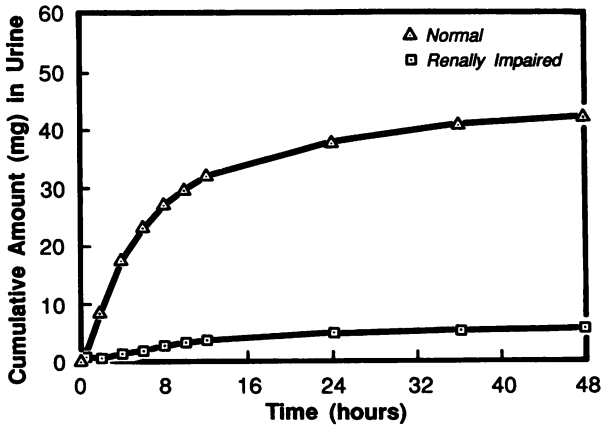

FIG. 2. Mean cumulative amount of roxithromycin in urine following administration of a 300-mg oral dose to normal volunteers and volunteers with severe renal impairment (CL_{CR}, <15 ml/min).

subjects with renal disease, the CL_P/F, CL_R, and CL_{NR} of roxithromycin were all significantly lower than in the subjects with normal renal function. The prolonged $t_{1/2\beta}$ reflects a decrease in roxithromycin CL_P/F in patients with severely impaired renal function.

Limited data on the pharmacokinetics of roxithromycin in healthy or renally impaired subjects have been published. Wise et al. evaluated the disposition of roxithromycin in 12 healthy volunteers after administration of a single 150-mg oral dose (13). The T_{max} and $t_{1/2\beta}$ of roxithromycin were 1.93 and 10.4 h, respectively, which are consistent with the findings of the present study (13).

After multiple oral doses (150 mg every 12 h for 3 days) to six healthy males, the $t_{1/2\beta}$ of roxithromycin was 13.2 ± 2.9 h (range, 9.7 to 18.5 h) (13). Although this $t_{1/2\beta}$ is more prolonged than that found in the present study, a smaller number of subjects and a more sensitive bioassay were used. Possible explanations for this longer $t_{1/2\beta}$ include an ability to detect lower roxithromycin plasma concentrations longer or nonlinear pharmacokinetics with this total daily dose (11). The V/F was not determined, and the authors stated that the CL_P could not be accurately measured.

There is only one other report of roxithromycin disposition in subjects with renal failure, in which a single oral dose of 150 mg was given to 12 healthy subjects and 12 subjects with renal failure (CL_{CR}, 4.4 to 71.7 ml/min). The C_{max}, $t_{1/2\beta}$, and AUC_{0-72} of roxithromycin were significantly higher in the renally impaired subjects than in the normal subjects, with the $t_{1/2\beta}$ (17.9 h) and CL_R (0.57 ml/min) similar to present study results (D. Tremblay, C. Verger, B. Saint-Salvi, D. Robinet, and C. Manuel, 3rd World Conf. Clin. Pharmacol. Ther., Stockholm, Sweden, 1986, abstr. no. 1204). The CL_R of roxithromycin and the percentage of unchanged drug recovered in the urine correlated with CL_{CR}, although CL_P did not.

Urinary excretion generally plays a minor role in the clearance of roxithromycin, with only about 13% of an oral dose being recovered in the urine. Fecal excretion of unaltered drug is the major route of elimination for roxithromycin, although metabolism to at least three inactive metabolites does occur (11). While the effect of renal disease on the disposition of renally eliminated drugs has been well recognized, renal disease may also alter the CL_{NR} of drugs (2, 8). For example, the CL_{NR} of cefotaxime was found to be significantly impaired, compared with that in normal subjects, in subjects with severe renal disease not yet receiving dialytic therapy (8). This study demonstrates decreased clearance, both renal and nonrenal, of roxithromycin in severe renal disease.

Perhaps the most compelling argument for dosage adjustment of roxithromycin for subjects with renal disease is its chemical and pharmacological similarity to erythromycin, which has been demonstrated to be ototoxic, especially when dosage correction is not used in subjects with renal disease (4, 7; J. P. Mèry and A. Kanfer, Letter, N. Engl. J. Med. **301**:944, 1979). The pharmacokinetics of erythromycin are known to be altered in chronic renal failure; the bioavailability, V, and $t_{1/2\beta}$ are all increased, necessitating dosage reduction in renal disease (6, 7, 12). From a clinical viewpoint, erythromycin-induced ototoxicity has been associated with elevated erythromycin concentrations in serum (7; Mèry and Kanfer, Letter). Ototoxicity has not been reported with roxithromycin; however, the recognition of erythromycin-induced deafness was not initially described. Hence, dosage reduction with roxithromycin is justified for safety reasons, since accumulation of roxithromycin occurs in patients with CL_{CR}s of <15 ml/min.

The use of roxithromycin in antimicrobial therapy will generally be in the outpatient treatment of diseases now being treated with erythromycin, namely infections of the upper respiratory tract and skin structure infections (10). For organisms frequently implicated in these infections (e.g., *Branhamella catarrhalis*, *Legionella pneumophila*, *Neisseria gonorrhoeae*, *Streptococcus pneumoniae*, and *Mycoplasma pneumoniae*), roxithromycin MICs are 0.8 to 1.6 μg/ml for 90% of strains tested (1, 5). Concentrations of roxithromycin in plasma remained greater than this range for at least 24 h in subjects with normal renal function and for at least 48 h in subjects with renal impairment.

A dosing regimen of 150 mg of roxithromycin orally every 12 h for the normal group of subjects studied would be expected to produce at steady state maximal and minimal concentrations in plasma of 6.6 and 2.3 μg/ml, respectively. In contrast, a regimen of 150 mg of roxithromycin orally every 24 h in the group with severe renal disease would be expected to yield maximal and minimal concentrations of 6.6 and 2.3 μg/ml in plasma.

In summary, the disposition of roxithromycin is significantly altered in patients with severe renal insufficiency (CL_{CR}, <15 ml/min). Thus, it is recommended that a doubling of the roxithromycin dosing interval be considered for this patient population.

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