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Pharmacokinetics and Tissue Penetration of Roxithromycin after Multiple Dosing

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The pharmacokinetics of the macrolide roxithromycin (RU 28965) were studied during and after administration of 150 mg every 12 h for 3 days (five doses) in six volunteers. The concentrations in serum, blister fluid, and urine were measured. Mean levels in serum taken at 1.5 h after the morning dose increased from 4.4 μg/ml on day 1 to 5.9 μg/ml on day 2 and 7.4 μg/ml on day 3. The mean serum and blister fluid elimination half-lives on day 3 were 13.2 and 12.5 h, respectively. Roxithromycin penetrated blister fluid well; the mean percent penetration (as measured by the ratio of areas under the curve) was 85%. After the final dose, a mean of 10.5% of that dose was recovered in 12 h as microbiologically active compound.

Roxithromycin (RU 28965), a new macrolide antimicrobial agent, is an oral ether oxime derivative of erythromycin. It possesses the same spectrum of antimicrobial activity as erythromycin (1, 7) but is slightly less active in vitro. Preliminary information available on the pharmacokinetics of roxithromycin suggests that it is well absorbed and gives levels in serum considerably greater than does erythromycin (H. B. Lassman, S. K. Puri, I. Ho, R. Sabo, and M. J. Mezzino, J. Clin. Pharmacol., in press). Thus, it is possible that roxithromycin may be administered at lower doses or less frequently than erythromycin. In this study we investigated the pharmacokinetics of roxithromycin after multiple dosing. The penetration of the agent into chemically induced blister fluid, the composition of which is similar to that of exudate evoked by a mild inflammatory reaction (10), was also studied.

MATERIALS AND METHODS

Six healthy male volunteers, with a mean age of 27 years (range, 24 to 35 years), a mean weight of 75.8 kg (range, 71.5 to 81.2 kg), and a mean height of 177 cm (range, 170 to 183 cm), provided written informed consent for the study, which had been approved by the Dudley Road Hospital Ethical Committee. They had no history of allergy to antimicrobial agents, and physical examination, routine hematology, blood chemistry, and urinalysis studies performed on each subject before and after the study were normal. These parameters were all normal on entry into the study. The volunteers each received a total of five doses of 150 mg of roxithromycin at 12-h intervals. All subjects fasted from 11 p.m. On the morning of day 1 a 150-mg dose of roxithromycin was orally administered with 200 ml of water. Subjects remained at rest for 2 h. A standard breakfast was then taken, and they could move around freely; fluid was allowed ad libitum. After 4 h a normal diet was allowed. Blood samples were taken on days 1 and 2 immediately before and at 1.5 h after administration of the morning dose of 150 mg of roxithromycin. Fasting was repeated from 11:00 p.m. each evening. On the evening of day 2 (again fasting from 11:00 p.m.), volunteers strapped two 0.2% cantharides-impregnated plasters (1 by 1 cm) onto the anterior surface of one forearm. On the morning of day 3, the final dose of roxithromycin was administered as before. Blood samples were taken at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, and 26 h after dosing. The cantharides-induced blisters were sampled (with a fine needle) at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 26 h after the dose. Urine samples were collected at 0 to 4, 4 to 8, and 8 to 12 h on days 1 and 2 and at 0 to 12, 12 to 24, and 24 to 48 h after the last dose on day 3.

Samples were assayed within 2 h of collection (except overnight urine samples) by a microbiological method employing Oxoid Antibiotic Medium no. 1 (pH 8.5; Oxoid, Basingstoke, England) and *Sarcina lutea* DRH 2114 as the indicator organism. The serum and blister fluid samples were assayed against standards prepared in 100% and 70% human serum, respectively. The urine standards were prepared in phosphate-buffered saline (pH 8.5). The assay plates were incubated overnight at 37°C. The lower limits of sensitivity of the assays were 0.5 μg/ml for serum and blister fluid and 0.06 μg/ml for urine. The coefficient of variation of the assay was 8.8%, and the mean percent error plus two standard deviations of the percent error was 17.6%.

Pharmacokinetic analysis was performed on individual data by routine graphical methods (5, 6).

RESULTS

Levels of roxithromycin attained in serum on days 1, 2, and 3 and in blister fluid on day 3 are shown in Table 1. Derived pharmacokinetic parameters are shown in Table 2.

Roxithromycin was rapidly absorbed, with the mean 1.5-h levels being 4.4 μg/ml on day 1, 5.9 μg/ml on day 2, and 7.4 μg/ml on day 3. There was considerable individual variation in maximum concentration in serum, C_{max}, on day 3, ranging from 5.2 to 12.0 μg/ml. On day 3, C_{max} was attained at a mean time (T_{max}) of 1.0 h, which was close to the anticipated T_{max} chosen on days 1 and 2 (i.e., 1.5 h).

One volunteer (no. 1) had lower peak levels of roxithromycin in both serum and blister fluid. As this agent is bound to α_1-acid-glycoprotein (Roussel Laboratories, personal communication), the levels of this protein were measured in volunteers 1, 2, and 3. It was interesting to note that the α_1-acid-glycoprotein levels in volunteer 1 were lower in both serum and blister fluid than were the levels in the two other volunteers (data not shown), the differences being significant at the 5% level.

The mean serum elimination half-life of roxithromycin was

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TABLE 1. Concentrations of roxithromycin in serum and blister fluid after 150 mg orally every 12 h for 3 days

Volunteer	Serum concn (μg/ml)														
	Day 1		Day 2		Day 3										
	Pre	1.5 h	Pre	1.5 h	Pre	0.25 h	0.5 h	0.75 h	1.0 h	1.5 h	2 h	3 h	4 h	5 h	6 h
1	NDL[a]	0.6	1.0	2.5	1.2	1.3	3.3	4.9	4.6	5.2	5.1	4.6	2.8	2.6	2.1
2	NDL	4.6	1.7	5.0	1.8	3.9	6.7	10.1	7.1	7.2	6.8	7.5	4.9	4.4	3.5
3	NDL	2.9	1.6	6.7	2.6	2.8	3.5	12.0	9.4	9.2	8.2	8.4	6.5	5.6	4.5
4	NDL	5.8	2.2	9.6	2.2	2.4	10.2	9.1	7.7	8.3	6.8	8.2	7.4	4.2	3.8
5	NDL	6.2	2.2	6.5	2.9	2.7	7.7	7.4	6.5	6.8	9.2	7.9	6.4	4.8	4.8
6	NDL	6.0	2.1	5.3	2.5	3.3	9.1	9.5	8.7	7.7	7.0	6.1	6.6	4.4	5.1
Mean	NDL	4.4	1.8	5.9	2.2	2.7	6.7	8.9	7.3	7.4	7.2	7.1	5.6	4.3	4.0
SD		2.2	0.5	2.3	0.6	0.9	2.9	2.4	1.7	1.4	1.4	1.5	1.7	1.0	1.1

13.2 h, with a marked range of 9.6 to 18.5 h. The volunteer with the shortest elimination half-life attained the greatest value of C_{max} (12.0 μg/ml).

Roxithromycin penetrated blister fluid moderately rapidly on day 3; the level in blister fluid at 1 h was 37% (standard deviation, 19%) of that in serum at the same time, and that at 2 h was 49% (standard deviation, 22%) of that in serum. The mean maximum level (C_{max}) in blister fluid was not attained until 4 h; at 6 h the levels in blister fluid and serum were similar, and thereafter they declined at a similar rate. The mean half-life of elimination from blister fluid (12.5 h) was similar to that in serum, but there was greater individual variation. The mean percent penetration, calculated from the ratio of the individual area under the curve from 0 h to infinity ($AUC_{0-\infty}$) blister to $AUC_{0-\infty}$ serum was 85%, with marked individual variations from 50.3 to 129.7%.

The total clearance of roxithromycin could not be accurately measured in this study. Calculated over 0 to 12 h, the mean clearance was 44.2 ml/min; however, this is likely to be an overestimate of the true value. The urine concentration was 25.6 μg/ml (standard deviation, 24.7 μg/ml) 0 to 4 h after the final dose, and it fell to 70 μg/ml (standard deviation, 3.5 μg/ml) over 12 to 24 h.

No side effects were attributable to roxithromycin. Hematology, blood chemistry, and urinalysis remained within normal limits.

TABLE 2. Pharmacokinetic parameters derived on day 3

Parameter[a]	Mean ± SD	Range
Serum		
T_{max} (h)	1.0 ± 0.6	0.5–2.0
C_{max} (μg/ml)	9.2 ± 2.3	5.2–12.0
$t_{1/2\beta}$ (h)	13.2 ± 2.9	9.7–18.5
k_{el} (h^{-1})	0.05 ± 0.11	0.038–0.071
CL (ml/min)	23.4 ± 7.9	17.4–39.0
$AUC_{0-\infty}$ (μg · h/ml)	114.4 ± 27.9	64.0–144.0
Blister		
T_{max} (h)	4.0 ± 1.7	2.0–6.0
C_{max} (μg/ml)	5.0 ± 2.2	2.3–9.0
$t_{1/2\beta}$ (h)	12.5 ± 4.5	7.8–19.0
$AUC_{0-\infty}$ (μg · h/ml)	90.9 ± 36.0	58.3–154.0
% Penetration	85.0 ± 31.1	50.3–129.7
Urine (cumulative mg excreted after final dose)		
0–12 h	15.8 ± 5.4	6.4–21.0
0–24 h	20.7 ± 6.6	8.4–26.7
0–48 h	24.8 ± 7.5	10.1–31.6

[a] $t_{1/2\beta}$, Elimination half-life; k_{el}, elimination rate constant; CL, clearance; $AUC_{0-\infty}$, area under the concentration-time curve from 0 h to ∞. For other abbreviations, see text.

DISCUSSION

As the mean serum elimination half-life of roxithromycin is 13.2 h, accumulation of this agent will probably occur upon 12-h dosing for a total of five doses (i.e., over a total of 60 h). The pharmacokinetics are best described by a two-compartment model; thus, the time to 90% of steady-state concentration would be 43 h, and that to 99% of steady-state concentration would be 86 h (4). At 60 h, we therefore attained a percentage of steady-state concentration between these two values.

The pharmacokinetic data derived from this study agree with preliminary published dose-ranging studies (8). Puri and co-workers (8) found the serum half-life of roxithromycin to be rather variable, ranging from 10.7 h (after 50 mg twice daily) to 17 h (after 400 mg once daily), and Tremblay et al. (9) found a mean serum half-life after 300 mg of 12.0 h. The maximum concentration achieved in serum (C_{max}) appears to increase with the dose in a linear fashion (8); however, later studies suggest nonlinear kinetics (Lassman et al., in press). With the formulation studied, we achieved a mean C_{max} on day 3 of 9.2 μg/ml, almost identical to the value in the previous study (Lassman et al., in press) (9.3 μg/ml after 150 mg every 12 h for 11 days). The rapid absorption of roxithromycin has been confirmed and described (9; Lassman et al., in press).

The kidneys provide only a minor route for roxithromycin elimination, with a mean of only 15.8 mg recovered in the urine as microbiologically active compound during the 12 h after the final dose. Studies with a single dose of [^{14}C]roxithromycin suggest that 7 to 8% of the dose is eliminated in the urine, there being three major metabolites (the decladinose and mono- and didemethylated roxithromycins); 50 to 55% is eliminated in the feces (in which two further metabolites have been noted); and 10 to 20% of the dose can be accounted for in expired CO_2 (Roussel Laboratories, personal communication).

Inflammatory fluid penetration was not as rapid as we have found with 4-quinolones (11) and certain β-lactams (10). This may be related to the high protein binding of roxithromycin, which is 86 to 91% at 10 μg/ml (R. Wise, unpublished data). The elimination rate of roxithromycin from inflammatory fluid is similar to that from serum. The degree of penetration is high (85%) but variable. Roxithromycin is bound mainly to α_1-acid-glycoprotein (unlike β-

TABLE 1—*Continued*

Blister fluid concn (μg/ml) on day 3													
7 h	8 h	12 h	26 h	0.5 h	1.0 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h	12 h	26 h
2.1	1.9	1.4	0.7	1.0	1.3	1.9	1.9	2.3	1.8	2.1	2.0	2.3	1.3	1.1
3.4	3.3	2.6	1.9	1.6	1.9	1.9	3.2	3.8	3.6	4.2	3.2	3.5	2.3	1.3
4.3	3.7	2.6	1.1	2.4	2.7	3.0	3.7	3.8	4.0	4.1	3.8	3.9	2.7	NT[b]
4.2	3.4	2.4	1.5	2.1	2.2	5.8	9.0	4.8	6.5	4.7	5.6	4.8	3.7	1.6
4.2	3.2	2.2	1.3	2.7	3.0	3.7	4.9	5.6	NT	4.0	3.9	3.3	2.3	1.8
4.3	4.6	3.2	1.6	2.6	3.0	4.8	4.6	3.9	NT	NT	NT	NT	1.9	NT
3.7	3.4	2.4	1.3	2.1	2.4	3.5	4.6	4.0	4.0	3.8	3.7	3.6	2.0	1.4
0.9	0.9	0.6	0.4	0.7	0.7	1.6	2.4	1.1	2.0	1.0	1.3	0.9	1.2	0.3

[a] NDL, No detectable level.
[b] NT, Not tested.

lactams) (Wise, unpublished data), and the difference in levels of this protein which we found between volunteers might explain the differing serum and blister fluid levels.

A 250-mg oral dose of erythromycin base, ethyl succinate, or stearate gives peak serum levels of 0.2 to 0.8 μg/ml, and a similar dose of the estolate gives peak levels of 1.4 to 1.7 μg/ml (3). The microencapsulated form of erythromycin base results in higher serum levels, but blister fluid penetration is slow, T_{max} being at 5 to 7 h (2). This present study shows that higher concentrations of roxithromycin in serum were achieved than would be expected from a comparable oral dose of erythromycin. Comparative cross-over studies should be performed to confirm this point.

Roxithromycin has been shown to be active in vitro against gram-positive cocci, *Haemophilus* spp., *Neisseria* spp., *Legionella pneumophila*, and *Campylobacter* spp. (1). When the levels attained in this study in serum and inflammatory fluid are compared with the in vitro activity, it might be expected that this dose of roxithromycin given twice daily would be effective against *Staphylococcus aureus* (MIC for 90% of strains [MIC_{90}], ≤0.8 μg/ml), *Streptococcus pyogenes* and *Streptococcus pneumoniae* (MIC_{90}, 1.6 μg/ml), and *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Legionella pneumophila*, and *Campylobacter* spp. (MIC_{90}, 0.8 μg/ml). Strains of *Staphylococcus epidermidis* (MIC_{90}, 3.1 μg/ml) and *Streptococcus faecalis* (MIC_{90}, 6.3 μg/ml) might be expected to respond to a higher dose. The superior pharmacokinetics, in particular the longer serum half-life, suggest that this agent might be given on a twice-daily basis.

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