Pharmacokinetics of Intravenous Erythromycin

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Abstract □ Erythromycin pharmacokinetics were examined following intravenous infusion to male subjects. The biological half-life of erythromycin in serum was 2 hr in individuals with normal renal function. The half-life varied in cases of reduced renal function, with values of 3.9 and 7.0 hr occurring in two subjects with severe renal impairment. Postinfusion serum erythromycin levels were adequately described by two-compartment model kinetics, and values for the distribution volume of the central compartment and the overall distribution are described. Estimated erythromycin distribution volumes in normal individuals may facilitate calculation of absorption efficiencies of erythromycin and its salts after oral doses.

Keyphrases □ Erythromycin—pharmacokinetics after intravenous administration in humans □ Pharmacokinetics—erythromycin after intravenous administration in humans □ Antibacterials—erythromycin, pharmacokinetics after intravenous administration in humans

Erythromycin is actively cleared from the body by the liver (1), and only 10–15% of the drug is excreted in microbiologically active form by the kidneys (2). Therefore, the half-life of circulating antibiotic should not be influenced significantly by variations in renal function. In an early study (3), the serum half-life of erythromycin increased from 1.5 hr in normal individuals to 4.8–5.8 hr in anuric patients. A preliminary report indicated that the erythromycin half-life increased only to 2.5 hr in severe uremia (4). This value appeared more consistent with the minor contribution by the kidneys to erythromycin clearance.

This report details erythromycin pharmacokinetics following intravenous infusion in individuals with normal and impaired renal function. The major study objectives were to describe erythromycin distribution in the body accurately and to examine the influence of compromised renal function on both its distribution and clearance characteristics.

EXPERIMENTAL

Subjects—Seven male individuals[1] participated. Physical details, creatinine clearance, and serum creatinine values of subjects and also clinical conditions are described in Table I. Creatinine clearance values are the means from five individual determinations (three for Subject 6, one for Subject 7) obtained during 48 hr following erythromycin doses. All individuals had normal liver function, as indicated by blood biochemistry values within the normal range.

Protocols—Subjects 1–6 received 500 mg of erythromycin base equivalents as the lactobionate salt[2], by continuous infusion over 30 min into an arm vein, in a solution of 5% dextrose in water. One month later, Subjects 6 and 7 received 500 mg of erythromycin base equivalents as the glucoheptonate salt[3] in an identical manner. In Subjects 5–7, erythromycin doses were administered 24 hr following dialysis. Infusion was started at approximately 8 am, about 1 hr after breakfast.

Blood samples (5 ml) were taken immediately before the infusion was started, at the end of the infusion, and at 1, 2, 3, 4, 6, 8, 12, and 24 hr after the end of the infusion. Urine was quantitatively collected at intervals during and following the infusion. Erythromycin activity in serum and urine was measured by a standard microbiological cup-plate diffusion method, using *Staphylococcus aureus* (6538P) as the test organism. Subjects received no antibiotic drugs, other than the required doses of erythromycin, for 1 week before and during a study.

Table I—Subject Physical Details

Subject	Age, yr	Weight, kg	Height, m	Cl_{cr}[a], ml/min	C_{cr}[b], mg %	Condition
1	36	75	1.8	118	1.1	Normal
2	52	75	1.6	78	1.1	Diabetic, sebaceous cyst on neck
3	58	52	1.8	105	1.0	Rheumatoid arthritis
4	70	77	1.8	43	2.3	Sclerotic cardiovascular disease, postmyocardial infarction, streptococcal cellulitis, rheumatoid arthritis
5	33	75	1.8	5.3	8.7	Severe hypertension, chronic renal failure (dialysis)
6(a)[c]	41	69	1.7	3.4	10.7	Chronic renal failure, renal transplant recipient with chronic rejection (dialysis)
6(b)[c]	41	69	1.7	3.2	10.3	Chronic renal failure, renal transplant recipient with chronic rejection (dialysis)
7	46	60	1.6	<1.0	17.4	Hypertension, small kidneys with chronic renal failure (dialysis)

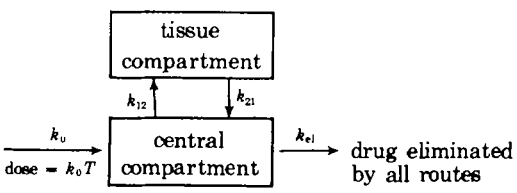
[a] Creatinine clearance. [b] Serum creatinine. [c] Subject 6 was studied on two separate occasions.

RESULTS

Individual postinfusion serum erythromycin levels declined in a biphasic manner, as reported previously (2). Serum erythromycin levels are summarized in Table II, and typical serum profiles from two subjects are shown in Fig. 1. This type of profile is consistent with two-compartment model kinetics, with elimination occurring from the central compartment. Serum erythromycin levels were interpreted in terms of this model together with zero-order input (5). The model is depicted in Scheme I; serum erythromycin levels, C, are described by (5, 6):

$$C = \frac{k_0}{V_1 k_{el}}\left[\left(\frac{k_{el}-\beta}{\alpha-\beta}\right)(1-e^{-\alpha T})e^{-\alpha(t-T)} - \left(\frac{k_{el}-\alpha}{\alpha-\beta}\right)(1-e^{-\beta T})e^{-\beta(t-T)}\right] \quad \text{(Eq. 1)}$$

where k_0 is the zero-order rate constant for drug infusion; k_{12}, k_{21}, and k_{el} are first-order rate constants for drug distribution between central



Scheme I

[1] All subjects gave written informed consent. Six were patients in the Madison Veterans Administration Hospital; the other subject was W. A. Craig.
[2] Erythromycin Lactobionate, Abbott Laboratories, North Chicago, IL 60064.
[3] Ilotycin Glucoheptonate, Eli Lilly and Co., Indianapolis, IN 46225.

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Table II—Serum Erythromycin Concentrations

Subject	Serum Erythromycin Concentration								
	0 hr[a]	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr	24 hr
1	12.4	6.4	5.0	3.1	1.9	1.2	0.4	—[b]	—
2	9.9	5.0	2.5	2.0	1.3	1.0	0.4	—	—
3	12.2	3.9	2.5	1.3	0.8	0.5	0.2	—	—
4	9.9	4.0	2.0	1.6	1.0	0.6	0.4	—	—
5	7.8	2.5	2.0	1.6	1.2	0.7	0.4	—	—
6(a)	9.9	3.1	2.5	1.4	0.9	0.5	0.4	—	—
6(b)	8.1	2.5	1.6	1.0	0.9	0.6	0.4	0.2	—
7	7.9	4.9	3.8	2.4	2.0	1.6	1.2	1.0	0.2

[a] All sampling times were calculated from the end of infusion. [b] Below limit of detection, 0.1 μg/ml.

and peripheral compartments and also drug elimination, respectively; V_1 is the apparent distribution volume of the central compartment; T is the infusion time; and t is the total time elapsed since the start of the infusion. The complex rate constants α and β are given by:

$$\begin{matrix}\alpha \\ \beta\end{matrix} = 0.5\left[(k_{12} + k_{21} + k_{e1}) \pm \sqrt{(k_{12} + k_{21} + k_{e1})^2 - 4k_{21}k_{e1}}\right] \quad \text{(Eq. 2)}$$

where $\alpha > \beta$ and the elimination half-life is given by $\ln 2/\beta$.

Individual serum data were fitted to Eq. 1 graphically and subsequently by iterative least-squares analysis using the digital computer program NREG (5). Renal clearances of erythromycin were calculated from all urine collection intervals except the −0.5–2-hr interval (Table III).

Urinary recovery data are summarized in Table III, and values of pharmacokinetic parameters are given in Table IV.

A low recovery of erythromycin in 48-hr urine in subjects with normal renal function is consistent with previous reports (2). As renal function deteriorates, urinary recovery of antibiotic is reduced still further and is insignificant in severe uremia. The concentration of antibiotic in urine is also considerably reduced in uremia, although, among the uremic subjects, the concentration of antibiotic in urine was unrelated to urine volume.

Changes in renal function generally had only a small effect on the serum erythromycin half-life. Only Subject 7 showed considerable prolongation of serum levels compared to normal subjects; Subjects 5 and 6 showed a small effect. Uremic subjects tended to have somewhat lower serum erythromycin levels immediately after the end of the infusion. These reduced levels are associated with increased apparent distribution volumes in uremic subjects.

Considerable variation was observed in some pharmacokinetic values (Table IV), particularly the microscopic rate constants k_{12}, k_{21}, and k_{e1}.

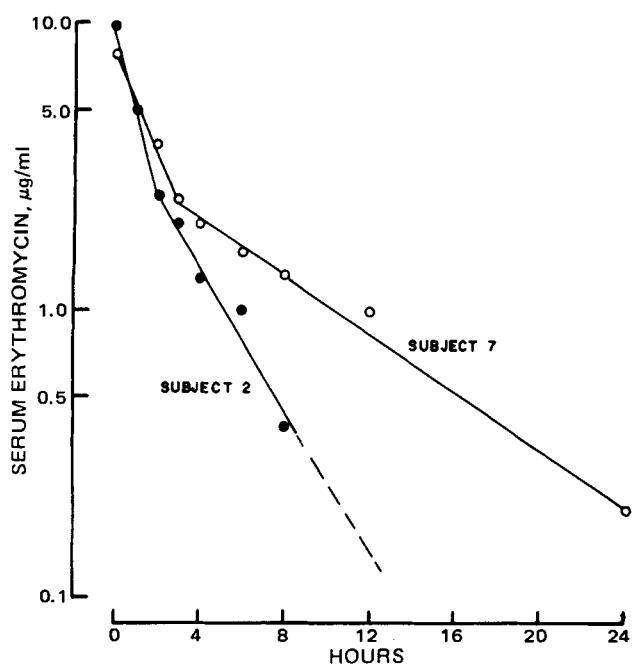

Figure 1—*Serum erythromycin levels in one normal subject and one uremic subject following intravenous infusion. Solid lines are computer lines of best fit using Eqs. 1 and 2. All times are calculated from the end of infusion.*

Table III—Concentrations of Erythromycin and Percentages of Dose Recovered in Urine

Subject		Collection Period, hr						48-hr Urine Volume, liters
		−0.5–2[a]	2–4	4–8	8–12	12–24	24–48	
1	Concentration[b]	125.1	80.7	51.2	12.5	0.1	0.0	2.3
	Percent[c]	8.0	9.2	10.7	11.4	11.4	11.4	
2	Concentration	195.4	60.6	24.9	9.7	0.5	0.0	2.9
	Percent	1.6	2.6	3.4	4.1	4.2	4.2	
3	Concentration	78.5	27.2	—	7.9[d]	0.3	0.0	3.2
	Percent	4.9	6.7	—	7.4	7.4	7.4	
4	Concentration	18.5	—	3.1[d]	0.4	0.0	0.0	2.8
	Percent	1.0	—	1.2	1.2	1.2	1.2	
5	Concentration	6.4	—	2.5[d]	0.3	0.0	0.0	1.4
	Percent	0.2	—	0.3	0.3	0.3	0.3	
6(a)	Concentration	—	—	—	0.8[d]	0.1	0.0	0.8
	Percent	—	—	—	<0.1	<0.1	<0.1	
6(b)	Concentration	—	0.8[d]	—	—	0.4[d]	0.0	0.4
	Percent	—	<0.1	—	—	<0.1	<0.1	
7	Concentration	—	—	—	—	3.1[d]	—	0.02
	Percent	—	—	—	—	<0.1	—	

[a] From the start of infusion until 2 hr postinfusion. [b] Concentration of antibiotic in urine (micrograms per milliliter). [c] Cumulative percent of dose excreted in urine. [d] Combined value for two or more collection intervals.

Subject 7 gave lower values for these constants and also exhibited a lower plasma clearance than all other subjects. It is not clear why these values were different in this subject compared to Subject 6 who had similarly impaired renal function. It is not a dosage form effect since both Subjects 6(b) and 7 received erythromycin glucoheptonate, which should, in any case, release the erythromycin cation in the body in the same way as the lactobionate.

The volume of the central, rapidly equilibrating, compartment increased from 45% of total body weight in normal individuals to 100% in severe uremia. The apparent total distribution of antibiotic, $V_{d(ss)}$, similarly increased from 57 to 109% of body weight. Negative correlations between these distribution parameters and creatinine clearance were quite good, with correlation coefficients of −0.62 ($p < 0.05$) and −0.71 ($p < 0.05$) being obtained for V_1 and $V_{d(ss)}$, respectively.

The very slight dependence of the overall erythromycin clearance on renal function is indicated by the serum and renal clearance values in Table IV. Although the correlation coefficient between erythromycin renal clearance and creatinine clearance was +0.8 ($p < 0.05$), there was no obvious trend in serum clearance values. This result was due to the

Table IV—Values of Pharmacokinetic Parameters

Parameter	Subject							
	1	2	3	4	5	6(a)	6(b)	7
α, hr^{-1}	1.7	0.8	1.4	1.6	2.1	1.2	0.4	0.2
β, hr^{-1}	0.36	0.34	0.35	0.29	0.23	0.33	0.18	0.01
$t_{1/2(elim)}$, hr	1.9	2.0	2.0	2.4	3.0	2.1	3.9	7.0
k_{12}, hr^{-1}	0.34	0.07	0.34	0.52	0.94	0.24	0.05	0.01
k_{21}, hr^{-1}	1.25	0.42	0.59	0.64	0.74	0.51	0.39	0.13
k_{e1}, hr^{-1}	0.49	0.63	0.87	0.71	0.66	0.80	0.30	0.14
V_1, %[a]	45	54	60	50	61	58	83	101
$V_{d(ss)}$[b], %	57	63	95	90	138	85	93	143
Cl_P[c], ml/min	275	428	452	453	502	525	285	141
Cl_R[d], ml/min	21	20	47	1.6	<1.0	<1.0	<1.0	<1.0
r^2[e]	+0.998	+0.991	+0.998	+0.999	+0.998	+0.989	+0.981	+0.992

[a] Calculated from V_1 = dose/$(A + B)$, where A and B are the intercepts on the y ordinate of the fast (α) and slow (β) segments of the biphasic plasma drug decay profile, expressed as percent of total body weight. [b] Overall apparent distribution volume: $V_{d(ss)} = V_1(k_{12} + k_{21})/k_{21}$. [c] Plasma clearance, calculated from $V_1 k_{e1}$. [d] Renal clearance of microbiologically active erythromycin. [e] Coefficient of determination: $(\Sigma obs^2 - \Sigma dev^2)/\Sigma obs^2$.

minor contribution of renal clearance to the overall erythromycin elimination and also to the compensating influences of increasing distribution volumes with decreasing elimination rate constants, both of which are involved in the calculation of serum clearance.

DISCUSSION

The changes in erythromycin elimination characteristics associated with the varying renal function observed support previous contentions that clearance of this antibiotic from the circulation is generally not influenced markedly by renal impairment (3, 4). The regression of β *versus* creatinine clearance was described by the linear expression $y = 0.21 + 0.001x$ ($r = +0.74$, $p < 0.05$), which is numerically similar to the expression reported previously (4); the linear regression of k_{el} *versus* creatinine clearance was described by $y = 0.49 + 0.002x$ ($r = +0.36$, $p > 0.05$).

The large distribution volumes (Table IV) are consistent with reported extensive tissue penetration of erythromycin (7–10). The apparent increase in distribution with decreasing renal function was possibly due to the displacement of this highly protein-bound drug from serum proteins in renal failure, resulting in a larger proportion of drug distributing into extravascular tissues. This phenomenon was demonstrated previously for a number of highly protein-bound drugs both *in vivo* (11, 12) and *in vitro* (13). Application of this concept to erythromycin needs to be verified since protein binding was not measured in the present study.

Although extensive tissue distribution by erythromycin is confirmed by the present data, the degree of tissue penetration is probably considerably underestimated. Drug bound to circulating proteins is not immediately available for extravascular distribution and, provided the drug is not bound to other tissues, the drug concentration in extravascular fluids tends to equilibrate with the concentration of free drug in serum. If the distribution volumes are calculated on this basis, and circulating drug is assumed to be approximately 90% protein bound (14), then calculated volumes are approximately 10 times greater than those given in Table IV. Since erythromycin is sequestered by certain tissues (7) and since there is no information on tissue binding of erythromycin, its true distribution volume cannot be calculated with any accuracy.

Although the calculated distribution volumes in Table IV may be underestimates of true values, they are reasonably consistent among normal individuals (Subjects 1–3) and may thus provide a basis for calculating absolute absorption efficiencies from oral doses of erythromycin or its salts.

REFERENCES

(1) J. B. Hammond and R. S. Griffith, *Clin. Pharm. Ther.*, **2**, 308 (1961).

(2) R. S. Griffith, D. M. Johnstone, and J. W. Smith, *Antibiot. Annu.*, **1953–1954**, 496.

(3) C. M. Kunin and M. Finland, *J. Clin. Invest.*, **38**, 1509 (1959).

(4) P. G. Welling, W. A. Craig, and C. M. Kunin, *Clin. Pharmacol. Ther.*, **18**, 45 (1975).

(5) P. G. Welling, W. R. Shaw, S. J. Uman, F. L. S. Tse, and W. A. Craig, *Antimicrob. Agents Chemother.*, **8**, 532 (1975).

(6) J. G. Wagner, "Fundamentals of Clinical Pharmacokinetics," Drug Intelligence Publications, Hamilton, Ill., 1975, p. 100.

(7) C.-C. Lee, R. C. Anderson, and K. K. Chen, *Antibiot. Chemother.*, **3**, 920 (1953).

(8) C.-C. Lee and R. O. Froman, *ibid.*, **11**, 107 (1960).

(9) R. H. Parker, *Mod. Treatment*, **6**, 1071 (1969).

(10) D. G. Winningham, N. J. Nemoy, and T. A. Stamey, *Nature*, **219**, 139 (1968).

(11) P. G. Welling, W. A. Craig, G. L. Amidon, and C. M. Kunin, *J. Infect. Dis., Suppl.*, **128**, S556 (1973).

(12) P. G. Welling, W. A. Craig, G. L. Amidon, and C. M. Kunin, *Clin. Pharmacol. Ther.*, **15**, 344 (1974).

(13) W. A. Craig, P. G. Welling, J. P. Wagnild, and C. M. Kunin, *Proc. 8th Int. Congr. Chemother., Athens*, **1973**, 722.

(14) R. G. Wiegand and A. H. C. Chun, *J. Pharm. Sci.*, **61**, 425 (1972).

Physicochemical Properties of Amphoteric β-Lactam Antibiotics I: Stability, Solubility, and Dissolution Behavior of Amino Penicillins as a Function of pH

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Abstract □ The degradation rate, solubility, and dissolution rate of amino penicillins, amoxicillin, ampicillin, epicillin, and cyclacillin, were determined quantitatively as a function of pH. In the pH range studied, 0.30–10.50, the degradation of amoxicillin and epicillin followed pseudo-first-order kinetics to give the same type of pH–rate profiles as those of ampicillin and cyclacillin. Cyclacillin anhydrate was the most soluble, followed in order by ampicillin anhydrate, ampicillin trihydrate, amoxicillin trihydrate, and epicillin anhydrate. These pH–solubility profiles showed U-shaped curves. The dissolution rate constants from the rotating disk were analyzed by the simultaneous chemical reaction and diffusion models. Their relative bioavailability after a single oral administration was assessed from their physicochemical properties determined *in vitro*.

Keyphrases □ Penicillins, various amino—stability, solubility, and dissolution rates, effect of pH □ Stability—various amino penicillins, effect of pH □ Solubility—various amino penicillins, effect of pH □ Dissolution rates—various amino penicillins, effect of pH □ Antibacterials—various amino penicillins, stability, solubility, and dissolution rates, effect of pH

Amphoteric penicillins like ampicillin, amoxicillin, cyclacillin, and epicillin exhibit a broad spectrum of antibacterial activity, are very acid stable, and are used orally (1). After a single equal oral dose, the peak serum concentration was four times higher for cyclacillin (2) and two times higher for amoxicillin (3–6) than for ampicillin; the peak for epicillin was significantly lower (6).

The physicochemical properties and GI membrane permeabilities of these amphoteric penicillins may cause significant differences in their serum concentrations. An

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