INTERSUBJECT AND DOSE-RELATED VARIABILITY AFTER INTRAVENOUS ADMINISTRATION OF ERYTHROMYCIN

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- 1 It is well-known that considerable variability and unpredictability in serum concentrations results from orally administered erythromycin.
- 2 Disposition kinetics and their variability were studied in 24 healthy subjects after a single dose of erythromycin lactobionate and four doses were studied to evaluate dose-related variability in five other subjects.
- 3 Erythromycin kinetics were adequately described by a classical two compartment open model with little intersubject variability.
- 4 Dose-related variability occurred. Clearance was independent of dose but $T_{1/2}$ and V_{dss} increased with dose.
- 5 Data are presented to show that non-invasive sampling of urine and saliva are of limited value in studying erythromycin pharmacokinetics.

Introduction

Erythromycin is widely prescribed in general practice as one of a variety of orally administered biopharmaceutical preparations. However, considerable variability and unpredictability in serum concentrations result from doses administered this way (Chun & Seitz, 1977; Parsons, Haddock & Hossack, 1975). It is not known how much of the variability is derived from the absorption, or the distribution and elimination of erythromycin. In order to examine this more closely, the present study was designed (1) to examine the variability in erythromycin pharmacokinetics after single dose intravenous administration in a large number of subjects: (2) to determine the linearity of pharmacokinetic parameters after administration of different doses to the same subjects: (3) to evaluate the usefulness of non-invasive sampling techniques in studying erythromycin pharmacokinetics.

Methods

Two intravenous dosage regimens were administered. Regimen 1, designed to evaluate intersubject variability, consisted of the administration of 250 mg (base equivalent) of erythromycin lactobionate (Erythrocin i.v.[®] Abbott Laboratories Pty. Limited,

freshly prepared according to package insert) infused over 3 min. Regimen 2 was designed to evaluate the linearity of pharmacokinetics over 125, 250, 500 and 900 mg doses. Each dose was infused over 15 min in random order one week apart.

Subjects

Regimen 1 was evaluated in 24 healthy medical student volunteers aged 17–23 years, whose physical characteristics are given in Table 1a and whose haematological, serum and urine biochemical screening tests were normal. Subjects abstained from alcohol and antimicrobial drugs during and in the week preceding the study. Subjects fasted overnight prior to their intravenous infusions and consumed light meals of sandwiches and liquid refreshments at fixed times of the day.

Regimen 2 was evaluated in the five subjects whose physical characteristics are detailed in Table 1b. The preparation of these subjects was identical to those undergoing Regimen 1. Three subjects completed the full dosing schedule (four doses). One subject completed two doses and another subject completed three doses.

Table 1 Physical characteristics of subjects participating in intravenous study (Mean $\pm$ s.d.)*(a) Regimen 1*

	Males	Females	All
<i>n</i>	12	12	24
Age	19.3 $\pm$ 0.6	19.2 $\pm$ 1.9	19.2 $\pm$ 1.4
Weight (kg)	70.2 $\pm$ 7.3	57.9 $\pm$ 7.0	64.0 $\pm$ 9.4
Height (cm)	179 $\pm$ 4	166 $\pm$ 4	172 $\pm$ 8
Body surface area (m ²)	1.87 $\pm$ 0.12	1.64 $\pm$ 0.10	1.76 $\pm$ 0.16

(b) Regimen 2

Subject	Sex	Age (years)	Weight (kg)	Dose (mg)			
				125	250	500	900
22	M	19	71.0	×	×	×	×
23	M	19	77.3	×	×	×	×
24	F	19	62.2	×	×	×	×
25	F	19	63.2	×	×	—	—
28	M	20	61.2	×	×	×	—

— = not studied

Drug administration and sampling procedures

Intravenous cannulae were inserted between 08.00 and 09.00 h on the morning of each study day. A scalp vein needle was inserted in the back of the hand for the administration of erythromycin, and an indwelling teflon catheter in the cephalic vein of the contralateral arm for blood sampling. Blood samples (5 ml) were collected using a double stopcock arrangement kept patent with heparinized saline and with precautions against contamination. Blood samples were collected immediately before infusion and at 8, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 270, 300, 360 and 420 min. Subjects received their infusions in the supine position and were allowed mild activity within the confines of a hospital ward 30 min after completion of injections.

For both regimens, urine was collected immediately before infusions and at hourly intervals thereafter. In Regimen 2, unstimulated whole saliva (0.3–0.5 ml) was also collected at the time of each urine collection. Serum, urine and saliva samples were stored frozen prior to assay. Bioassays for erythromycin were carried out according to the methods of Grove & Randall (1955) using *Sarcina lutea* ATCC 9341 as the principal test organism. All assays with initial results > 2 mg/l were repeated using *Bacillus pumilis* NCTC 8241 as the test organism.

Pharmacokinetic and statistical analyses

Anthropometric data, as well as erythromycin concentration-time data were entered into a digital computer (Digital Equipment Corporation DEC System-10) data base using the interactive system

PPMS (Austin & Mather, 1978). Post-infusion erythromycin serum concentrations (C_t -time (t) data were analysed using the interactive non-linear least squares regression procedure (BMDX85). Data were fitted to a biexponential equation (Equation 1) using reciprocal of concentration as a weighting factor. The coefficients (A , B) of Equation 1 were corrected for infusion time and the pharmacokinetic constants of the classical two compartment open model were derived using standard techniques (Wagner, 1975).

$$C_t = A e^{-\alpha t} + B e^{-\beta t} \quad (1)$$

Saliva concentration-time data were adequately described using a monoexponential relationship implying a one-compartment open model. The slope of the urinary excretion rate-mid time of collection interval was used to calculate urinary half-life of erythromycin. Renal clearance (Cl_R) was estimated from the cumulative fraction of dose (f_u) appearing in urine and total body clearance (serum) (Cl_S) using Equation 2.

$$Cl_R = f_u \cdot Cl_S \quad (2)$$

The source of intersubject variability was examined by correlation analysis between the various pharmacokinetic parameters and physical variables using SPSS (Nie, Hull, Jenkins, Steinbrenner & Bent, 1975).

Adverse effects

The nature, frequency and severity of adverse effects was evaluated by a physician member of the investigation team (C.R.P.).

Table 2 Pharmacokinetic parameters describing erythromycin disposition (Regimen 1) (mean $\pm$ s.d.) erythromycin lactobionate (250 mg base equivalent/3 min)

	Males	Females	All
V_C (l)	11.9 $\pm$ 4.5	19.5 $\pm$ 8.4	15.7 $\pm$ 7.7*
V_C (l/kg)	0.17 $\pm$ 0.06	0.34 $\pm$ 0.14	0.26 $\pm$ 0.14*
V_{dss} (l)	46.2 $\pm$ 11.0	42.6 $\pm$ 12.3	44.4 $\pm$ 11.4
V_{dss} (l/kg)	0.66 $\pm$ 0.12	0.75 $\pm$ 0.24	0.20 $\pm$ 0.19
$T_{1/2\alpha}$ (h)	0.09 $\pm$ 0.04	0.14 $\pm$ 0.09	0.11 $\pm$ 0.07
$T_{1/2\beta}$ (h)	1.6 $\pm$ 0.2	1.3 $\pm$ 0.4	1.5 $\pm$ 0.3
Cl_S (l/h)	25.1 $\pm$ 6.1	27.5 $\pm$ 8.8	26.3 $\pm$ 7.5
Cl_S (l h ⁻¹ kg ⁻¹)	0.36 $\pm$ 0.08	0.49 $\pm$ 0.19	0.42 $\pm$ 0.15**
Cl_R (l/h)	3.8 $\pm$ 2.6	3.1 $\pm$ 2.2	3.4 $\pm$ 2.4
f_u	0.14 $\pm$ 0.06	0.11 $\pm$ 0.07	0.12 $\pm$ 0.07
$T_{1/2}$ urine (h)	1.0 $\pm$ 0.2	1.2 $\pm$ 0.2	1.1 $\pm$ 0.2

*Significant difference between males and females $P=0.01$

**Significant difference between males and females $P=0.04$

Cl_S total body clearance (serum), Cl_R renal clearance, f_u fraction of dose excreted unchanged in urine, $T_{1/2\alpha}$ fast half-life calculated from serum data, $T_{1/2\beta}$ slow half-life calculated from serum data, $T_{1/2}$ urine slow half-life calculated from urine data, V_C initial dilution volume, V_{dss} apparent volume of distribution at steady-state equilibrium

Results

Regimen 1: Intersubject variability

Pharmacokinetic parameters describing disposition of erythromycin following the administration of 250 mg (base equivalent) are given in Table 2. A difference was found in the initial dilution volume (V_C) between sexes ($P < 0.01$). Variability arising from physical characteristics was examined by correlation analysis between physical and pharmacokinetic parameters. Significant correlations were found between $T_{1/2\beta}$ and body weight and BSA

($r=0.35$; $P=0.04$; $n=24$). V_{dss} was correlated with body weight and BSA only for males ($r=0.62$; $P=0.017$ and $r=0.69$; $P=0.006$ respectively, $n=12$). There was a marginal sex difference with Cl_S being positively correlated with body surface area males ($r=0.58$; $P=0.024$; $n=12$) and negatively for females ($r=0.51$; $P=0.04$; $n=12$).

Regimen 2: Dose-related variability

Mean serum concentrations and pharmacokinetic parameters derived from erythromycin doses of 125, 250, 500 and 900 mg are given in Figure 1 and Table

Figure 1 Mean ($\pm$ s.d.) post-infusion serum concentrations of erythromycin following intravenous infusion of (a) 250 mg over 3 min and (b) 125 ($\circ$), 250 ($\bullet$), 500 ($\triangle$) and 900 ($\blacktriangle$) mg of erythromycin lactobionate (base equivalent) over 15 min.

Table 3 Pharmacokinetic parameters describing erythromycin disposition in relation to dose (mean $\pm$ s.d.) (Regimen 2)

<i>n</i>	Dose (mg base equivalent)			
	125 5	250* 5	500 4	900 3
(a) Serum				
V_C (l)	10.3 $\pm$ 1.9	18.6 $\pm$ 17.6	17.9 $\pm$ 4.8	31.3 $\pm$ 29.2
V_{dss} (l)	33.0 $\pm$ 4.5	40.4 $\pm$ 25.1	70.3 $\pm$ 11.4	76.7 $\pm$ 26.6
$T_{1/2\alpha}$ (h)	0.11 $\pm$ 0.02	0.08 $\pm$ 0.04	0.12 $\pm$ 0.03	0.16 $\pm$ 0.15
$T_{1/2\beta}$ (h)	1.3 $\pm$ 0.1	1.3 $\pm$ 0.2	2.4 $\pm$ 0.4	2.4 $\pm$ 0.4
Cl_S (l/h)	28.1 $\pm$ 5.9	28.9 $\pm$ 14.4	25.3 $\pm$ 4.3	26.3 $\pm$ 11.8
AUC (mg l ⁻¹ h)	4.6 $\pm$ 0.9	10.5 $\pm$ 3.0	19.4 $\pm$ 3.3	41.0 $\pm$ 23.1
(b) Urine				
f_u	5.6 $\pm$ 2.3	4.8 $\pm$ 1.2	10.3 $\pm$ 2.3	17.1 $\pm$ 11.0
Cl_R (l/h)	1.5 $\pm$ 0.4	1.3 $\pm$ 0.8	2.7 $\pm$ 0.5	4.4 $\pm$ 3.6
$T_{1/2\text{urine}}$ (h)	1.2 $\pm$ 0.2	1.2 $\pm$ 0.2	1.3 $\pm$ 0.2	1.4 $\pm$ 0.3
(c) Saliva				
$V_{d\text{sal}}$ (l)	140 $\pm$ 80	141 $\pm$ 81	133 $\pm$ 113	92 $\pm$ 76
Cl_{sal} (l/h)	104 $\pm$ 59	86 $\pm$ 44	62 $\pm$ 42	41 $\pm$ 29
$T_{1/2\text{sal}}$ (h)	1.0 $\pm$ 0.1	1.1 $\pm$ 0.1	1.4 $\pm$ 0.3	1.5 $\pm$ 0.3

*=One subject demonstrated monoexponential decline.

Cl_{sal} salivary clearance, $T_{1/2\text{sal}}$ slow half-life calculated from saliva data, $V_{d\text{sal}}$ apparent volume of distribution calculated by extrapolation from saliva data. For other abbreviations, see footnote to Table 2.

3. There were differences between the two lower and the two higher doses. This was most obvious when considering V_{dss} and $T_{1/2\beta}$ with the lower values occurring for 125 and 250 mg doses. There were no differences in Cl_S between doses, as AUC was directly proportional to dose ($AUC = 0.045 \times \text{dose} - 0.76$, $r^2 = 0.76$, $P < 0.001$, $n = 17$). However, there was a trend for Cl_R and f_u to increase with dose. Urinary half-life was not correlated with serum half-life although the values were generally very similar. Cl_R was not correlated with Cl_S .

Saliva concentrations were correlated with serum concentrations over the entire range encountered (Figure 2). Half-lives derived from analysis of erythromycin concentrations in saliva were similar to those from serum and showed the same tendency towards dose dependence (Table 4). However, volumes of distribution and clearances derived from saliva were not correlated with those derived from serum. Saliva clearances showed dose dependence which was not reflected in volume of distribution (Table 4). There was marked intersubject variation in the average saliva: serum concentration ratio. Saliva was not sampled until 1 h after administration of erythromycin in order to allow for conclusion of the redistribution phase. It was consistently observed that the saliva: serum concentration ratio at 1 h was considerably higher than at all subsequent samplings (Figure 3). Subsequently, the ratio appeared to remain essentially constant for each individual (Table 5).

Adverse effects

Gastrointestinal adverse effects were reported by 83% of the subjects receiving Regimen 1 (250 mg/3 min) and 60–100% of the subjects receiving Regimen 2 (125–900 mg/15 min) (Table 6). They were variously described as 'acute hunger', 'sick in the stomach', 'type of stomach cramp but with no intention of vomiting', 'guts ache' and 'gnawing sensation'. These started from 5 to 45 min, irrespective of the dose or duration of infusion. Local reactions occurred in 67%

Figure 2 Relationship between saliva (Y) and serum concentrations (X) for one individual subject (No. 22) as a function of increasing dose ($Y = 0.39X - 0.06$; $r^2 = 0.96$, $P < 0.001$, $n = 21$). ○ 125 mg, ● 250 mg, △ 500 mg and ▲ 900 mg.

Table 4 Pharmacokinetic constants for individual subjects: Regimen 2

Subject	Dose (mg)	V_c (l)	V_{dss} (l)	Cl_S (l/h)	Cl_R (l/h)	$T_{1/2}$ (h)	$T_{1/2}^{sal}$ (h)	$T_{1/2}^{urine}$ (h)	$V_{d^{sal}}$ (l)	Cl_{sal} (l/h)
22	125	12	39	34.0	1.5	1.2	0.7	1.4	127	119
	250	34	83	45.3	2.6	1.5	1.1	1.3	169	108
	500	24	88	26.4	1.9	2.9	1.4	1.3	178	86
	900	19	92	29.2	8.5	2.6	1.7	1.0	180	74
23	125	9	28	28.0	0.8	1.2	1.0	1.4	54	39
	250	3	19	18.5	0.6	1.2	1.1	1.1	66	40
	500	12	68	28.9	2.8	2.1	1.1	1.6	33	21
	900	65	92	36.3	2.7	2.0	1.2	1.7	51	30
24	125	11	30	22.2	1.9	1.3	1.1	1.0	111	72
	250	8	31	23.0	0.9	1.2	0.9	1.1	53	40
	500	18	62	20.6	2.7	2.4	1.1	1.3	50	30
	900	10	46	13.3	1.9	2.6	1.6	1.4	45	20
25	125	11	36	23.2	1.6	1.4	1.0	1.1	138	96
	250	41*	41*	21.1	1.2	1.4	1.2	1.0	166	98
28	125	8	32	30.6	1.5	1.2	1.0	1.2	272	196
	250	6	28	23.0	1.2	1.3	1.2	1.4	249	142
	900	17	64	28.6	3.2	2.1	1.7	1.1	272	109

* = Monoexponential decline

For abbreviations see footnotes to Tables 2 and 3.

Figure 3 Serum concentration-time relationship for one individual subject No. 24, dose 250 mg (solid line, ○). Superimposed on this plot are saliva concentrations (broken line, ●) illustrating parallel decline after the 1 h sample.

of Regimen 1 subjects and comprised erythema and deep pain at the site of infusion and forearm, sometimes extending to the shoulder. These lasted 30–60 min after commencement of the infusion. The local reactions could be relieved partially by flushing the administration catheter with 20 ml of heparinized saline solution. Subjective central nervous system reactions were also reported by 21% of Regimen 1 subjects. These consisted of faintness and dizziness, sweating and hot flushes.

Table 5 Regression analyses for serum (X) and saliva concentrations (Y)

Subject	n	$Y = AX + B$	r^2	$P <$
22	25	$Y = 0.54X - 0.15$	0.882	0.001
	21*	$Y = 0.39X - 0.06$	0.920	0.001
23	26	$Y = 2.28X - 1.11$	0.859	0.001
	22*	$Y = 1.14X - 0.24$	0.846	0.001
24	26	$Y = 1.22X - 0.84$	0.837	0.001
	22*	$Y = 0.79X - 0.34$	0.951	0.001
25	11	$Y = 0.30X - 0.03$	0.508	0.05
	9*	$Y = 0.13X - 0.01$	0.945	0.001
28	16	$Y = 0.35X - 0.06$	0.835	0.001
	13*	$Y = 0.25X - 0.01$	0.697	0.001

* = Values for 1 h omitted (see text)

Table 6 Relative frequency (%) of adverse effects

<i>Regimen 1</i>		<i>Gastrointestinal</i>	<i>Local reaction</i>	<i>Central nervous system</i>
Absent	17		33	79
Noticeable	25		13	8
Pronounced	58		54	13

<i>Regimen 2</i>		<i>Gastrointestinal</i>				<i>Local reaction</i>				<i>Central nervous system</i>			
<i>Dose (mg)</i>		125	250	500	900	125	250	500	900	125	250	500	900
Absent	40	0	25	0	20	40	50	0	100	100	100	100	
Noticeable	0	0	0	0	20	0	0	0	0	0	0	0	0
Pronounced	60	100	75	100	60	60	50	100	0	0	0	0	0

One subject undergoing regimen 2 was withdrawn from the study, having received the 250 mg and 125 mg doses and exhibiting extreme manifestations of the adverse effects. This subject was subsequently tested for placebo response using injections of heparinized saline both alone and with benzyl alcohol at the same concentration as the preservative present in the erythromycin injection. No adverse effects were provoked by either of these erythromycin-free preparations. Several other volunteer subjects, including three of the investigators, were similarly infused (double-blind) with the two placebo preparations and no significant reactions were elicited.

Discussion

Although erythromycin has had over twenty-five years of clinical use, a detailed analysis of its pharmacokinetic properties has been lacking. These data and estimates of their variability may enable more flexible and rational use of this drug as well as provide insights to the problems associated with its oral use.

The pharmacokinetic properties of erythromycin in general confirm previously reported data derived from less comprehensive studies; viz. $T_{1/2} \approx 1.5$ h, $f_u \approx 15\%$ (Wilson & Van Bostel, 1978).

Sex differences in kinetics of antibiotics are known (Giudicelli & Tillement, 1977) and have been noted previously for erythromycin (Lake & Bell, 1969). The sex difference in serum concentrations reported for erythromycin by Lake and Bell (1969), which was not derived from rigorous pharmacokinetic study, was claimed to represent differences in total body water. The sex inequality found in the present study indicates that for V_C , females > males (Table 2), whereas the previous study suggested the opposite. Despite the academic significance of these sex differences, they are of minor clinical importance and do not constitute a major source of variability. Serum concentration-time profiles of erythromycin in males

and females were not sufficiently different over the 7 h study period to warrant dosage adjustment.

The data for individual subjects presented in Table 4 indicate some evidence of nonlinear pharmacokinetics of erythromycin as a function of dose: as dose increased $T_{1/2}$ increased and V_{dss} increased. Reasons for this apparent nonlinear behaviour were not investigated but may be related to changes in plasma protein binding over the concentration range encountered. Plasma protein binding of erythromycin is high and is in the range where its effects are important (Gordon, Regamey & Kirby, 1973; Wiegand & Chun, 1972).

The usefulness of drug saliva concentration measurements has been emphasized recently (Danhof & Breimer, 1978). It would be expected that erythromycin, being a basic drug (pK_a 8.8) would be secreted into saliva where the pH is commonly between 6 and 7. Erythromycin was found in the saliva of all subjects in concentrations which were generally proportional to serum concentration (Table 5). Half-lives calculated from saliva were generally similar to values obtained from serum, and they also reflected the apparent dose-dependence phenomenon. The correlation between pharmacokinetic parameters estimated from serum and saliva was poor, however, indicating that estimates obtained from saliva are not useful predictors of the corresponding serum pharmacokinetic constants. The usefulness of saliva concentration measurements can be extended if the saliva: serum concentration ratio is determined for each individual subject.

The irregularities shown in the mean serum concentration-time curves accurately reflect the curves of most individual subjects in both regimens (see Figures 1 and 3). Computer curve-fitting techniques neglect these irregularities by ascribing them to random noise. Closer examination reveals that these irregularities occurred during and after the subjects' midday meals. Possible explanations might include: secretions into the gastrointestinal tract with subsequent reabsorption (Boggiano & Gleeson, 1976; Holland & Quay, 1976); displacement from serum

proteins by fatty acid or other food components; or biliary recycling (Hammond & Griffiths, 1961). Metabolite secretion into serum is also possible, but the putative metabolites of erythromycin are considerably less microbiologically active than the parent compound (Mao & Tardrew, 1965) and would be unlikely to contribute significantly to the microbiological assay.

The prescribing details for erythromycin lactobionate acknowledge 'occasional venous irritation which may be minimized by the use of slow and diluted injections'. Venous irritation has also been shown (Eremin & Marshall, 1977) to result from standard non-buffered intravenous fluid preparations having a pH of 3.6 to 6.0 but infused for longer periods (24 h) than in the present study. Benzyl alcohol preservative did not elicit the same response nor any other adverse effects. The significance of the gastrointestinal adverse effects should be evaluated against the benefits of the antimicrobial therapy.

Since its introduction into medical practice over twenty-five years ago, erythromycin has been recognized as a remarkably safe antibiotic with a wide range of activity (Gould, 1977). Its use has been characterized by unpredictability and variability in serum concentrations when used by the oral route. The present studies have shown conclusively that the majority of this variability is not due to wide ranges of inter-subject differences in pharmacokinetic disposition characteristics. Further, despite some indications of nonlinearity with rather extreme infusion rates, erythromycin is a very predictable drug when used intravenously and this should encourage confidence in its intravenous use.

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