ABSORPTION AND BIOAVAILABILITY OF ORAL ERYTHROMYCIN

L.E. MATHER¹, K.L. AUSTIN¹, C.R. PHILPOT², & P.J. McDONALD²

¹Department of Anaesthesia and Intensive Care and

²Department of Clinical Microbiology,

Flinders Medical Centre,

The Flinders University of South Australia,

Bedford Park, South Australia 5042, Australia

1 Extent and rate of absorption of erythromycin were studied in 24 healthy volunteers whose disposition kinetics after i.v. injections had been previously documented.

2 Two clinically attractive oral dosage regimens were administered: erythromycin stearate tablets 1 h before meals (Regimen A), and erythromycin base capsules 30 min after start of meals (Regimen B), each equivalent to erythromycin 250 mg, 6 h apart for 9 doses.

3 Serum concentrations of erythromycin measured during the 1st and 9th (steady-state) dosing intervals resulted in higher maximum serum concentrations for Regimen A (median 1.1, range 0-3.3 and 2.7, 0.6-7.3 mg/l for Doses 1 and 9, respectively) compared with Regimen B (0.4, 0-2.2 and 1.4, 0.2-4.9 mg/l).

4 Absorption occurred earlier with Regimen A with times to maximum concentrations (median, range) being 128, 60->360 and 118, 75-210 min for doses 1 and 9 respectively, (lag times 75, 15->360 and 73, 10-110 min) compared with 303, 130->360 and 173, 45->360 min (lag times 183, 70->360 and 190, 20-330 min) for Regimen B.

5 Where it could be assessed, absolute bioavailability for Regimen A was approximately 30% (Dose 1) and 65% (Dose 9) and 40% for both doses of Regimen B.

6 Whereas individual serum concentration-time curves were accurately predicted by the mean for Regimen A, predictability for Regimen B was impossible due to prolonged and variable lag times.

7 The large intersubject variability in erythromycin serum concentration after oral administration, has been shown conclusively to be related to variability in absorption kinetics and absolute bioavailability rather than to variability in disposition kinetics.

Introduction

Large intersubject variability in serum concentrations of erythromycin occurs after oral administration even under standardised conditions (Chun & Seitz, 1974, 1977). It has been shown that intersubject variability in pharmacokinetic parameters after intravenous erythromycin is small (Austin *et al.*, 1980), hence it may be inferred that the majority of intersubject variability is due to erratic absorption and differences in absolute bioavailability. However, data describing bioavailability, absorption rates and their variability after single and multiple doses have not been reported.

In a previous study it was reported that a new preparation of erythromycin base (pelletised, encapsulated, enteric coated) generated higher maximum serum concentrations and areas under the serum concentration-time curve on the first and the fifth (steady-state) doses when compared to an equivalent

dose of a widely-used preparation of erythromycin stearate (McDonald, Mather & Story, 1977). In that study, a cross-over design was used with both erythromycin preparations being taken 1 h before the ingestion of a standardised breakfast. Results of that study also suggested that the improvement in relative bioavailability resulting from dosage regimens of the new erythromycin base product might be large enough that the ingestion of food would have no deleterious effects on erythromycin absorption, thus extending the clinical utility of this product. Indeed, a recent study supported this suggestion (Rutland, Berend & Marlin, 1979) and this contrasts with the well documented effects of food on the oral absorption of erythromycin salts (Welling *et al.*, 1978). To examine this point further, two clinically attractive dosage regimens were designed to extend the original study by comparing erythromycin serum concentrations

after ingestion of enteric coated erythromycin base capsules taken after meals with those from erythromycin stearate film-coated tablets ingested before meals in the same subjects. Each subject participating in this study also participated in a study of pharmacokinetic variability after intravenous erythromycin (Austin *et al.*, 1980). Hence from the combined oral and intravenous data the rate and extent of bioavailability of erythromycin could be determined for each dosage regimen.

Methods

Study design and dosage regimens

The present study was designed and conducted taking into account guidelines for the conduct of biopharmaceutical studies by the American Pharmaceutical Association Academy of Pharmaceutical Sciences (Dittert *et al.*, 1972) and for the conduct of erythromycin bioavailability studies in particular (Nightingale, Dittert & Tozer, 1976). Subjects of this study were twenty-four healthy medical student volunteers who had participated previously at least one week apart in an intravenous erythromycin study conducted under identical conditions of diet and activity and whose erythromycin disposition parameters were known from that study (Austin *et al.*, 1980). A synopsis of the pertinent data of the subjects is given in Table 1. It is emphasised that the purpose of this study was the comparison of two clinically attractive dosage regimens and not the evaluation of a food-drug interaction. The study was ratified by the ethics review committee of the institution where the investigation was carried out.

Erythromycin stearate and erythromycin base were administered in random order in a cross-over design with one week between the commencement of regimens. Regimen A consisted of erythromycin stearate film-coated tablets (Erythrocin Filmtab®, Formulation 6346), Abbott Laboratories Pty. Ltd, Sydney, Australia), while Regimen B consisted of capsules of enteric-coated erythromycin base (Eryc®, F.H. Faulding and Company Limited, Adelaide, Australia), each equivalent to 250 mg erythromycin base taken 6 h apart for nine doses. Erythromycin stearate tablets were taken 60 min before the start of meals while erythromycin base capsules were taken 30 min after the start of meals. Meals were standardised on Days 1 and 3, corresponding to study doses 1 and 9. At other times, similar food constituents were taken by all subjects. Alcohol and antimicrobial drugs were not taken during the course of the study. On study days, breakfast consisted of cereal, milk, toast and either tea or coffee. Lunch consisted of sandwiches, canned fruit and ice cream, fruit juice or milk or tea or coffee.

Table 1 Physical characteristics of subjects and AUC data following intravenous erythromycin

Subject number	Sex	Weight (kg)	AUC† (mg l ⁻¹ min)
1	F	52.4	625
2	F	57.8	777
3	F	53.3	485
4	F	65.6	803
5	M	71.2	900
6	F	57.7	524
7	F	72.6	818
9	M	73.5	704
10	M	70.4	769
11	M	64.5	698
12	F	51.9	754
13	F	64.3	644
14	F	52.3	549
15	M	61.4	682
17	M	82.7	457
19	M	65.5	679
20	F	60.5	348
21	M	61.2	510
26	F	48.1	348
27	F	57.7	446
29	M	75.0	409
30	M	61.8	676
31	M	79.8	473
32	M	74.9	579

* Individual data for subjects previously reported in summary form (Austin *et al.*, 1980).

†AUC after intravenous erythromycin lactobionate (250 mg base equivalent).

Sampling and analysis

An indwelling teflon catheter was inserted for the collection of venous blood samples as previously described (Austin *et al.*, 1980). Blood samples (5 ml) were collected immediately before ingestion of the study dose and at 15 min intervals for 2.5 h, then at 30 min intervals until 6 h after ingestion of the first and ninth dose.

Whole blood from seven additional subjects was anticoagulated with herapin (2 U/ml) and spiked to contain erythromycin base 1.25, 2.5 and 10 mg/l and incubated 1 h at room temperature. Plasma was harvested from each and the erythromycin blood:plasma concentration ratio determined. The percentage of the erythromycin in whole blood associated with the erythrocytes was calculated from Equation 1. Assuming an equivalence between serum and plasma with respect to erythrocyte equilibration of erythromycin, these data were used to calculate the expected first pass extraction after oral absorption (see **Appendix** and glossary of terms used).

$$\%R = 100 \times C_B - C_p (100 - HCt) / C_B \quad (1)$$

Erythromycin concentrations in serum and plasma were determined according to standard methods of bioassay as previously described (see Austin *et al.*, 1980). Although a bioassay procedure has the potential problem of detection of active metabolites, 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 assayed concentrations.

Pharmacokinetic analysis

From the serum concentration-time curves for each subject's first and ninth dose, the following parameters were determined:

- 1 The maximum erythromycin serum concentration, the time at which this occurred and the lag time by inspection of the data.
- 2 The area under the serum concentration-time curve for 6 h, i.e. one dosing interval, using the trapezoidal rule. For first dose studies, this was added to the estimated area from 6 h to infinity (Wagner & Ayres, 1977).
- 3 The absolute bioavailability using separate techniques:
 - (a) using the model independent method from AUC using Equations 2 and 3
 - (b) Using the model dependent method based on micro rate constants from the previously

derived i.v. data to give the asymptote of the amount absorbed/dose (Loo & Riegelman, 1968).

For Dose 1:

$$FF^* = \frac{AUC_6 + AUC_6^2}{AUC_{i.v.}} \times \frac{D_{i.v.}}{D_{po}}$$

Since $D_{i.v.} = D_{po}$,

$$FF^* = \frac{AUC_6 + (C_{6h}/\beta)}{AUC_{i.v.}} \quad (2)$$

For Dose 9, since $D_{i.v.} = D_{po}$:

$$FF^* = \frac{AUC_6}{AUC_{i.v.}} \quad (3)$$

- 4 The apparent rate of absorption was examined from the slope of the rate of bioavailability derived from the Loo & Riegelman (1968) calculation taking into account the lag time and the fraction of dose systemically bioavailable (Notari, DeYoung & Reuning, 1972).

Results

Serum concentration analysis

There was a marked difference in the mean serum concentration-time curves of erythromycin between the two dosage regimens (Figure 1). Whereas the mean curve for the stearate administered 1 h before food (Regimen A) showed a well-defined maximum

Figure 1 Serum concentration-time curves (mean $\pm$ s.d.) following oral ingestion of erythromycin as stearate after fasting (O—O) or base after food (●---●) each equivalent to 250 mg ($n=24$, cross-over study). (a) First dose. (b) Ninth dose.

for both Doses 1 and 9, the mean curve for the base preparation after food (Regimen B) showed a sustained, but lower, serum concentration-time profile. In the case of Regimen A, the mean serum curve generally represented the curves for individual subjects with the important exception that 7 of the 24 subjects did not achieve serum concentrations > 0.1 mg/l within 6 h after the first dose (Table 2). These subjects were termed 'poor absorbers'. In contrast, the mean serum concentration-time curve after Regimen B did not represent those for the individual subjects after either dose. There were 5 poor absorbers after ingestion of the first dose of Regimen B. Four subjects for Regimen A and 11 in Regimen B did not demonstrate a maximum concentration during the first 6 h after ingestion of the first dose as the serum concentrations were still rising at the end of the first study period. These subjects were termed 'late absorbers'. After the ninth dose of both regimens (Table 3) there were no poor absorbers but there were 9 late absorbers in Regimen B, Dose 1. Three of the 5 poor absorbers in Regimen B,

Dose 1 were also poor absorbers in Regimen A, Dose 1. Three of the 4 late absorbers in Regimen A, Dose 1 were also late absorbers of Regimen B. Six of the 9 late absorbers in the ninth dose in Regimen B were also late absorbers of the first dose of Regimen B.

Because $T_{\max}$ and T_{lag} could not be measured in some subjects (i.e. values > 360 min) their $C_{\max}$ and AUC values were not comparable between regimens. Further, it is obvious that the data in Tables 2 and 3 were not drawn from a normal distribution. Hence, comparison of variables between regimens could be based only on the sign of their difference and on the median and range. Significant differences between regimens ($P < 0.05$, sign test) existed with respect to $C_{\max}$ (Dose 9 only), $T_{\max}$ (Doses 1 and 9), AUC (Dose 9 only), and T_{lag} (Doses 1 and 9).

The large variability in T_{lag} for Regimen B was the main reason for the flattened shape of the mean serum concentration curves since the majority of individual curves showed a reasonably well-defined peak. Because the individual curves were represented by the means only for the stearate, meaning-

Table 2 Individual values for $C_{\max}$, $T_{\max}$, T_{lag} and AUC for first dose of each regimen

Subject number	Regimen A				Regimen B			
	$C_{\max}$ (mg/l)	$T_{\max}$ (min)	T_{lag} (min)	AUC* (mg l ⁻¹ min)	$C_{\max}$ (mg/l)	$T_{\max}$ (min)	T_{lag} (min)	AUC* (mg l ⁻¹ min)
1	>0.04	>360	>360	(2)	0	>360	>360	0
2	1.4	127	85	247	>1.0	>360	255	(53)
3	>0.1	>360	>360	(1)	0	>360	>360	0
4	2.6	150	85	275	1.3	140	95	328
5	1.1	180	30	124	0.7	240	70	156
6	3.3	105	60	275	1.6	150	125	273
7	2.1	120	65	290	1.6	135	120	300
9	0.4	100	75	98	>0.1	>360	300	(3)
10	2.7	150	40	274	>0.5	>360	300	(18)
11	0.1	240	75	21	>0.4	>360	305	(14)
12	2.6	113	35	280	1.3	210	115	268
13	0.2	300	190	52	>0.4	>360	290	(20)
14	1.7	104	55	158	>0.3	>360	200	(20)
15	1.8	125	100	222	0.7	270	200	144
17	1.1	150	100	189	>0.1	>360	230	(7)
19	0	>360	>360	0	0.6	330	160	(75)
20	0.05	90	55	89	0.4	285	150	(31)
21	0	>360	>360	0	>0.2	>360	180	(14)
26	1.3	100	15	131	0.8	200	160	147
27	2.0	100	45	257	1.2	300	140	209
29	0.4	60	45	24	0.3	300	115	(32)
30	1.9	90	70	210	2.2	180	155	216
31	0.06	210	180	6	0.1	240	>360	(2)
32	1.9	210	90	352	>0.2	>360	315	(4)
Median	1.1	128†	75†	131	0.4	303	183	32
Minimum	0	60	15	0	0	135	70	0
Maximum	3.3	>360	>360	352	2.2	>360	>360	328

* AUC values in parenthesis indicate AUC to 6 h instead of AUC to infinity. For these cases AUC to infinity could not be calculated because serum concentrations were still increasing at the end of the sampling period and terminal slope could not be calculated.

† Significant regimen difference ($P < 0.05$, sign test)

Table 3 Individual values for $C_{\max}$, $T_{\max}$, T_{lag} and AUC for ninth dose of each regimen

Subject number	Regimen A				Regimen B			
	$C_{\max}$ (mg/l)	$T_{\max}$ (min)	T_{lag} (min)	AUC (mg l ⁻¹ min)	$C_{\max}$ (mg/l)	$T_{\max}$ (min)	T_{lag} (min)	AUC (mg l ⁻¹ min)
1	1.9	135	80	340	4.9	50	20	438
2	3.5	135	70	569	1.9	340	130	368
3	5.9	110	60	530	0.2	45	330	28
4	3.4	105	10	368	2.0	120	75	381
5	4.0	120	90	643	2.6	135	30	455
6	3.8	105	40	383	2.1	150	95	275
7	3.5	115	65	521	2.5	135	95	404
9	3.6	140	100	435	>0.5	>360	330	88
10	1.3	150	100	216	1.6	270	190	258
11	2.0	120	85	277	>0.7	>360	190	190
12	1.3	130	90	218	4.1	170	90	66
13	2.0	120	80	239	>0.6	>360	250	55
14	2.9	115	80	485	>1.6	>360	310	247
15	0.8	140	55	187	>2.0	>360	300	157
17	0.6	210	80	98	0.5	45	250	72
19	1.9	150	65	265	1.3	330	290	251
20	3.4	90	60	339	0.6	140	110	114
21	2.7	115	80	388	>0.9	>360	230	198
26	1.9	75	30	244	2.3	75	45	237
27	3.7	105	35	664	2.3	135	35	535
29	1.2	100	90	180	>0.7	>360	210	138
30	7.3	80	50	995	>1.4	>360	210	319
31	0.7	135	110	102	1.3	135	95	214
32	2.8	100	25	104	>0.7	>360	330	124
Median	2.7¶	118¶	73¶	341¶	1.4	173	190	239
Minimum	0.6	75	10	98	0.2	45	20	28
Maximum	7.3	210	110	995	4.9	>360	330	666

¶ Significant regimen difference ($P < 0.05$, sign test).

ful comparisons could only be obtained by taking full advantage of the cross-over study design. Differences between the two regimens can be seen by comparing the individual differences in serum concentration-time profiles (Figure 2). Higher concentrations for Regimen A occurred during the time period 1–3.5 h after Dose 1 ($P < 0.05$ Wilcoxon test for matched pairs, t -test for paired data). The delayed absorption seen following ingestion of erythromycin base after food in Regimen B and produced a negative difference at 5.5 and 6 h ($P < 0.05$) and also for the first 45 min after the 9th dose ($P < 0.05$). Subsequently, Regimen A again produced higher concentrations over the period 1.5–3.5 h following injection of the ninth dose before once more displaying the delayed absorption with higher late concentrations in Regimen B.

Extent and rate of bioavailability

After the first dose, estimates of bioavailability for both preparations were assessed in 20 subjects for Regimen A and 9 subjects for Regimen B (Table 4).

For fasting subjects, approximately 30% of the first dose of stearate was bioavailable compared with 65% of the ninth dose. After the ingestion of food, approximately 40% of base was bioavailable after both doses. However, individual differences were large and apparently inexplicable on biopharmaceutical grounds. Where an asymptote of the amount absorbed/dose was able to be estimated (e.g. Figure 3), this value was in good agreement with that derived from the model independent AUC method (Table 4).

The rate of absorption assessed from the slope of the fraction of bioavailable dose absorbed/time suggested that the absorption process could not be described readily by a single first order rate constant. Some subjects appeared best described by a sequence of first order rates, others by a zero order process and others by combination of zero order and first order processes (Figure 4). Approximation of a single first order rate constant could be made for each curve and yielded typical absorption half-lives of 20–40 min. Approximation of a single zero order process yielded typical absorption rates of 0.5–1.5 mg/min (Table 5). Statistical analysis of absorption rate data from Regi-

Figure 2 Differences in serum concentrations, stearate-base (mean $\pm$ s.d.) as a function of time for doses 1 (a) and 9 (b). ($n = 24$, cross-over study). Significant regimen differences $P < 0.05$.

* Wilcoxon test for matched pairs.

Δ t -test for paired data.

men A suggested that zero order and first order rate constants best fit the data with approximately equal frequencies. Insufficient data were available for Regimen B to attempt statistical analysis.

Figure 3 Distribution of erythromycin between absorption site (O—O), central compartment (Δ—Δ) and peripheral compartment (□—□) as calculated by the Loo-Riegelman method. Data for Regimen A, dose 1, Subject 32.

Blood:plasma concentration ratio and erythrocyte uptake

Erythrocytes and other cellular components accumulated erythromycin compared to the plasma. Hence, whole blood concentrations exceeded plasma concentrations. There was no consistent tendency for concentration-dependence of either the blood:plasma concentration ratio or % associated with erythrocytes (%R). Variability of both λ (2.3 ± 0.3 s.d.) and %R (75 ± 3) was small between subjects with %R being proportional to HCt ($r = 0.71$, $P < 0.001$; $n = 21$; %R = $35.9 + 0.93 \times \text{HCt}$).

Adverse effects

Fourteen subjects reported gastrointestinal adverse effects. These were equally divided between the two regimens and both sexes were equally affected. Effects ranged from mild (flatus, slight diarrhoea and abdominal discomfort) to more severe abdominal distress (pains, moderate diarrhoea and nausea). All effects resolved satisfactorily without treatment.

Table 4 Estimated bioavailability estimated by the AUC method (Eq. 2,3)

Subject number	Regimen (Dose)			
	A(1)	B(1)	A(9)	B(9)
1	ND	ND	0.55	0.70
2	0.32 (0.33)*	ND	0.73	0.47
3	ND	ND	1.09	0.06
4	0.34 (0.36)	0.41	0.46	0.47
5	0.24 (0.22)	0.17 (0.19)	0.72	0.51
6	0.52 (0.53)	0.52 (0.47)	0.73	0.53
7	0.35 (0.37)	0.38	0.64	0.49
9	0.14 (0.14)	ND	0.62	0.13
10	0.36 (0.41)	ND	0.28	0.34
11	0.03 (0.03)	ND	0.40	0.25
12	0.37 (0.40)	0.36	0.30	0.88
13	0.08 (0.05)	ND	0.37	0.09
14	0.29 (0.30)	ND	0.88	0.45
15	0.33 (0.35)	0.21	0.28	0.23
17	0.41 (0.41)	ND	0.31	0.16
19	ND	ND	0.39	0.37
20	0.26 (0.25)	ND	0.97	0.33
21	ND	ND	0.76	0.39
26	0.38 (0.39)	0.42	0.70	0.68
27	0.58 (0.61)	0.47 (0.54)	1.49	1.20
29	0.06 (0.07)	ND	0.44	0.34
30	0.31 (0.33)	0.37	1.47	0.47
31	0.02 (0.02)	ND	0.22	0.45
32	0.61 (0.60)	ND	0.70	0.21
Median	0.33	0.38	0.63	0.40
Minimum	0.02	0.17	0.22	0.06
Maximum	0.61	0.52	1.49	1.20

* Figures in parenthesis are values determined from the asymptote of the Loo-Riegelman calculation.

ND = Not determined due to inability to estimate the terminal slope.

Discussion

The literature is abundant with comparative studies of serum concentrations following dosage of the various forms of erythromycin in man, (e.g. Chun & Seitz, 1977; Parsons, Paddock & Hossack, 1977; Wilson & van Boxtel, 1978). The present study incorporates several desirable attributes not previously contained in a single study, *viz.*: (a) a very frequent sampling to detect long lag times, rapid rises in serum concentrations and to accurately identify both the timing and level of the maximum serum concentrations, (b) not only first-dose but also steady-state (ninth dose) sampling was undertaken; (c) each subject also received an intravenous dose of erythromycin so that absolute bioavailability and absorption rates could be calculated and compared; absolute bioavailability data for erythromycin have not previously been available.

Some care is required in interpreting comparative

studies represented by mean serum concentration data such as reported in Figure 1. Taking these data at face value may lead to wrong conclusions. It might appear that the regimen comprising erythromycin stearate film-coated tablets taken before meals always generated higher serum concentrations than that comprising enteric coated erythromycin base capsules taken after meals (Tables 2 and 3; Figures 1 and 2). However, in 25% of subjects, the reverse was true. Furthermore, the appearance of the mean erythromycin base curve in suggesting sustained high serum concentrations is spurious. The appearance of this curve is due almost solely to the individual differences in T_{lag} which tended to be greater and more variable for Dose 9 of the base preparation. Comparison of T_{lag} for erythromycin base after food (present study ± 3 h) with the value previously obtained under fasting conditions (± 1 h) (McDonald *et al.*, 1977) strongly suggest that the delay in absorption is an effect of the food and not of the particular formulation. Similarly, in the present study the C_{max} of erythromycin base after food was little more than one-half that found previously for the same preparation taken fasting (McDonald *et al.*, 1977). These results contrast sharply with those of Rutland *et al.* (1979) who reported no effect of food on the absorption of their preparation of erythromycin base.

Because of the large variability in time taken for the onset of erythromycin absorption as well as the variability in the actual absorption rate, mean serum concentration curves for different preparations or regimens must be interpreted taking special account of the characteristics of individual serum concentration-time curves. Advantage may be taken of the cross-over study design by simply subtracting the concentration-time curve for one preparation from the other for each individual subject. In this way trends in differences can be evaluated accurately. This technique has shown the differences between the stearate-fasting regimen and the base after food regimen (Figure 2) more clearly than by a comparison of the mean curves (Figure 1).

For both preparations, once absorption had started it was rapid. Because of the large T_{lag} of the base preparation, C_{max} and AUC data are biased against the base preparation. In retrospect, a longer dosing interval and sampling period (10–12 h) may well have revealed more 'favourable' results with the base regimen than was found using the times chosen for the present study. The agreement between the bioavailable fraction of first dose for each regimen (where this could be determined) suggests that erythromycin absorption and the poor absorber problem may be related more to physiology more than to biopharmaceutics. Poor absorbers represent an appreciable proportion of the population in single dose studies (Bell, 1971); however the data in Table 3

Figure 4 Absorption of erythromycin in two subjects plotted on semi-logarithmic co-ordinates [(a) and (c)] and cartesian co-ordinates [(b) and (d)] for Regimen A, dose 1, subjects 32 (a,b) and 4 (c,d). After taking into account the lag time, absorption rate for subject 32 appeared better described by zero order kinetics and subject 4 by first order kinetics. Inflections in the data are caused by minor irregularities in the smoothness of the original serum concentration-time data.

support the suggestion of Triggs & Neaverson (1973) that they are rare in multiple dose studies. The probable therapeutic significance of poor absorption is that the antimicrobial drug effect will start later in poor absorbers. The pharmacological significance is that absorption of the early doses either occurs late or not at all, and further information is required to clarify this point.

Interpretation of erythromycin absorption as a zero order process was proposed by Colburn, DiSanto & Gibaldi (1977). It is not possible to differentiate unequivocally first order from zero order absorption from the data in the present study (Figure 4), but our results do support their conclusions that erythromycin is absorbed at a constant rate, at least in some subjects. In other subjects multiple first order rates may simply reflect progression through the gastrointestinal tract.

From the intravenous data, it may be calculated

that the first-pass extraction of erythromycin is less than 10% (see **Appendix**). Hence, approximately 90% of the dose would be systemically bioavailable. Reasons for the much lower bioavailability after oral dosing observed in the present study (Table 4) are not fully explained. Erythromycin has been said to exert a stimulatory action on the gastrointestinal tract (American Hospital Formulary Service, 1977) and this may be the reason for the subjects experiencing gastrointestinal side effects. Hence it is possible that in some cases erythromycin may be propelled through the small intestine so rapidly that absorption cannot take place (Lee, Anderson & Chen, 1954), rather than a failure of the biopharmaceutical preparation to disintegrate and dissolve in the gut. Therefore, food may even delay the passage through the small intestine in such a way to improve the absorption characteristics of erythromycin and evidence for this has been reviewed (Melandar, 1978).

Table 5 Absorption rate derived from the rate of bioavailability according to a zero order or first order process.
Data for Regimen A, Dose 1 only.

Subject number	Ko (% BD/min)	Ko (mg/min)	X ²	Ka (min ⁻¹)	T _{1/2} abs (min)	X ²
2	1.24	1.0	0.011	0.031	22	0.002
4	0.42	0.4	0.027	0.015	46	0.011
5	0.65	0.4	0.004	0.009	77	0.013
6	1.75	2.3	0.026	0.042	17	0.026
7	0.85	0.7	0.023	0.025	28	0.005
9	0.36	1.0	0.007	0.008	87	0.001
11	0.47	0.04	0.015	0.007	99	0.029
12	1.14	1.1	0.015	0.017	41	0.004
13	0.86	0.2	0.036	0.019	36	0.005
14	0.59	0.4	0.001	0.140	5	0.025
15	1.09	0.9	0.041	0.048	14	0.001
17	0.77	0.8	0.027	0.021	33	0.007
26	0.96	0.9	0.007	0.020	35	0.015
29	0.19	0.03	0.041	0.007	99	0.038
31	0.29	0.02	0.065	0.021	33	0.031
32	0.38	1.0	0.002	0.014	53	0.009

Ko Zero order absorption rate constant.

Ka First order absorption rate.

T_{1/2} abs Absorption half-life.

X² Reduced chi-square for least squares regression (smaller value indicates better fit) (Bevington, 1969).

BD Bioavailable dose.

The authors gratefully acknowledge the clinical and technical assistance of their colleagues in performing these studies. In particular, we wish to thank Dr J. Turnidge, Dr H. Pruul, Mr C. McLean, Mr K. Parkin and Mr P. Phillips.

Appendix

Calculation of theoretical bioavailability

$$F^* = 1 - Cl_m / HBF$$

$$Cl_m = (Cl_s - Cl_r) / \lambda$$

$$Cl_m = (26.3 - 3.4) / 2.3$$

$$Cl_m = 10 \text{ l/h}$$

$$F^* = 1 - 10/90$$

$$F^* = 0.9$$

Where: HBF = total hepatic blood flow, taken as 90 l/h.
Cl_m = Metabolic clearance.
Cl_s = Total body clearance (serum), taken as 26.3 l/h (Austin *et al.*, 1980).
Cl_r = Renal clearance, taken as 3.4 l/h (Austin *et al.*, 1980).
λ = Whole blood:plasma (or serum) concentration ratio, taken as 2.3.

Glossary of terms used

AUC Area under serum concentration-time curve.

AUC₆ AUC over one 6 h dosing interval.

AUC_{6-∞} AUC between 6 h and ∞.

AUC_{i.v.} AUC to infinity after intravenous dose.

C_{max} Maximum serum concentration.

C_{6h} Serum concentration at 6 h.

C_B Whole blood concentration.

C_P Concentration in plasma corresponding to C_B.

λ Ratio C_B:C_P.

%R % drug in whole blood associated with erythrocytes.

T_{max} Time at which C_{max} occurs.

T_{lag} Estimated lag time before absorption commences.

HC t Haematocrit.

HBF Total hepatic blood flow.

D_{IV} Intravenous dose giving AUC_{i.v.}

D_{PO} Oral dose giving AUC₆.

Cl_s Total body clearance (serum) = D_{i.v.}/AUC_{i.v.}

Cl_m Metabolic clearance.

Cl_r Renal clearance.

β Apparent terminal slope of log concentration-time relationship after D_{PO}.

F Fraction of D_{PO} absorbed through the gut wall unchanged.

F* Systemic availability.

FF* Bioavailability.

A₁/D Amount absorbed/dose from Loo-Riegelman calculation.

References

- AMERICAN HOSPITAL FORMULATORY SERVICE (1977). Washington D.C. American Society of Hospital Pharmacists Incorporated.
- AUSTIN, K.L., MATHER, L.E., PHILPOT, C.R. & McDONALD, P.J. (1980). Intersubject and dose-related variability after intravenous administration of erythromycin. *Br. J. clin. Pharmacol.*, **10**, 273–279.
- BELL, S.M. (1971). A comparison of absorption after oral administration of erythromycin estolate and erythromycin stearate. *Med. J. Aust.*, **11**, 1280–1283.
- BEVINGTON, P.R. (1969). *Data reduction and error analysis for the physical sciences*, Chapter 10. New York: McGraw-Hill.
- CHUN, A.H.C., & SEITZ, J.A. (1974). Drug bioavailability information and its utility. *J. Am. pharm. Ass.*, NS14: 407–414.
- CHUN, A.H.C. & SEITZ, J.A. (1977). Pharmacokinetics and biological availability of erythromycin. *Infection*, **5** (Suppl 1) 14–22.
- COLBURN, W.A., DiSANTO, A.R. & GIBALDI, M. (1977). Pharmacokinetics of erythromycin on repeated dosing. *J. clin. Pharmacol.*, **17**, 592–600.
- DITTERT, L.W., CRESSMAN, W.A., KAPLAN, S.A., RIEGELMAN, S. & WAGNER, J.G. (1972). *Guidelines for biopharmaceutical studies in man*. Washington, D.C. A.Ph.A. Academy of Pharmaceutical Sciences.
- LAKE, B., & BELL, S.M. (1969). Variations in absorption of erythromycin. *Med. J. Aust.*, **1**, 449–453.
- LEE, C.C., ANDERSON, R.C. & CHEN, K.K. (1954). Site of absorption of erythromycin in rats. *Antibiot. Chemother.*, **4**, 926–930.
- LOO, J.C.K. & RIEGELMAN, S. (1968). New method for calculating the intrinsic absorption rate of drugs. *J. pharm. Sci.*, **57**, 918–928.
- McDONALD, P.J., MATHER, L.E. & STORY, M.J. (1977). Studies on absorption of a newly developed enteric-coated erythromycin base. *J. clin. Pharmacol.*, **17**, 601–606.
- MAO, J.C. & TARDREW, P.L. (1965). Demethylation of erythromycin by rabbit tissues *in vitro*. *Biochem. Pharmacol.*, **14**, 1049–1058.
- MELANDER, A. (1978). Influence of food on bioavailability of drugs. *Clin. Pharmacokinet.*, **3**, 337–351.
- NIGHTINGALE, C.H., DITTERT, L.W. & TOZER, T.N. (1976). Bioavailability monograph. Erythromycin. *J. Am. pharm. Ass.*, NS16: 203–206.
- NOTARI, R.E., DeYOUNG, J.L. & REUNING, R.H. (1972). The effect of parallel first order drug loss from site of administration on calculated values for absorption rate constants. *J. pharm. Sci.*, **61**, 135–138.
- PARSONS, R.L., PADDOCK, N. & HOSSACK, A. (1977). Particular aspects of the pharmacokinetics of erythromycin. *Infection*, **5** (Suppl 1): 23–28.
- RUTLAND, J., BEREND, N. & MARLIN, G.E. (1979). The influence of food on the bioavailability of new formulations of erythromycin stearate and base. *Br. J. clin. Pharmacol.*, **8**, 343–347.
- TRIGGS, E. & NEAVERSON, M.A. (1973). Bioavailability of erythromycin. *Med. J. Aust.*, **11**, 344.
- WAGNER, J.A. & AYRES, J.W. (1977). Bioavailability assessment: Methods to estimate total area (AUC 0– ∞) and total amount excreted (Ae) and importance of blood and urine sampling scheme with application to digoxin. *J. Pharm. Biopharm.*, **5**: 533–557.
- WELLING, P.G., HUANG, H., HEWITT, P.F. & LYONS, L.L. (1978). Bioavailability of erythromycin stearate: Influence of food and fluid volume. *J. pharm. Sci.*, **67**, 764–766.
- WILSON, J.T. & VAN BOXTEL, C.J. (1978). Pharmacokinetics of erythromycin in man. *Antibiot. Chemother.*, **25**, 181–203.

(Received September 11, 1980)