Evaluation of the Intestinal Absorption of Erythromycin in Man: Absolute Bioavailability and Comparison with Enteric Coated Erythromycin

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Received January 25, 1994; accepted August 24, 1994

To determine the role of acid hydrolysis on the gastrointestinal absorption of erythromycin , six healthy subjects received erythromycin as a 240 mg intravenous dose , a 250 mg oral solution administered via endoscope directly into the duodenum and bypassing the stomach, and an enteric-coated 250 mg capsule. Blood samples were collected for 6 hours and serum erythromycin quantified by a microbiological method. The time to achieve maximum serum concentrations for the solution was 0.25 ± 0.08 (mean ± SD) hours and for the capsule was 2.92 ± 0.55 hours. The absolute bioavailability of erythromycin from the capsule was 32 ± 7% and for the duodenal solution 43 ± 14%. The ratio of the areas under the serum erythromycin concentration-time curve of capsule to solution was 80 ± 28% (range 38 to 110%). There is substantial loss of erythromycin apart from gastric acid hydrolysis, which cannot be accounted for by hepatic first-pass metabolism. Attempts to further improve the oral bioavailability of erythromycin beyond 50% by manipulation of formulation are likely to be futile.

KEY WORDS: erythromycin; intestinal absorption, pharmacokinetics; bioavailability.

INTRODUCTION

Erythromycin is poorly absorbed from the gastrointestinal tract after oral administration because of extensive acid hydrolysis in the stomach (1,2). Various methods have been adopted to improve the bioavailability of erythromycin. These include enteric-coated tablets, enteric-coated pellets in hard gelatin capsules (3), less soluble salts, such as the stearate (4,5), and prodrugs, such as erythromycin ethylsuccinate (6). These formulations are aimed specifically to decrease the acid degradation of erythromycin in the stomach (2). Although there have been marked improvements in oral erythromycin formulations which allow increased amounts of the drug to reach the systemic circulation (3,7-13), it is not known whether optimum delivery has yet been achieved. Although acid degradation in the stomach is a documented cause of poor oral availability of erythromycin (2), other factors could also be involved. Metabolism to produce N-demethylerythromycin (14) and other metabolites could occur in the gut lumen, gut wall, or liver before reaching the general circulation. It is not known which of the above factors might influence the variable absorption characteristics observed for orally administered erythromycin.

The aim of this study was to investigate the relative absorption of erythromycin from a solution administered directly into the duodenum compared with commercially available capsules containing enteric-coated pellets and intravenously administered erythromycin lactobionate.

MATERIALS AND METHODS

Study Design

Six healthy subjects freely gave written informed consent to participate in the study. Approval to perform the study was granted by the Human Ethics Committee of the Royal Adelaide Hospital and the Committee on the Ethics of Human Experimentation of the University of Adelaide. All subjects were judged to be in good health following a physical examination, and complete blood and urine biochemical tests. Females were confirmed not to be pregnant at the time of the study. Subject details are shown in Table 1.

Formulation, Dosing, and Sample Collection

Each subject was allocated to receive the three erythromycin formulations via different routes as described below. A 7 day washout period was used between treatment phases. Random allocation to the three treatments was not conducted as it was considered unethical to ask healthy volunteers to undergo the procedures of drug administration via the oral or intravenous routes if it was unlikely that they would tolerate endoscopy. Hence all subjects received erythromycin solution by the duodenal route and then the intravenous and solid capsule formulations were randomized. Details of the formulations are:

a. Erythromycin powder, USP/BP, potency 0.92 mg/mg was used ex-stock (F.H. Faulding & Co. Limited, Adelaide, Australia; QA No. 5F6222). The erythromycin powder 271 mg, and 25 mg citric acid, were dissolved in 20 ml double distilled water. This solution was administered within 2 hours of preparation via an endoscope at the Royal Adelaide Hospital endoscopy theatre to each subject after an overnight fast. Premedication with diazepam 5 mg and fentanyl 50 μg was followed by amethocaine pharyngeal topical anaesthesia. A standard fibreoptic endoscope (Olympus® $GIFP_3$ duodeno scope, 8 mm diameter) was introduced into the second part of the duodenum so that its tip was just beyond the duodenal papilla. The solution of erythromycin was delivered through a thin plastic cannula inserted through the biopsy channel of the endoscope. Duodenal aspirate in one subject confirmed an intraluminal pH of 8. The erythromycin solution was delivered in 20 ml over 1 minute, followed by 30 ml of water, after which the cannula and endoscope were removed. The subjects remained lying on their left side for a further 5 minutes before walking to an adjacent observation area, where

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0724-8741/95/0100-0149$07.50/0

Table I. Subject Characteristics

Subject	Age (yr)	Sex	Weight (kg)	Height (cm)	Smoker (cigarettes/day)
1	20	M	64	170	9
2	20	M	73	182	0
3	20	M	48	169	0
4	20	F	60	157	0
5	20	F	53	168	5
6	21	F	66	168	3

they tested supine for a further 40 - 60 minutes. A pilot study had shown negligible binding of erythromycin to the plastic cannula.

b. Erythromycin base 250 mg in enteric-coated pellets (Eryc® Capsules, F.H. Faulding & Co. Limited, Adelaide, Australia; Lot no. 4H3661C) was administered with 50 ml of water. Although higher volumes of water are normally used with oral medications, a lower volume was used to relate more closely to the volume administered in the duodenal solution.

c. Erythromycin lactobionate equivalent to erythromycin 300 mg (Erythrocin IV®, Abbott Australasia Pty, Ltd., Kurnell, Australia; Lot No. 63-063AF) was dissolved in 12 ml of water for injections: 10 ml was further diluted to 25 ml, and 24 ml (containing erythromycin 240 mg) was infused over 30 minutes. The infusion was administered through a forearm vein in the contralateral arm to blood sampling using an 18-gauge 1.4 cm long sterile butterfly connecting tube attached to a Sage infusion pump (Sage Instruments, subsidiary of Orion Research Inc., Cambridge MA, USA).

The subjects were instructed to take no medication for at least 7 days prior to and during the study, to follow meal instructions, including a 12 hour overnight fast, and to avoid strenuous activity. Lunch was served 3 hours after dose administration. Fluid intake was unrestricted after 3 hours. Blood samples (2 ml) were collected at the following times from an intravenous catheter and stylet (Jelco®[Critikon Corp., Tampa, Fla., USA]) placed in a forearm vein - capsule formulation : 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5 and 6 hours; intravenous solution: 0, 10, 20, 30 (end of infusion), 35, 40, 50 minutes, 1, 1.25, 1.5, 2, 2.5, 3.5, 4.5, 5.5 and 6.5 hours; duodenal solution: 0, 6, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 minutes, 2, 2.25, 2.5, 2.75, 3, 4, 5, 6 hours.

Assay

Blood samples were allowed to stand for 1 hour, then following centrifugation at 3000 × g , the sera were stored at −20 °C until analysis. Serum samples were assayed as described previously (11) using a microbiological plate method with Micrococcus luteus (ATCC 9341) as the test organism. The assay was linear over the concentration range 0.10 to 3.0 mg/L, and high (1.64 mg/L) and low (0.55 mg/L) quality control samples assayed in duplicate with each set of subjects' samples resulted in accuracy and precision of 96.6 ± 9.2% and 120.8 ± 10.9%, respectively.

Pharmacokinetic Methods

The area under the serum erythromycin concentration versus time curve from zero time to the time (t_{last}) of last blood collection [$AUC_s(0\text{-}t_{last})$] was calculated by the linear trapezoidal method. The slowest disposition rate constant (λ_z) was calculated from the terminal linear portion of the log concentration versus time curve for each subject and the half-life was calculated at $0.693/\lambda_z$. The area from the last serum erythromycin concentration to infinity was calculated using the estimated serum erythromycin concentration (C_{last}) and the slowest disposition rate constant determined after intravenous (IV) erythromycin administration as C_{last}/λ_z. The total area under the curve from zero to infinity(AUC) was calculated as $AUC_s(0\text{-}t_{last}) + C_{last}/\lambda_z$. Total body clearance from serum (CL_s) was calculated as Dose/AUC. The area under the first moment of the curve (AUMC) was calculated in an analogous manner as for AUC. The mean residence time calculated for an IV bolus dose (MRT_{IV}), mean absorption time for duodenal solution (MAT_{DS}), mean dissolution time for oral capsules (MDT_{OC}), apparent volume of distribution (V_z) and volume of distribution at steady state (V_{ss}) were calculated from (15):

$$MRT_{IV} = AUMC/AUC - \text{Infusion Time}/2$$

$$MAT_{DS} = MRT_{DS} - MRT_{IV}$$

$$MDT_{OC} = MRT_{OC} - MRT_{DS}$$

$$V_z = \frac{\text{Dose}}{\lambda_z \times AUC}$$

$$V_{ss} = \frac{\text{Dose} \times AUMC}{AUC^2}$$

Table II. Pharmacokinetic Data for Erythromycin After Intravenous Administration in 6 Healthy Subjects

Subject	CL_s (ml/min/kg)	V_z (L/kg)	V_{ss} (L/kg)	λ_z (hr^{-1})	$t_{1/2}$ (hr)	MRT (hr)
1	3.81	0.54	0.34	0.423	1.64	1.47
2	7.77	0.88	0.40	0.528	1.31	0.88
3	7.49	0.86	0.58	0.523	1.33	1.29
4	6.47	0.88	0.52	0.440	1.57	1.34
5	9.41	1.51	0.63	0.375	1.85	1.12
6	3.54	0.47	0.24	0.455	1.52	1.11
Mean	6.42	0.86	0.45	0.457	1.54	1.19
SD	2.33	0.37	0.15	0.059	0.20	0.22
CV (%)	36	43	34	13	13	18

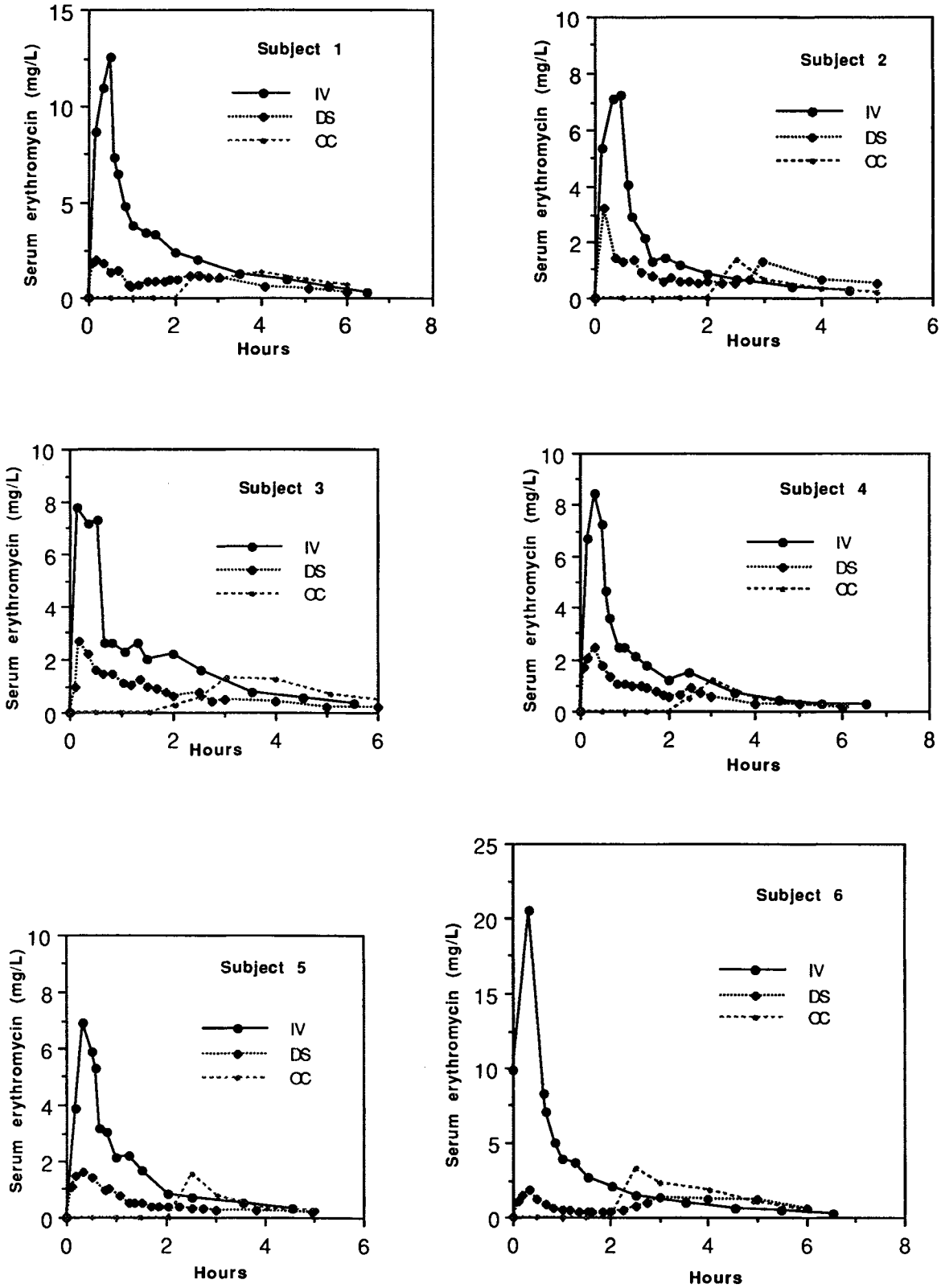

Fig. 1. Serum erythromycin concentration-time profiles in 6 healthy young subjects following a 240 mg intravenous (IV) dose, a solution containing 250 mg erythromycin administered directly into the duodenum (DS) and a 250 mg erythromycin enteric coated oral capsule formulation (OC).

The bioavailability (relative and absolute) was calculated by dividing the dose-normalized AUC values for one treatment by the AUC for the comparative treatment. The peak serum erythromycin concentration (C_{max}) and the time to peak concentration (t_{max}) were obtained by visual inspection of the serum erythromycin concentration-time profiles for each subject. The values for the AUC and C_{max} for the intravenous administration were adjusted to allow for the small difference in dose.

Statistical Methods

All data were calculated as mean, standard deviation(SD) and coefficient of variation(CV). Wilcoxon matched-pairs signed ranked test were used to determine if there were significant differences ($p < 0.05$) between the dosing regimens.

RESULTS AND DISCUSSION

All subjects successfully completed the trial with no dropouts. There was a single protocol violation by subject 2 who took 8 - 10 aspirin tablets 5 days before the study for a head cold. However, this subject did not have any symptoms on the first study day.

The erythromycin pharmacokinetic parameters after intravenous administration are listed in Table II. The total body clearance values of 382 ± 127 ml/min (unadjusted for weight) are similar to the literature values of 417 ml/min (16), 438 ml/min (17) and 570 ml/min (18). The volumes of distribution were one half those reported in previous publications (16, 17, 19) whereas half-life values were similar. Serum erythromycin concentration versus time profiles are shown for individual subjects in Figure 1. As expected for an enteric-coated formulation, there was a marked delay in the time taken to reach peak concentrations compared with the solution administered directly into the duodenum. With the duodenal solution, the three male subjects reached maximum serum erythromycin concentrations at 10 minutes compared with the three females at 20 minutes. This observation may suggest an apparent gender difference and requires further study. The earlier maximum serum erythromycin concentration observed in males was consistent with a previous report (2). In five of the subjects, there was a second rise in serum erythromycin concentration between 2.25 and 3 hours following intraduodenal administration. This was quite large in Subjects 1, 2 and 6, but small in Subjects 4 and 5. There was no similar secondary rise detected following intravenous infusion or oral capsule (Figure 1) ingestion.

Bioavailability data for the two oral formulations are shown in Table III. For the duodenal solution, bioavailability was less than 50% (mean 43%) in all subjects (except subject 2). For the oral capsule formulation, bioavailability was also low (mean 32%) with a smaller degree of intersubject variability and was just significantly less than that of the duodenal solution, although the magnitude of the difference was small. The relative bioavailability of the capsule was 80% that of the duodenal solution. Table IV lists the absorption data and mean residence, absorption and dissolution times for the various formulations. The apparently long mean absorption time of 58 minutes could be due to enterohepatic cycling or gastrointestinal secretion and subsequent reabsorption of erythromycin. The median dissolution time of 67 minutes for the capsule formulation would be consistent with its formulation characteristics.

Table III. Comparison of Area Under the Serum Erythromycin Concentration-Time Curve (AUC-mg/Lxh) Following Erythromycin Administration Via Three Different Routes (Intravenous, IV; Duodenal Solution, DS: Oral Capsule, OC). The AUC's Have Been Normalised for a 250 mg Dose

Subject	IV	DS	OC	$\frac{AUC_{DS}}{AUC_{IV}}$	$\frac{AUC_{OC}}{AUC_{IV}}$	$\frac{AUC_{OC}}{AUC_{DS}}$
1	17.1	5.7	5.6	0.34	0.33	0.98
2	7.3	5.2	2.0	0.72	0.27	0.38
3	11.6	4.6	4.4	0.40	0.38	0.97
4	10.7	4.4	2.4	0.41	0.22	0.55
5	8.4	3.1	2.4	0.37	0.29	0.80
6	17.8	6.9	7.6	0.39	0.43	1.10
Mean	12.2	5.0	4.1	0.43	0.32*	0.80
SD	4.4	1.3	2.2	0.14	0.07	0.28
CV (%)	36	26	54	32	23	35

* $p = 0.047$ (one sided significance level) compared with AUC_{DS}/AUC_{IV}.

The most important finding of this study was the low bioavailability of erythromycin when administered directly into the duodenum. It has been generally accepted that erythromycin has a low bioavailability due to hydrolysis in the acidic environment of the stomach. Although this cannot be disputed, it is evident that in addition, there are other factors contributing to its low bioavailability. One of these could be hepatic first-pass extraction. The fraction escaping this can be calculated as one minus the systemic blood clearance divided by hepatic blood flow (1500 ml/min). The whole blood to plasma concentration ratio for erythromycin is 2.32 (21). This would result in a systemic blood clearance of about 164 ml/min (380/2.32). Hence the hepatic extraction ratio and estimated bioavailability should be 0.11 and 89% respectively. As a result of this analysis there is a large discrepancy between the measured bioavailability of duodenally administered erythromycin of 43% and that predicted 89%. Hence there must be loss of orally administered erythromycin due to other mechanisms, which could include gut wall metabolism and/or poor absorption . However, given the moderate degree of lipophilicity of erythromycin (21), poor absorption would not be expected to be significant. This pharmacokinetic analysis indicates that for erythromycin, bioavailability is low due to hydrolysis in the acid environment in the stomach and a second mechanism which at present is unknown but in magnitude is significant as it reduces the bioavailability to about 43% from that expected of 89%. The technique of intraduodenal drug administration has provided valuable information on erythromycin availability and has been used successfully with other xenobiotics (22,23).

There were no adverse effects noted for the oral capsules or the duodenal solution. Intubation of the duodenum for all subjects was performed easily. Subject 2 was observed to have a rugose but normal proximal stomach, a gastric antrum with extensive patchy reddening and multiple erosions at the centre of each red patch. The pylorus, duodenal cap and second part of the duodenum were all normal. It was

Table IV. Absorption Data for Erythromycin Following Direct Instillation of a Solution into the Duodenum (DS) and Following Oral Administration of Enteric-Coated Pellets in Gelatin Capsules (OC). See Methods for Explanation of Abbreviations

Subject	t_{max} (hr)		C_{max} (mg/L)		MRT (hr)		MAT (hr)	MDT (hr)
	DS	OC	DS	OC	DS	OC	DS	OC
1	0.17	4.0	1.98	1.28	2.39	3.53	0.93	1.14
2	0.17	2.5	3.24	1.36	2.08	2.87	1.28	0.79
3	0.18	3.0	2.69	1.29	1.86	3.50	0.58	1.64
4	0.33	3.0	2.43	1.20	1.89	3.38	0.55	1.49
5	0.33	2.5	1.64	1.58	1.78	2.99	0.66	1.21
6	0.33	2.5	1.82	3.25	3.00	3.39	1.89	0.39
Mean	0.25	2.92*	2.3	1.66	2.17	3.28**	0.97	1.11
SD	0.08	0.53	0.55	0.79	0.46	0.28	0.52	0.46
CV (%)	32	18	24	48	21	9	53	41

* $p = 0.001$ DS versus OC; ** $p = 0.004$ DS versus OC.

likely that the ulceration and other signs were secondary to the earlier consumption of aspirin. Subject 2 retched 3 or 4 times on introduction of erythromycin solution through the endoscope. No further adverse events occurred when he was quickly extubated. All other intubations were uneventful. During administration of the intravenous solution, all subjects complained of pain at the site of infusion, associated with mild erythema, with pain in some cases radiating from the shoulder. This local irritation lasted for between 10 and 15 minutes after the end of the infusion and is consistent with that reported in the literature (17). The lack of gastrointestinal side-effects following intravenous administration is inconsistent with that reported previously (24) and is probably due to the lower dose and longer time of infusion. Biochemical and haematological tests remained normal.

CONCLUSIONS

The results found for orally and intravenously administered erythromycin are consistent with those found in earlier studies. Maximum serum erythromycin concentrations following the orally administered capsules were much lower than the concentrations observed for intravenous erythromycin. The time of the peak concentrations for the capsule were also delayed as expected for an enteric-coated formulation. Administration directly into the duodenum allowed further insight into possible factors which may influence the variable absorption of erythromycin into the systemic circulation. Attempts to further improve the oral bioavailability of erythromycin beyond 50% by manipulating the formulation characteristics are likely to be futile. Even when the acid environment of the stomach has been bypassed, there are additional, and at present unknown factors, which prevent the drug from reaching the systemic circulation. Enteric coated formulations of erythromycin, such as the one studied, with bioavailability values of 20 to 40%, probably represent the maximum possible delivery of drug into the systemic circulation.

ACKNOWLEDGMENTS

The authors wish to thank Michele Fong Lim and staff for serum erythromycin analyses, Gary Hamann for literature searches (all of F.H. Faulding & Co. Limited), Julie Keal, Debra Siebert and Michelle Smith for assistance with the clinical component of the study. Financial support was provided by F.H. Faulding & Co. Limited.

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