(13) G. L. Mattock, I. J. McGilveray, and D. Cook, *Can. J. Pharm. Sci.*, **6**, 35 (1971).
(14) G. Ramachander, F. D. Williams, and J. F. Emele, *J. Pharm. Sci.*, **66**, 1047 (1977).
(15) R. E. Tedeschi, D. H. Tedeschi, J. T. Hitchens, L. Cook, P. A. Mattis, and E. J. Fellows, *J. Pharmacol. Exp. Ther.*, **126**, 338 (1959).
(16) G. Levy and H. Yamada, *J. Pharm. Sci.*, **60**, 215 (1971).

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Bioavailability of Erythromycin Stearate: Influence of Food and Fluid Volume

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Abstract □ The influence of various test meals and coadministered water volumes on erythromycin stearate bioavailability from orally dosed film-coated tablets was studied in healthy human subjects. Serum erythromycin levels were uniformly reduced by all test meals, with the reduction in mean peak serum levels varying from 47 to 60%. Serum erythromycin levels also were reduced significantly in fasted individuals when the accompanying water volume was reduced from 250 to 20 ml. The apparent drug absorption rate constant was not influenced by treatments. This result is probably due to rapid degradation of solubilized, unabsorbed drug in the GI tract. Higher and more uniform serum erythromycin levels are obtained when erythromycin stearate tablets are given on an empty stomach together with an adequate water volume.

Keyphrases □ Erythromycin stearate—bioavailability, effect of food and fluid volume, humans □ Bioavailability—erythromycin stearate, effect of food and fluid volume, humans □ Absorption, GI—erythromycin stearate, effect of food and fluid volume, humans □ Antibacterials—erythromycin stearate, bioavailability, effect of food and fluid volume, humans

Since the introduction of erythromycin in 1952 (1) and subsequent observations that the drug may be irregularly absorbed from the GI tract (2), a large number of derivatives and formulations have been prepared to optimize its stability and absorption.

The bioavailability of one such derivative, erythromycin stearate, has been examined from an oral suspension (3, 4) and film-coated tablets (4–6). One study (4) suggested that erythromycin stearate in film-coated tablets may be absorbed into the circulation at a faster rate than erythromycin base from coated tablets. However, the overall absorption efficiency of antibiotic from the two dosage forms was similar.

Reports on the influence of food on erythromycin stearate absorption are conflicting. Absorption from the suspension appears not to be influenced by food (3), while absorption from film-coated tablets is reduced (5, 6). However, the reported studies have several shortcomings in that the types and sizes of meals and the time intervals between eating and dosing were generally not specified. Furthermore, the volumes of fluid ingested with the drug were not described. The only mention of fluid volume occurred in one study (6) where subjects took the drug with as much fluid as desired.

In view of the marked influence that different meals, varying time intervals between food and drug ingestion, and volumes of fluid taken with a drug may have on drug absorption (7), this study examined erythromycin stearate bioavailability in human volunteers with these factors carefully controlled.

EXPERIMENTAL

The overall design was similar to that described previously (8). Subjects were two female and four male healthy volunteers. The females were 22 and 24 years old and weighed 64 and 50 kg. The males were 22–33 years old (mean 27) and weighed 66–82 kg (mean 73). All subjects were shown to be in good physical condition by medical examination.

Protocol—Verbal assurance was obtained from all subjects that they had taken no known enzyme-inducing agents for 1 month, and no other drugs for 1 week, preceding the study. Subjects were instructed to take no drugs other than the required doses of erythromycin stearate during the study.

Subjects were fasted overnight before each treatment and were permitted to eat no food, apart from test meals, until 4 hr after dosing. On the morning of a treatment, each subject drank 250 ml of water on arising, at least 1 hr before dosing. Medication was administered at 8:00 am; blood samples (~5 ml) were collected from a forearm vein for serum in vacuum tubes[1] immediately before and at 0.5, 1, 2, 4, 6, 8, and 12 hr after dosing. Serum was deep frozen (−18°) until assayed. Assays were routinely carried out within 1 week of sampling.

Treatments—Erythromycin stearate was administered as single 500-mg doses consisting of two 250-mg film-coated tablets[2]. High carbohydrate, high protein, and high fat meals were prepared and standardized as described previously (9). The following treatments were administered:

Treatment 1—Two tablets with 250 ml of water immediately following a standard high carbohydrate meal.

Treatment 2—Two tablets with 250 ml of water immediately following a standard high fat meal.

Treatment 3—Two tablets with 250 ml of water immediately following a standard high protein meal.

Treatment 4—Two tablets with 20 ml of water on a fasted stomach.

Treatment 5—Two tablets with 250 ml of water on a fasted stomach.

[1] Vacutainers.
[2] Bristamycin, Bristol Laboratories.

Table I—Average Serum Erythromycin Concentrations (±1 *SD*) from All Treatments

Treatment	Serum Erythromycin Level, μg/ml							
	0.0 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr
1 Carbohydrate	0	0.01 ± 0.02	0.17 ± 0.41	1.16 ± 1.40	0.59 ± 0.47	0.29 ± 0.21	0.13 ± 0.01	0.04 ± 0.03
2 Fat	0	0.11 ± 0.17	0.41 ± 0.24	1.43 ± 0.85	0.66 ± 0.22	0.24 ± 0.10	0.11 ± 0.05	0.03 ± 0.02
3 Protein	0	0.05 ± 0.06	0.36 ± 0.49	1.03 ± 0.89	0.49 ± 0.18	0.19 ± 0.09	0.10 ± 0.05	0.03 ± 0.02
4 Fasting 20 ml	0	0.05 ± 0.10	0.59 ± 0.42	1.43 ± 0.55	1.30 ± 0.49	0.69 ± 0.27	0.40 ± 0.18	0.14 ± 0.08
5 Fasting 250 ml	0	0.36 ± 0.43	1.33 ± 1.08	2.65 ± 1.14	1.73 ± 0.51	0.83 ± 0.27	0.41 ± 0.16	0.13 ± 0.09
Paired *t*-test[a]	0	NSD[b]	5 > 1	5 > 3,4	4 > 1–3; 5 > 1–4	4,5 > 1–3	4,5 > 1–3	4,5 > 1–3

[a] Differences significant at $p < 0.05$. [b] No significant differences.

Tablets were swallowed whole. Problems associated with test meal preparation made treatment randomization impractical, and all subjects received the same treatment at the same time. Treatments were administered at least 1 week apart.

Assay—Serum erythromycin levels were determined using a microbiological cup plate diffusion method with *Sarcina lutea* (ATCC 9341) as the test organism and neomycin assay agar[3] as the growth medium.

Data Analysis—Individual serum erythromycin levels were fitted to a one-compartment open model with first-order absorption and elimination, using the program NREG on a digital computer[4] as described previously (8). Attempts to use more complex models to fit the individual data sets produced only slight increases in coefficients of determination and caused considerable increases in variances of pharmacokinetic constants.

Serum erythromycin levels at each sampling time and also pharmacokinetic constants were compared among and between treatments by analysis of variance and by paired *t*-test (8).

RESULTS

Mean serum erythromycin levels, together with the results of statistical analysis, are given in Table I; the data are summarized in Fig. 1. Circulating levels of erythromycin were reduced significantly by the test meals throughout the entire sampling period. Although peak erythromycin levels occurred at approximately the same time from all treatments, antibiotic concentrations were generally reduced to one-half the fasted values by the high fat meal and to somewhat less than one-half the fasted values by the high carbohydrate and high protein meals.

Serum erythromycin levels also were reduced when the accompanying water volume was changed from 250 to 20 ml in fasted individuals. The resulting serum erythromycin profiles were intermediate between those obtained from the other fasting treatment and those from postprandial doses. The 2- and 4-hr erythromycin levels were significantly reduced by the low water volume in fasted subjects. Serum erythromycin levels tended to be more consistent among subjects from Treatment 5 than from all other treatments. Although the high fat meal tended to produce somewhat higher serum erythromycin levels than the other meals at 2 and 4 hr, differences in erythromycin levels among nonfasted treatments were not significant.

The similar times of peak erythromycin levels in all treatments (Table II) suggest that the lower levels observed after nonfasted treatments and, to a lesser extent, after the low water volume treatment are caused by a reduction in the overall extent of drug absorption rather than the rate.

Mean values of all pharmacokinetic constants, obtained from individual data sets, are given in Table II.

The rather low coefficients of determination observed with all treatments were due to the considerable variance in the data, both among individuals and in the same individual. Considerable scatter in circulating levels of erythromycin following oral doses of various erythromycin formulations was reported previously (3–6).

Despite the considerable differences in serum erythromycin profiles from fasted and nonfasted treatments, there were no significant differences between the absorption rate constants or their associated absorption half-times. The lag time for appearance of drug in serum was higher following the high fat treatment than all other treatments. However, there was considerable individual variation in this value.

The rate constant for elimination of erythromycin from serum was also essentially treatment independent, although this parameter was significantly higher after the high protein meal compared to the low water volume treatment.

Differences in the extent of erythromycin stearate absorption from the different treatments are indicated by the *FD/V* values and by the areas under serum erythromycin level *versus* time curves. The *FD/V* value, which provides a rate-independent estimate of relative drug absorption, shows that erythromycin stearate absorption was impaired by about 43% in fasted individuals when the accompanying water volume was reduced from 250 to 20 ml. The test meals reduced absorption by 53–64%.

Similar reductions due to low water volume and test meals were obtained in truncated areas under serum level curves to 2 and 12 hr after dosing and also in total areas from zero to infinite time. However, differences in the 0–12-hr and total areas between the two fasted treatments were somewhat less than the differences in *FD/V* values because of the somewhat larger elimination rate constants after Treatment 5 compared to those after Treatment 4. Considerable individual variation was observed in some area values. However, unlike the situation with lag times, the variation in area values tended to be less with the fasted treatments than with the nonfasted treatments.

DISCUSSION

The observed reduction in the overall absorption efficiency of erythromycin stearate due to food and also to low fluid volumes, and yet the relative constancy of the absorption rate constant between treatments, may readily be rationalized in terms of the various factors contributing to the magnitude of k_a. Perrier and Gibaldi (10) showed that the apparent absorption rate constant, obtained from standard blood level curve-stripping techniques, reflects the overall rate of drug loss from the absorption site by all processes rather than the intrinsic absorption rate constant.

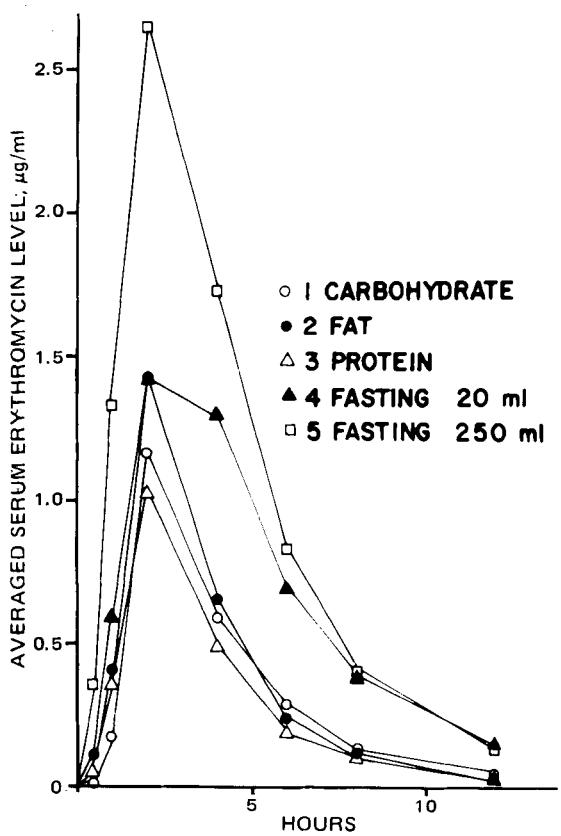

Figure 1—*Mean serum erythromycin levels.*

[3] Bacto antibiotic medium 11, Difco Laboratories.
[4] Univac model 1110.

Table II—Values of Pharmacokinetic Constants (±1 *SD*)

Constant	Treatment 1	2	3	4	5	Paired *t*-Test
k_a[a], hr^{-1}	0.59 ± 0.26	0.68 ± 0.28	0.66 ± 0.34	0.57 ± 0.20	0.61 ± 0.25	NSD
$t_{1/2\ (abs)}$[b], hr	1.5 ± 0.9	1.2 ± 0.6	1.3 ± 0.6	1.3 ± 0.4	1.3 ± 0.5	NSD
k_{el}[c], hr^{-1}	0.36 ± 0.03	0.42 ± 0.06	0.42 ± 0.15	0.30 ± 0.08	0.36 ± 0.07	3 > 4
$t_{1/2\ (elim)}$[d], hr	1.9 ± 0.1	1.7 ± 0.3	1.8 ± 0.5	2.5 ± 0.8	2.0 ± 0.4	NSD
FD/V[e], μg/ml	1.8 ± 1.6	2.2 ± 1.1	1.7 ± 0.9	2.7 ± 0.9	4.7 ± 1.2	5 > 1–4
t_0[f], hr	0.83 ± 0.68	0.17 ± 0.26	0.25 ± 0.42	0.25 ± 0.27	0.08 ± 0.20	1 > 2–5
r^2[g]	0.80 ± 0.01	0.85 ± 0.10	0.73 ± 0.10	0.92 ± 0.06	0.88 ± 0.07	4 > 1,3
Area[h] 0 → 2, μg hr/ml	0.5 ± 0.7	1.1 ± 0.5	0.8 ± 0.6	1.2 ± 0.6	2.5 ± 1.0	5 > 1–4
Area[h] 0 → 12, μg hr/ml	4.1 ± 3.5	4.7 ± 1.8	3.6 ± 2.0	8.2 ± 2.7	11.9 ± 2.1	4 > 1–3; 5 > 1–4
Area[i] 0 → ∞, μg hr/ml	4.8 ± 3.9	5.2 ± 2.0	4.0 ± 2.1	9.3 ± 3.0	13.2 ± 2.6	4 > 1–3; 5 > 1–4
Peak height, μg/ml	1.3 ± 1.3	1.4 ± 0.8	1.2 ± 0.7	1.7 ± 0.5	3.0 ± 0.9	5 > 1–4
Time of peak height, hr	3.3 ± 1.6	2.3 ± 0.8	2.2 ± 1.0	3.0 ± 1.1	2.7 ± 1.0	NSD

[a] First-order rate constant for appearance of erythromycin in serum. [b] Absorption half-time. [c] First-order rate constant for loss of erythromycin from serum. [d] Elimination half-life. [e] Fraction (F) of administered dose (D) absorbed, expressed as a concentration in its distribution volume (V) in the body. [f] Lag time between dosing and the appearance of erythromycin in serum. [g] Coefficient of determination ($\Sigma\ obs^2 - \Sigma\ dev^2)/\Sigma\ obs^2$. [h] Obtained by trapezoidal rule. [i] Obtained from the relationship FD/Vk_{el} = Area 0 → ∞.

Erythromycin stearate is acid labile. Once the film coating of the tablet has been penetrated during prolonged residence in the stomach due to food, the presence of which tends to neutralize the gastric acidity, the drug is lost from this site because of absorption into the bloodstream, stomach emptying with subsequent absorption from the small intestine, and acid-catalyzed degradation. Although these various factors must contribute differently to the observed values of k_a in the different treatments, the data in this study indicate that the sum of their different contributions is similar.

These results show that the efficiency of erythromycin stearate absorption from film-coated tablets is markedly reduced by three test meals. Therefore, these observations are consistent with previous studies in which mean peak serum erythromycin levels were reduced by food by about 40% (5) and about 60% (6). Both studies reported greater individual variation in circulating erythromycin levels than presently obtained. This result may be due to insufficient control of diets and fluid volumes in the earlier studies.

In addition, the results show that reduction in accompanying fluid volume can depress serum erythromycin levels significantly. This result is probably related to the low aqueous solubility of erythromycin stearate. Reduction of the water volume might be expected to inhibit considerably the dissolution of erythromycin stearate and, hence, its bioavailability. However, solubility cannot be the only contributing factor. Because the drug also must be in solution to be chemically degraded, one would expect the absorption rate constant to be similarly reduced. Although the k_a value for Treatment 4 tended to be low, differences in the value of this constant between treatments were not significant.

A probable explanation for this phenomenon may be that, with the smaller administered water volume, stomach emptying is delayed relative to that with the larger volume (11) and there is less dilution of gastric acidic secretions. These effects would result in delayed transit of drug to the optimal absorption sites in the small intestine with increased chance of acid-catalyzed degradation. Reduction in accompanying fluid volume reduced the rate or extent of absorption of other fat-soluble drugs (8, 9). This property appears to be common to this type of compound.

During a recent study, serum erythromycin levels were measured following intravenous doses[5]. Data from this dosage form were analyzed in terms of the two-compartment model; the overall distribution volume, V_{dss}, based on circulating levels of combined free and bound erythromycin, was calculated to be approximately 70% of body weight in normal individuals.

Substitution of this value into individual FD/V values obtained in the present study permits the value of FD, the fraction of the administered dose that is ultimately absorbed, to be calculated. Expressing this value as a percentage of the 500-mg dose yields the following values for the different treatments: carbohydrate, 18.3 ± 18.4%; fat, 21.5 ± 12.3%; protein, 16.1 ± 8.5%; fasting with 20 ml of water, 26.3 ± 10.9%; and fasting with 250 ml of water, 44.5 ± 13.8%.

Although these percentages are only approximations, they indicate the efficiency of erythromycin stearate absorption from this dosage form and may explain the considerable individual variations in circulating levels of this antibiotic after oral doses.

The results obtained show that test meals may markedly inhibit the bioavailability of erythromycin stearate from orally dosed tablets, giving rise to depressed circulating levels of antibiotic. Additionally, they show that absorption is inhibited if an inadequate volume of fluid is ingested with the drug. It is, therefore, recommended that erythromycin stearate tablets be administered, wherever possible, on an empty stomach and accompanied by an adequate volume of water.

These results and recommendations are based on a single-dose study. The influence of food and fluid volumes on the absorption of various erythromycin products following both single and repeated doses is currently being investigated.

[5] P. G. Welling and W. A. Craig, unpublished data.

REFERENCES

(1) J. M. McGuire, R. L. Bunch, R. C. Anderson, H. E. Boaz, H. E. Flynn, H. M. Powell, and J. W. Smith, *Antibiot. Chemother.*, **2**, 281 (1952).

(2) L. E. Josselyn and J. C. Sylvester, *ibid.*, **3**, 63 (1952).

(3) J. C. Sylvester and L. E. Josselyn, *ibid.*, **3**, 930 (1953).

(4) L. E. Josselyn, C. Endicott, and J. C. Sylvester, *Antibiot. Annu.*, **1954–1955**, 279.

(5) H. A. Hirsch and M. Finland, *Am. J. Med. Sci.*, **237**, 55 (1959).

(6) W. E. Clapper, M. Mostyn, and G. H. Meade, *Antibiot. Med. Clin. Ther.*, **7**, 91 (1960).

(7) P. G. Welling, *J. Pharmacokinet. Biopharm.*, **5**, 291 (1977).

(8) P. G. Welling, H. Huang, P. A. Koch, W. A. Craig, and P. O. Madsen, *J. Pharm. Sci.*, **66**, 549 (1977).

(9) P. G. Welling, L. L. Lyons, W. A. Craig, and G. A. Trochta, *Clin. Pharmacol. Ther.*, **17**, 475 (1975).

(10) D. Perrier and M. Gibaldi, *J. Pharm. Sci.*, **62**, 225 (1973).

(11) J. N. Hunt and I. MacDonald, *J. Physiol. (London)*, **126**, 459 (1954).

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