Plasma Levels following Single and Repeated Doses of Erythromycin Estolate and Erythromycin Stearate

P. G. WELLING *x, R. L. ELLIOTT, M. E. PITTERLE, H. P. CORRICK-WEST, and L. L. LYONS

Received February 6, 1978, from the *Center for Health Sciences, School of Pharmacy, University of Wisconsin, Madison, WI 53706.* Accepted for publication June 21, 1978. *Present address: Department of Clinical Pharmacology and Therapeutics, School of Medicine, University of Birmingham, Birmingham, B15 2TJ, England.

Abstract □ The pharmacokinetics of erythromycin and erythromycin 2′-propanoate were studied in healthy male volunteers following single and repeated doses of erythromycin stearate tablets, erythromycin estolate capsules, and a suspension. Estolate dosages gave rise to higher plasma levels of total drug than the stearate. However, the stearate yielded higher plasma levels of erythromycin base. Absorption of all dosage forms, except the suspension, was delayed, and pharmacokinetic interpretation of both single- and multiple-dose data required incorporation of an absorption lag time. The absorption of erythromycin stearate was inhibited by food and also by low fluid volumes in fasted subjects. Absorption of erythromycin estolate was increased in the presence of food and was not greatly affected by fluid volume. Although single-dose data poorly predicted circulating levels of erythromycin following repeated doses, trends observed after single doses were maintained during chronic treatment.

Keyphrases □ Erythromycin base and 2′-propanoate—bioavailability in humans, effect of food and fluid volume □ Bioavailability—erythromycin base and 2′-propanoate in humans, effect of food and fluid volumes □ Antibacterials—erythromycin base and 2′-propanoate, bioavailability in humans, effect of food and fluid volume

Despite the widespread use of erythromycin, there is still uncertainty regarding its optimum oral dosage form. Erythromycin absorption from formulations containing erythromycin base and from different esters and salts varied (1–6).

Factors influencing erythromycin absorption recently were reviewed (7). Most studies reported delayed or reduced absorption of erythromycin base or stearate in the presence of food (8–11). Absorption of erythromycin estolate appeared not to be influenced markedly while that of erythromycin ethylsuccinate increased in nonfasted individuals (10–14). Suspension formulations apparently were not influenced by the absence or presence of food (12, 15). However, results vary greatly.

The subject of erythromycin absorption has been confused by observations that the bioavailability of erythromycin stearate is inhibited by reduced fluid volumes (16) and that absorption characteristics from a single dose may have no relation to those following repeated doses (17). The notion that absorption of erythromycin estolate is superior to most other erythromycin dosage forms was challenged by Wiegand and Chun (18).

In the present study, circulating drug levels were compared following single and repeated doses of erythromycin stearate and erythromycin estolate. Plasma levels of erythromycin base and the propanoate ester were measured separately after dosing erythromycin estolate by a modification of the method of Tserng and Wagner (19).

EXPERIMENTAL

Ten healthy male volunteers, 21–42 years old (mean 29) and between 61 and 89 kg (mean 73), were in good physical condition with normal blood and urine laboratory values. There were no histories of drug allergy. Informed consent was obtained from each subject.

Table I—Summary of Treatments

Number[a]	Description
1	2 × 250-mg erythromycin estolate capsules with 250 ml of water after breakfast
2	2 × 250-mg erythromycin estolate capsules with 250 ml of water after overnight fast
3	2 × 250-mg erythromycin estolate capsules with 25 ml of water after overnight fast
4	Erythromycin estolate suspension, 5 mg/kg, with 250 ml of water after overnight fast
5	2 × 250-mg erythromycin stearate tablets with 250 ml of water after breakfast
6	2 × 250-mg erythromycin stearate tablets with 250 ml of water after overnight fast
7	2 × 250-mg erythromycin stearate tablets with 25 ml of water after overnight fast

[a] Each treatment was administered as a single dose and again following repeated doses.

Protocols—Subjects[1] were requested to take no drugs for 1 week before a study and no drugs other than required erythromycin doses during a study. Subjects conducted their normal daily tasks during the entire experiment.

Each subject received seven different treatments (Table I) randomized using one 7 × 7 Latin square and three rows of another. At least 2 weeks were allowed between treatments. Each treatment was administered as a single and repeated dosage regimen.

Dosing and Sampling Schedules—Subjects fasted overnight before a treatment and ate no food except test meals until 4 hr postdosing. On the morning of a treatment, subjects drank 250 ml of water at least 1 hr before dosing. Drugs were administered at 8 am. Blood samples (~6 ml) were taken from a forearm vein into vacuum tubes[2] containing heparin as an anticoagulant at 0, 0.5, 1, 2, 4, 6, 8, and 12 hr. Five additional and identical doses were given at 6-hr intervals starting 24 hr after the initial dose, the final dose being given at 8 am on the 3rd day. Further blood samples were then taken as after the initial dose.

In Treatments 1 and 5, the first and last doses of erythromycin estolate or erythromycin stearate were given immediately following a standard breakfast of corn flakes with milk, two slices of buttered toast, coffee with cream, and 2 teaspoonfuls of sugar. Intermediate doses were taken immediately following normal meals, the 2-am dose being taken following a light snack. In all other treatments, the first and last doses were given in the fasting state while intermediate doses were taken at least 2 hr before or after meals. With all single and repeated doses, the volume of water ingested with the drug dose was as indicated in Table I.

The dose of the suspension in Treatment 4 was selected on the basis of a recent recommendation that erythromycin suspension should be dosed at a level of 20 mg/ml/day for the treatment of streptococcal pharyngitis in children (20). Although this dosage is somewhat lower than that of the tablets and capsules, the dosage range was similar for a given individual. Therefore, the suspension data were considered together with those from other treatments, with adjustments where appropriate, while providing information on plasma drug levels obtained with this particular regimen.

Erythromycin estolate capsules[3] and suspension[4] and erythromycin stearate tablets[5] were commercial products.

[1] Faculty, technical staff, or graduate students.
[2] Vacutainers.
[3] Ilosone capsules, 250 mg, Eli Lilly and Co., Indianapolis, Ind.
[4] Ilosone liquid suspension, Eli Lilly and Co., Indianapolis, Ind.
[5] Filmtabs, Abbott Laboratories, Chicago, Ill.; purchased from University Hospitals, Madison, Wis.

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Table II—Results of Statistical Comparison of Drug Levels in Plasma following Single-Dose Treatments [a]

Drug Level Compared	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr
Ester[b]	4 > 1,3	2-4 > 1 4 > 3	NSD[c]	1 > 2-4	1 > 2-4	1 > 2-4	1 > 2-4
Base[d]	2,4 > 1,5 4 > 3	1 > 2-7 5-7 > 2-4	6,7 > 1-5	1 > 2,4 5-7 > 2-4	1 > 2,4 5-7 > 2-4	1 > 2-4,5,7 6 > 2,5,7 5-7 > 4	1 > 2,4,6,7 5-7 > 2
Total[e]	4 > 1-3,5-7	2-4,6 > 1 2,3 > 5,7 4 > 3,5-7	4,6 > 5	1 > 2-7	1 > 2-7 2-4 > 7	1 > 2-7 2,3,6 > 5,7	1 > 2-7 2-4 > 5-7

[a] All data were analyzed by an analysis of variance while individual treatments were compared by a paired t test. Differences were considered significant when $p < 0.05$. [b] Plasma levels compared among Treatments 1–4. [c] No significant differences. [d] Plasma levels compared among Treatments 1–7. [e] Comparison included total levels from all treatments, plasma levels of erythromycin base from Treatments 5–7 being considered as total levels.

Assay—Plasma samples from subjects receiving erythromycin stearate were promptly frozen (−20°) until assayed. These samples were assayed for antibiotic activity with a microbiological cup–plate diffusion method. Samples were diluted when necessary with 0.05 *M* phosphate buffer, pH 7.9. The test organism was *Sarcina lutea* (ATCC 9341) growing on neomycin assay agar[6].

All assays were done in triplicate. The relationship between the inhibition zone of bacterial growth and the logarithm of erythromycin concentration was linear over plasma erythromycin concentrations of 0.1–20.0 μg/ml. Assay reproducibility was ±8% at the lower concentration range and ±3% at the higher.

Plasmas from subjects receiving erythromycin estolate were assayed for both erythromycin 2′-propanoate and erythromycin base by a method adapted from one described previously (19). The major modification consisted of substituting the microbiological end-point for the fluorometric method used originally (19). The microbiological method was adopted because of its relative simplicity compared to the fluorometric procedure and also to avoid any interference by microbiologically inactive but fluorescing metabolites.

Further small modifications were incorporated, and the method finally used was as follows. Immediately following separation from whole blood, plasma was divided to obtain two 1-ml portions. One portion was acidified with 2 ml of 0.1 *M* phosphate buffer, pH 5.7, and extracted twice with 2 ml of ether. The ether extracts were combined. The other plasma portion was made basic with 2 ml of 0.1 *M* phosphate buffer, pH 8.5, and similarly extracted twice with 2 ml of ether. The ether extract of the acidified sample contained erythromycin 2′-propanoate while that of the basified sample contained both erythromycin 2′-propanoate and erythromycin base (19). Ether extracts were dried under nitrogen, and the residues were frozen until assayed.

On the day of the assay, 2 ml of 0.05 *M* phosphate buffer, pH 7.9, was added to each tube. Tubes then were incubated with occasional shaking at 37° for 5 hr to ensure complete ester hydrolysis. Final dilutions, when required, were done with 0.05 *M* phosphate buffer, pH 7.9, and the hydrolyzed samples were analyzed by the microbiological method described for erythromycin stearate.

This procedure yielded plasma levels of both combined ester and free base and also of erythromycin 2′-propanoate only. Levels of free base were obtained by subtraction. Repeated experiments with high purity drug standards showed that the assay achieved quantitative separation of erythromycin ester and free base. Equivalent amounts of erythromycin 2′-propanoate and free base gave identical assay readings in repeated trials following the 5-hr hydrolysis at 37° and pH 7.9, indicating complete conversion of the bacterially inactive ester to the base during the hydrolysis or during both the hydrolysis and incubation steps.

Analysis—Circulating levels of erythromycin following intravenous doses were described in terms of a two-compartment model (21); levels following oral doses were described in terms of a one-compartment model with either first-order (16, 22) or zero-order (17) absorption.

To differentiate the two oral dosing models, individual data sets for erythromycin following Treatments 5–7 and for both the propanoate ester and total erythromycin activity following Treatments 1–4 were analyzed using the one-compartment model with first- and zero-order absorption. Circulating levels of erythromycin base from Treatments 1–4 were not sufficiently defined for pharmacokinetic analysis.

In the first-order analysis, individual data sets were fitted to Eq. 1 following single doses and appropriate expansions of this equation following repeated doses:

$$C = \frac{FD}{V}\left(\frac{k_a}{k_a - k_{el}}\right)\left[e^{-k_{el}(t-t_{lag})} - e^{-k_a(t-t_{lag})}\right] \qquad \text{(Eq. 1)}$$

where C is the drug concentration in plasma; F is the fraction of the dose D absorbed; V is the apparent drug distribution volume; k_a and k_{el} are first-order rate constants for drug absorption and elimination, respectively; t is the time since dosing; and t_{lag} is the time elapsed between dosing and the time of appearance of measurable drug in plasma.

In the zero-order analysis, individual data sets from single doses were fitted simultaneously to Eqs. 2 and 3 for times less than and greater than the times of peak drug levels, respectively, and appropriate expansions of these expressions following repeated doses:

$$C = \frac{k_0 F}{Vk_{el}}\left[1 - e^{-k_{el}(t-t_{lag})}\right] \qquad t \leq t_{max} \qquad \text{(Eq. 2)}$$

$$C = \frac{k_0 F}{Vk_{el}}\left[1 - e^{-k_{el}(t_{max}-t_{lag})}\right]e^{-k_{el}(t-t_{max})} \qquad t > t_{max} \qquad \text{(Eq. 3)}$$

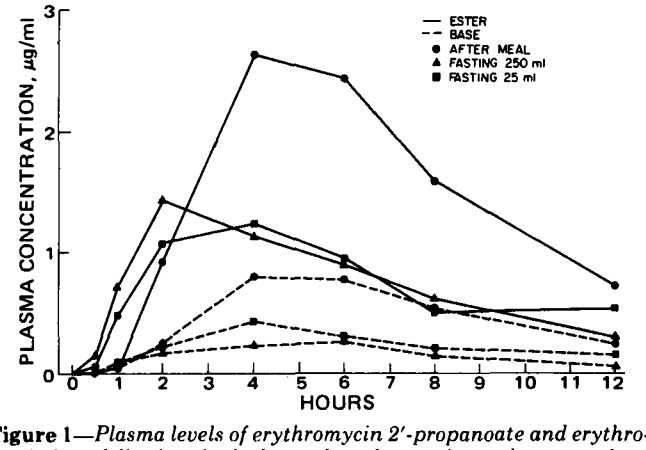

Figure 1—*Plasma levels of erythromycin 2′-propanoate and erythromycin base following single doses of erythromycin estolate capsules.*

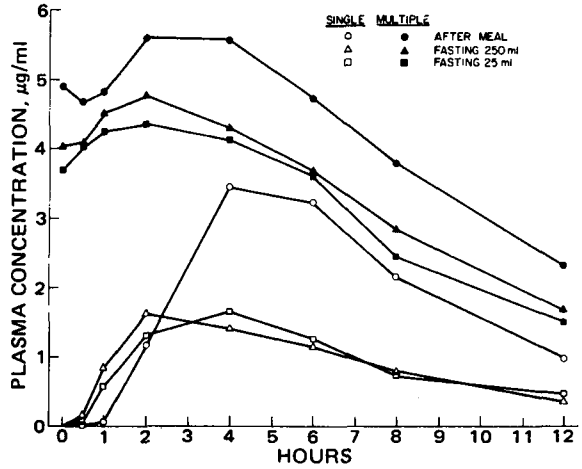

Figure 2—*Plasma levels of total erythromycin activity following single and repeated doses of erythromycin estolate capsules.*

[6] Bacto Antibiotic Medium No. 11, Difco Laboratories, Detroit, Mich.

Table III—Results of Statistical Comparison of Drug Levels in Plasma following Repeated Doses [a]

Drug Level Compared	0 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr
Ester	1 > 2-4	NSD	NSD	NSD	1 > 2-4	1 > 2-4	1 > 3,4	1 > 3
Base	NSD	NSD	NSD	5-7 > 1-4	5-7 > 1-4	6,7 > 1-4 6 > 5	6,7 > 3	1 > 2-7
Total	1-4 > 5-7	1-4 > 5-7	1-4 > 5-7	1-4 > 5-7	1-3 > 5-7 4 > 5,7	1 > 2-7 2-4 > 5-7 6 > 5	1 > 3-7 2-4 > 5-7	1 > 3-7 2-4 > 5-7

[a] Data were analyzed as in Table II. Comparisons of ester, base, and total drug levels were carried out as in Table II.

where k_0 is the zero-order rate constant for erythromycin absorption into the circulation, t_{max} is the time of observed peak drug level in plasma, and other symbols are as defined for Eq. 1.

In the first-order absorption case, initial estimates of k_a,k_{el}, and FD/V were obtained by standard graphical methods. Improved estimates of parameter values, together with statistical analysis, were obtained using the program NREG on a digital computer[7] (23). The value of t_{lag} was held constant. The value of k_{el} also was held constant during computer fitting to prevent it from converging to the same value as k_a.

Convergence of these constants during computer-fitting procedures was reported previously (24, 25) and can be explained in terms of the nature of Eq. 1. When k_a and k_{el} converge, usually due to data variance or insufficient data points, the function $FD/V[k_a/(k_a - k_{el})]$ becomes a large number while the function $[e^{-k_{el}(t-t_{lag})} - e^{-k_a(t-t_{lag})}]$ becomes very small. Owing to the long word length of the computer, the product of the two functions becomes a very flexible term for data fitting, but meaningless values of k_a and k_{el} are obtained. To avoid this analytical artifact, the more reliable of the two constants, k_{el}, was fixed at the graphical values.

Improved parameter estimates from single doses were used as initial estimates when computer fitting the repeated dose–plasma levels. In this case, both t_{lag} and k_{el} again were held constant.

In the zero-order absorption case, initial estimates of the value k_0F/V were obtained by dividing computer estimates of FD/V, obtained from the first-order case, by the value $t_{max} - t_{lag}$, *i.e.*, the apparent drug absorption time. Since there were only two variables, k_0F/V and k_{el}, both were allowed to float during computer analysis.

Plasma drug levels were compared between treatments by an analysis of variance and between particular treatments by a paired t test. Pharmacokinetic constants were similarly compared between treatments, between single and repeated doses, and, where appropriate, between pharmacokinetic models.

RESULTS

Plasma Levels—Mean plasma levels of erythromycin 2′-propanoate, erythromycin base, and total drug following single doses are summarized in Figs. 1–4. Statistical comparisons are given in Table II. Mean plasma levels and statistical comparisons following repeated doses are summarized in Figs. 5–7, and statistical comparisons are given in Table III.

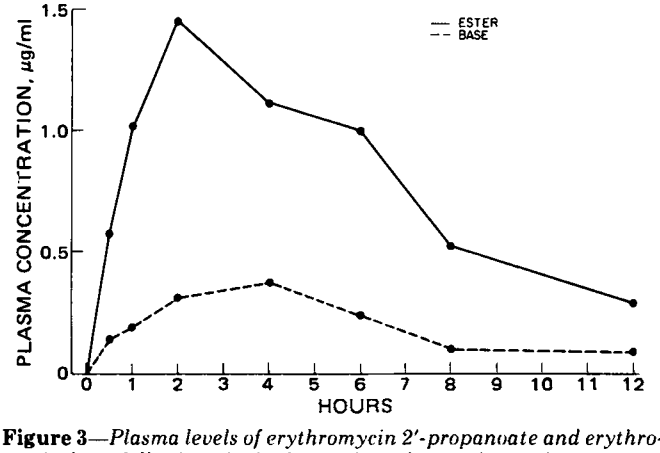

Figure 3—*Plasma levels of erythromycin 2′-propanoate and erythromycin base following single doses of erythromycin estolate suspension.*

From the single-dose data, it can be seen that the absorption of both erythromycin estolate and erythromycin stearate was delayed by food. In Treatment 1, antibiotic was not observed in plasma until 1 hr after dosing; levels were observed within 0.5 hr with all other treatments.

Whereas postprandial dosing of the stearate caused plasma erythromycin levels to be lower compared to an equivalent fasting treatment, circulating levels of the propanoate ester and also of the free base were higher when erythromycin estolate was dosed to nonfasted subjects.

Although plasma levels of total drug tended to be higher from Treatments 1–4 compared to Treatments 5–7, higher levels of erythromycin base were obtained from the stearate dosage form regardless of how the drug was administered. While water volumes had little influence on the absorption of erythromycin estolate, plasma levels of erythromycin base were inhibited by low fluid volume after doses of erythromycin stearate to the same extent as by food. These latter results are consistent with those reported previously with a different brand of erythromycin stearate (16).

Plasma levels of both the propanoate and the base from the suspension dosage were somewhat higher than those obtained from equivalent capsule doses (Treatment 2), despite the somewhat lower dose of the suspension.

From Tables II and III and the figures, it is clear that the trends observed following single doses continued with repeated dosing, although differences between treatments tended to be less significant. Following repeated doses of erythromycin estolate capsules, Treatment 1 continued to yield high levels of propanoate and, to a lesser extent, free base. In fact, plasma levels of free base were consistent at about 1.0 μg/ml, declining slowly throughout the sampling period. Levels of erythromycin base were again uniformly higher from the stearate doses than from the estolate doses, and Treatment 6 again resulted in higher erythromycin levels than did Treatments 5 and 7.

The suspension dosage form yielded plasma levels of both the propanoate and the free base similar to those of the capsule doses. No significant lag time of absorption was observed with the suspension.

Plasma Level Ratios—Mean ratios of plasma propanoate ester to free base following estolate doses were somewhat high following Treatment 2 and were generally higher after initial doses than after repeated doses. The overall ratio following repeated doses was 3.5. This value was fairly constant during the sampling period, and there were no trends between treatments. The ratio obtained was consistent with that reported earlier in blood, serum, plasma, and urine of subjects receiving repeated doses of erythromycin estolate (26).

Pharmacokinetic Parameters—Model-independent parameters C_{max}, t_{max}, and areas under plasma level–time curves, are summarized in Table IV; statistical comparisons are given in Table V. The superior

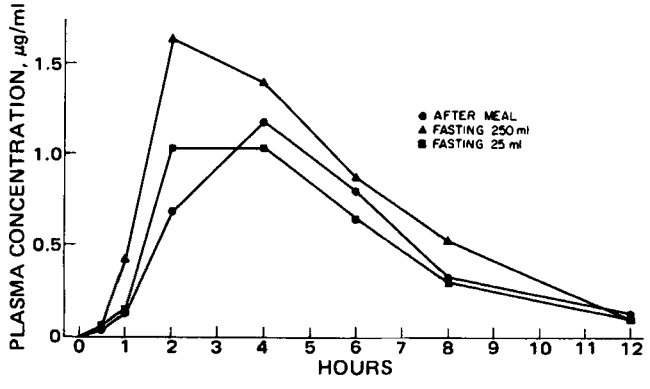

Figure 4—*Plasma levels of erythromycin following single doses of erythromycin stearate tablets.*

[7] Univac model 1108.

Table IV—Mean Peak Plasma Levels (C_{max}), Times of Peak Levels (t_{max}), and Areas[a] under Plasma Profiles (±1 *SD*) following Single and Repeated Doses

Treatment		C_{max}, μg/ml		t_{max}, hr		$AUC_{0\rightarrow 12\ hr}$, μg hr/ml, Single	$AUC_{0\rightarrow 6\ hr}$, μg hr/ml, Repeated
		Single	Repeated	Single	Repeated		
1	Ester	2.8 ± 0.4	4.5 ± 1.1	4.4 ± 1.1	2.4 ± 0.8	17.3 ± 2.9	23.8 ± 6.5
	Base	0.9 ± 0.5	1.8 ± 0.6	5.1 ± 1.5	2.9 ± 1.8	5.6 ± 2.7	7.7 ± 2.3
	Total	3.7 ± 0.8	5.8 ± 1.3	4.7 ± 1.0	2.8 ± 0.9	23.4 ± 5.6	31.5 ± 7.6
2	Ester	1.5 ± 0.7	3.7 ● 1.1	2.8 ± 1.4	1.9 ± 0.9	8.8 ± 4.3	18.2 ± 4.9
	Base	0.4 ± 0.3	1.5 ± 0.6	4.4 ± 1.8	1.9 ± 1.8	2.0 ± 1.2	7.3 ± 3.2
	Total	1.8 ± 0.8	5.0 ± 1.4	2.8 ± 1.4	1.6 ± 0.5	11.2 ± 4.5	25.8 ± 1.2
3	Ester	1.5 ± 0.8	3.5 ± 1.1	3.2 ± 1.4	1.7 ± 1.0	8.4 ± 4.3	17.7 ± 6.4
	Base	0.5 ± 0.5	1.7 ± 0.7	4.2 ± 1.8	2.9 ± 2.8	2.8 ± 2.9	6.6 ± 3.1
	Total	1.9 ± 1.1	4.6 ± 1.2	3.2 ± 1.4	1.6 ± 1.4	11.2 ± 6.7	24.5 ± 7.0
4	Ester	1.6 ± 0.7	3.7 ± 1.3	3.4 ± 1.9	1.5 ± 0.5	9.5 ± 3.2	18.8 ± 7.0
	Base	0.5 ± 0.3	1.9 ± 1.1	3.5 ± 1.7	2.0 ± 1.5	2.6 ± 1.7	8.1 ± 4.8
	Total	1.9 ± 0.9	5.3 ± 2.2	3.6 ± 1.6	2.0 ± 1.3	12.0 ± 4.8	26.3 ± 11.8
5	Base	1.4 ± 0.7	2.9 ± 1.0	4.0 ± 1.3	2.6 ± 1.0	6.3 ± 4.0	11.7 ± 4.6
6	Base	1.7 ± 0.5	3.5 ± 1.0	2.4 ± 0.8	2.9 ± 1.0	9.3 ± 3.5	15.4 ± 4.3
7	Base	1.3 ± 0.4	2.8 ± 0.6	2.8 ± 1.0	2.8 ± 1.0	6.1 ± 2.2	13.1 ± 4.0

[a] Areas measured by trapezoidal rule.

absorption of erythromycin 2′-propanoate from Treatment 1 was reflected in high C_{max} values after single doses and greater area values after both single and repeated doses. Although Treatments 1–4 tended to yield higher C_{max} and area values for total drug than the stearate treatments, values for the free base were generally higher with the stearate. Food gave rise to later t_{max} values compared to fasted treatments in most cases.

Results obtained from pharmacokinetic analysis using the first-order absorption model after single and repeated doses are given in Tables VI and VII. Comparison of the r^2 values shows that this model describes the repeated dose data somewhat better than those from single doses.

Comparison of Tables VI and VII and the results from zero-order analysis in Table VIII indicates that, while the zero-order model may describe single-dose data somewhat better, the first-order model is superior following repeated doses. Using Treatment 2 as an example, the relative accuracy of the two models is indicated in Fig. 8. These curves were obtained from averaged data, but they illustrate the improved fit by the zero-order model to single-dose data and the somewhat better fit by the first-order model to the repeated dose data.

The two models yielded different drug elimination rates. This difference was partially artifactual since the value of k_{el} was held constant in the first-order case. However, the high correlations obtained with the first-order model, particularly after repeated doses, suggest that the visual estimates of k_{el} were quite accurate. The elimination half-lives obtained with the zero-order model were longer than reported values (6, 21, 22) while those from the first-order model were in agreement with previous values.

The comparisons in Table IX are somewhat varied, but the k_a and t_{lag} values indicate relatively slow absorption from Treatment 1 and, to a lesser extent, Treatment 5.

Treatments 5–7 generally resulted in higher k_{el} values than Treatments 1–4, probably due to slow hydrolysis of the propanoate ester to free base in the body. The *FD/V* value, which is a rate-independent measure of relative bioavailability, was higher following Treatment 1 than following other estolate treatments after single doses and following Treatments 2 and 3 after repeated doses. Treatment 1 yielded higher *FD/V* values for total drug activity than Treatments 3, 5, and 7, while Treatments 2, 4, and 6 gave higher values than Treatment 7.

To obtain a more meaningful comparison of plasma drug levels obtained with suspension and capsule doses, C_{max}, *FD/V*, and area values from single doses of the suspension (Treatment 4) were normalized to a dose of 500 mg. There were no significant differences between the normalized values and those obtained from Treatment 2.

DISCUSSION

The results show that, although erythromycin estolate gives rise to higher plasma levels of total antibiotic than equivalent doses of erythromycin stearate, it produces lower, if somewhat more consistent, levels of the free base.

The clinical significance of this finding is uncertain. Esters of erythromycin were found to be antibacterially inactive until hydrolyzed (27), yet *in vivo* studies in animals showed erythromycin 2′-propanoate to be at least as effective as erythromycin base in curing bacterial infections (28). The problem is compounded by the observation that the propanoate ester is more extensively bound to plasma proteins and may penetrate tissues less effectively than the free base, although evidence for this hypothesis is slight (18).

The observation that food and reduced fluid volume both reduce erythromycin stearate absorption is consistent with results of previous studies (16). Increased absorption from erythromycin estolate in the presence of food was unexpected. However, increased estolate absorption from a suspension due to food was reported previously (12).

Reduced absorption of the acid-labile erythromycin stearate due to

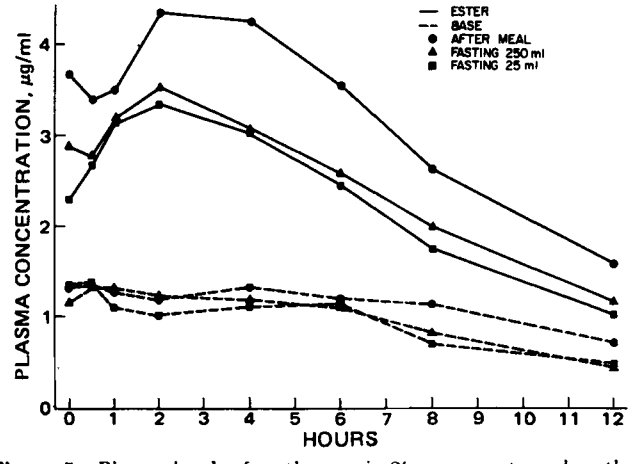

Figure 5—*Plasma levels of erythromycin 2′-propanoate and erythromycin base following repeated doses of erythromycin estolate capsules.*

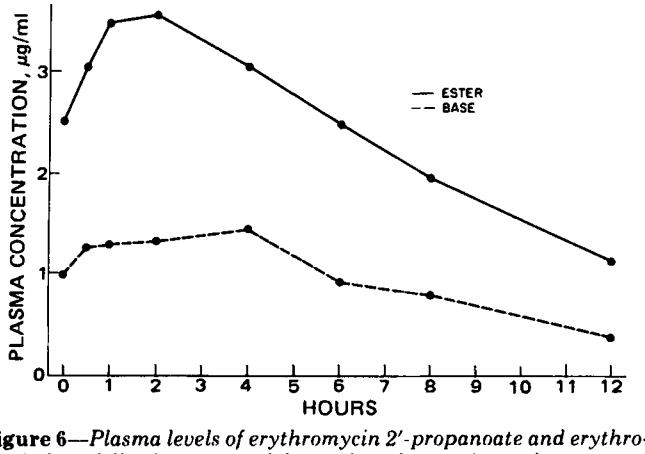

Figure 6—*Plasma levels of erythromycin 2′-propanoate and erythromycin base following repeated doses of erythromycin estolate suspension.*

Table V—Statistical Comparison of C_{max}, t_{max}, and AUC Values between Treatments following Single and Repeated Doses

Compound	C_{max}		t_{max}		$AUC_{0\text{-}12\ hr}$,	$AUC_{0\text{-}6\ hr}$,
	Single	Repeated	Single	Repeated	Single	Repeated
Ester	1 > 2-4	NSD	1 > 2-4	1 > 4	1 > 2-4	1 > 2-4
Base	5-7 > 2-4 6 > 1 > 2,4	5-7 > 1-4 6 > 5	1-3,5 > 6,7	NSD	1,5-7 > 2-4 6 > 5-7	5-7 > 1-3 6,7 > 4 6 > 5
Total	1 > 2-7 4,6 > 7	1-4 > 5-7 6 > 5	1 > 2-7 5 > 6,7	1 > 2-4 5-7 > 2,4	1 > 2-7 3,4,6 > 5,7 2,7	1-4 > 5-7 6 > 5

[a] Comparisons of ester, base, and total drug values were carried out as in Table II.

Table VI—Mean Values (±1 *SD*) of Pharmacokinetic Constants Obtained from Analysis of Individual Single-Dose Data Assuming a One-Compartment Model with First-Order Drug Input and Elimination

Treatment[a]	k_a, hr^{-1}	$t_{1/2}$ (absorbance), hr	k_{el}, hr^{-1}	$t_{1/2}$ (elimination), hr	t_{lag}, hr	FD/V, μg/ml	r^2 [b]
1 Ester	0.34 ± 0.09	2.2 ± 0.7	0.22 ± 0.05	3.3 ± 0.7	0.8 ± 0.26	5.4 ± 1.2	0.94 ± 0.02
Total	0.34 ± 0.10	2.3 ± 0.7	0.22 ± 0.04	3.5 ± 0.9	0.8 ± 0.26	7.2 ± 2.0	0.94 ± 0.02
2 Ester	0.75 ± 0.40	1.2 ± 0.7	0.20 ± 0.05	3.7 ± 1.1	0.2 ± 0.3	2.5 ± 1.1	0.95 ± 0.01
Total	0.69 ± 0.23	1.2 ± 0.5	0.20 ± 0.04	3.7 ± 0.9	0.4 ± 0.4	2.8 ± 1.1	0.95 ± 0.03
3 Ester	0.75 ± 0.39	1.3 ± 1.1	0.21 ± 0.08	3.7 ± 1.4	0.5 ± 0.3	2.4 ± 1.8	0.93 ± 0.05
Total	0.73 ± 0.41	1.6 ± 1.0	0.20 ± 0.05	3.7 ± 0.9	0.5 ± 0.3	3.0 ± 2.1	0.94 ± 0.05
4 Ester	0.67 ± 0.39	1.5 ± 1.0	0.22 ± 0.07	3.6 ± 1.5	0	2.8 ± 1.6	0.96 ± 0.03
Total	0.61 ± 0.32	1.5 ± 0.9	0.24 ± 0.07	3.1 ± 0.7	0	3.5 ± 2.0	0.96 ± 0.05
5 Base	0.61 ± 0.28	1.4 ± 0.5	0.37 ± 0.07	2.0 ± 0.4	1.3 ± 0.6	2.6 ± 1.8	0.87 ± 0.07
6 Base	0.59 ± 0.22	1.4 ± 0.6	0.36 ± 0.09	2.0 ± 0.5	0.6 ± 0.4	3.5 ± 1.2	0.94 ± 0.04
7 Base	0.61 ± 0.19	1.3 ± 0.5	0.30 ± 0.05	2.4 ± 0.4	0.6 ± 0.3	2.1 ± 0.07	0.91 ± 0.05

[a] Plasma erythromycin base levels from Treatments 1-4 were not subjected to pharmacokinetic analysis. [b] Coefficient of determination $(\Sigma^2_{obs} - \Sigma^2_{dev})/\Sigma^2_{obs}$.

Table VII—Mean Values (±1 *SD*) of Pharmacokinetic Constants Obtained from Analysis of Individual Data following Repeated Doses Assuming a One-Compartment Model with First-Order Drug Input and Elimination

Treatment[a]	k_a, hr^{-1}	$t_{1/2}$ (absorbance), hr	k_{el}, hr^{-1}	$t_{1/2}$ (elimination), hr	t_{lag}, hr	FD/V, μg/ml	r^2
1 Ester	0.34 ± 0.17	2.4 ± 1.0	0.22 ± 0.05	3.3 ± 0.7	0.7 ± 0.5	5.2 ± 1.3	0.99 ± 0.01
Total	0.28 ± 0.15	2.9 ± 1.0	0.22 ± 0.05	3.2 ± 0.6	0.6 ± 0.4	7.1 ± 1.6	0.99 ± 0.01
2 Ester	0.46 ± 0.37	2.0 ± 0.8	0.21 ± 0.05	3.6 ± 1.1	0.6 ± 0.6	3.8 ± 0.9	0.99 ± 0.01
Total	0.34 ± 0.10	2.3 ± 0.7	0.20 ± 0.04	3.7 ± 0.9	0.4 ± 0.4	5.6 ± 1.8	0.99 ± 0.01
3 Ester	0.40 ± 0.14	2.0 ± 0.7	0.21 ± 0.08	3.7 ± 1.4	0.1 ± 0.2	4.0 ± 2.2	0.99 ± 0.01
Total	0.37 ± 0.12	2.1 ± 0.7	0.20 ± 0.05	3.7 ± 1.0	0.2 ± 0.3	4.9 ± 1.7	0.99 ± 0.01
4 Ester	0.43 ± 0.16	1.9 ± 0.9	0.22 ± 0.07	3.6 ± 1.5	0	4.2 ± 2.1	0.99 ± 0.1
Total	0.37 ± 0.16	2.3 ± 1.4	0.30 ± 0.18	2.9 ± 1.0	0.2 ± 0.3	5.6 ± 2.0	0.99 ± 0.01
5 Base	0.48 ± 0.24	2.1 ± 1.8	0.37 ± 0.07	2.0 ± 0.4	0.6 ± 0.6	4.4 ± 1.5	0.91 ± 0.06
6 Base	0.49 ± 0.15	1.8 ± 1.1	0.34 ± 0.07	2.1 ± 0.5	0.5 ± 0.4	5.5 ± 1.8	0.93 ± 0.06
7 Base	0.43 ± 0.23	1.4 ± 1.7	0.30 ± 0.05	2.4 ± 0.4	0.3 ± 0.4	3.8 ± 1.3	0.93 ± 0.08

[a] Plasma erythromycin base levels from Treatments 1-4 were not subjected to pharmacokinetic analysis.

Table VIII—Mean Values (±1 *SD*) of Pharmacokinetic Constants Obtained from Analysis of Individual Single- and Multiple-Dose Data Assuming a One-Compartment Model with Zero-Order Input and First-Order Elimination

Treatment[a]	k_0F/V, μg/ml/hr	Single Dose			k_0F/V, μg/ml/hr	Repeated Dose		
		k_{el}, hr^{-1}	$t_{1/2}$ (elimination), hr	r^2		k_{el}, hr^{-1}	$t_{1/2}$ (elimination), hr	r^2
1 Ester	1.1 ± 0.2	0.12 ± 0.05	4.2 ± 1.5	0.98 ± 0.01	1.4 ± 0.5	0.14 ± 0.05	5.7 ± 1.9	0.98 ± 0.02
Total	1.4 ± 0.3	0.18 ± 0.04	4.0 ± 0.1	0.98 ± 0.01	1.3 ± 0.04	0.13 ± 1.0	5.8 ± 1.4	0.99 ± 0.01
2 Ester	0.91 ± 0.50	0.15 ± 0.06	5.5 ± 3.4	0.96 ± 0.03	1.2 ± 0.6	0.13 ± 0.03	5.6 ± 1.1	0.97 ± 0.03
Total	1.1 ± 0.6	0.17 ± 0.07	4.5 ± 1.8	0.96 ± 0.01	1.5 ± 0.7	0.11 ± 0.02	6.9 ● 1.4	0.96 ± 0.04
3 Ester	0.82 ± 0.42	0.22 ± 0.11	3.9 ± 1.9	0.96 ± 0.02	1.0 ± 0.5	0.12 ± 0.03	6.0 ± 1.5	0.95 ± 0.09
Total	0.95 ± 0.45	0.19 ± 0.07	4.2 ± 1.9	0.96 ± 0.02	1.3 ± 0.8	0.13 ± 0.03	5.7 ± 1.3	0.95 ± 0.05
4 Ester	0.98 ± 0.61	0.27 ± 0.11	3.8 ± 4.0	0.96 ± 0.02	1.0 ± 0.6	0.12 ± 0.03	6.1 ± 1.3	0.96 ± 0.04
Total	2.1 ± 1.5	0.29 ± 0.14	2.8 ± 1.2	0.94 ± 0.05	1.4 ± 0.6	0.38 ± 0.51	3.8 ± 1.9	0.95 ± 0.03
5 Base	0.95 ± 0.53	0.31 ± 0.04	2.3 ± 0.3	0.96 ± 0.04	1.6 ± 0.7	0.34 ± 0.17	2.2 ± 1.0	0.95 ± 0.03
6 Base	1.5 ± 0.70	0.22 ± 0.09	3.5 ± 0.9	0.95 ± 0.04	1.9 ± 1.0	0.34 ± 0.18	2.8 ± 2.4	0.95 ± 0.04
7 Base	1.8 ± 1.1	0.24 ± 0.05	2.9 ± 1.1	0.95 ± 0.05	1.1 ± 0.3	0.25 ± 0.16	3.5 ± 1.6	0.94 ± 0.07

[a] Plasma erythromycin base levels from Treatments 1-4 were not subjected to pharmacokinetic analysis.

Table IX—Statistical Comparison between Treatments of Some Pharmacokinetic Constants Described in Tables VI and VII

Compound[a]	k_a		k_{el}		t_{lag}		FD/V	
	Single	Repeated	Single	Repeated	Single	Repeated	Single	Repeated
Ester	2-4 > 1	NSD	NSD	—[b]	1 > 2,3 > 4	1,2 > 4	1 > 2-4	1 > 2,3
Base	NSD	NSD	5 > 7	—	5 > 6,7	NSD	6 > 7	6 > 7
Total	2-7 > 1	NSD	5-7 > 1-4	—	1 > 2-4 2,3,5-7 > 4	1 > 3,4	1 > 2-7 4 > 7	1 > 3,5,7 2,4,6 > 7

[a] Comparison of ester, base, and total drug values were carried out as in Table II, except that erythromycin base values were restricted to Treatments 5-7. [b] k_{el} was fixed at single-dose value.

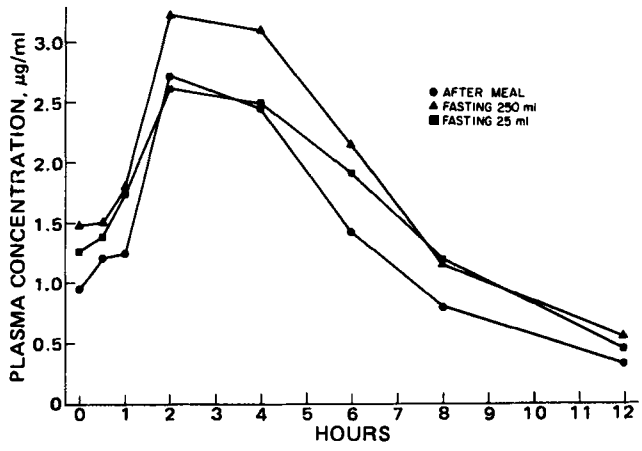

Figure 7—*Plasma levels of erythromycin following repeated doses of erythromycin stearate tablets.*

food and also low fluid volumes may be expected because both factors are likely to delay stomach emptying relative to that occurring after large water volume doses in the fasted state. Increased absorption of erythromycin estolate may be due to a longer stomach residence time increasing the extent of dissolution of this relatively acid-stable drug form. When the drug eventually passes from the stomach into the small intestine, it tends to be in solution form and is, therefore, rapidly and efficiently absorbed.

Results obtained with the erythromycin estolate suspension confirm that this dosage form gives rise to more rapid absorption than capsules. However, overall plasma levels are similar from the two formulations.

This study has not determined the most appropriate model to describe

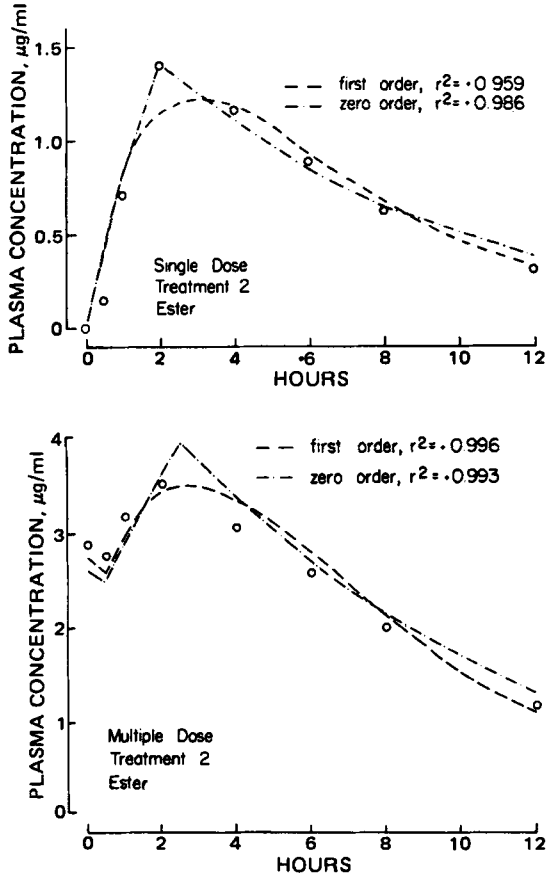

Figure 8—*Plasma curves obtained by fitting averaged data (O) from Treatment 2 following single (top) and repeated (bottom) doses using first- and zero-order absorption models.*

circulating erythromycin levels after oral dosing. After single-dose studies, plasma levels from both the estolate and stearate doses were described better using a zero-order absorption model. However, following repeated doses, the first-order model seemed more appropriate. The equivocal results obtained in this study contrast with those obtained by Colburn *et al.* (17) who presented considerable evidence of zero-order absorption using both enteric-coated erythromycin and film-coated erythromycin stearate tablets.

As indicated by Colburn *et al.* (17), single-dose plasma levels of erythromycin poorly predicted those obtained following repeated doses, with observed C_{max} values exceeding those predicted from single-dose data almost twofold. High drug levels during chronic dosing appear to be due to increased bioavailability, as reflected in *FD/V* values (Tables VI and VII), rather than absorption rates, which were somewhat lower after repeated dosing compared to single-dose values. Despite the poor relationship between single- and multiple-dose plasma levels of erythromycin, any treatment-dependent trends observed following single doses are likely to be maintained with repeated therapy.

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