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Bioavailability of Tetracycline and Doxycycline in Fasted and Nonfasted Subjects

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The influence of various test meals and fluid volumes on the relative bioavailability of commercial formulations of doxycycline hyclate and tetracycline hydrochloride was studied in healthy human volunteers. Serum levels of tetracycline were uniformly reduced by approximately 50% by all test meals, whereas serum levels of doxycycline were reduced by 20%. The reduction of tetracycline serum levels will likely be of clinical significance. The bioavailability of each drug was almost identical from an oral solution and from capsules in fasted subjects. The rate of doxycycline absorption was reduced when capsules were administered with a small volume of water, but the overall efficiency of absorption of both drugs was essentially independent of co-administered fluid volume. The use of 8-h serum data provides a reliable estimate of drug bioavailability for tetracycline and, to a lesser extent, for doxycycline.

Although the tetracycline antibiotics may be bactericidal to some microorganisms at high concentrations, their activity is primarily bacteriostatic (14). It is therefore important that circulating levels of these compounds be maintained above the minimum inhibitory concentration (MIC) for pathogenic organisms during a course of treatment. In view of this, there has been considerable interest in factors influencing the absorption of tetracyclines after oral doses and the degree to which these factors affect circulating levels of antibiotic.

Inhibition of absorption of the tetracyclines due to chelation by heavy-metal ions is extensively documented (8, 12, 16, 20, 21). Inhibition by antacid preparations is also well established. The latter effect appears to be due to a combined influence of heavy-metal ion chelation and also a decreased dissolution rate of tetracycline (2) or the dosage form in which it is contained (9). Milk and other dairy products inhibit the absorption of tetracyclines to varying degrees. Rosenblatt and associates (22) reported that doxycycline absorption was reduced by about 20% in the presence of skimmed milk, whereas the absorption of demethylchlortetracycline was reduced by about 70%. Mattila and associates (18) reported 50 to 60% reduction in bioavailability of tetracycline, oxytetracycline, and methacycline in the presence of whole milk whereas the absorption of doxycycline was not significantly affected. Interactions influencing the absorption of tetracyclines have recently been reviewed (19).

In view of the above, and also the superior tissue distribution (5, 10) and apparently longer biological half-life of doxycycline (11, 22), this lipid-soluble compound appears to have several advantages over other tetracyclines. From the results obtained with dairy products and also specific heavy metals, it is generally considered that food has less influence on the absorption of doxycycline than that of other tetracyclines. In this study, the influence of solid test meals and fluid volumes on the bioavailability of doxycycline and tetracycline was examined in healthy human volunteers under controlled conditions.

MATERIALS AND METHODS

Subjects were four male and two female healthy volunteers. Male subjects were aged between 21 and 36 years (mean, 26) and weighed between 66 and 98 kg (mean, 77). The two female subjects were aged 19 and 22 years and weighed 55 and 70 kg. All subjects were shown by medical examination to be in good physical condition with normal blood and urine laboratory values. There were no histories of drug allergies.

Protocols. The protocols followed were similar to those described previously (26; P. G. Welling, H. Huang, P. A. Koch, W. A. Craig, and P. O. Madsen, J. Pharm. Sci., in press). Subjects were advised to take no drugs for 1 week preceding the study and no drugs other than the required doses of doxycycline and tetracycline during the study. Subjects were fasted overnight before each treatment and were permitted to eat no food, apart from test meals, until 4 h after dosing. On the morning of a treatment, subjects drank 250 ml of water on arising, at least 1 h before dosing. Drugs were administered at 8 a.m., and blood samples (~4 ml) were

taken from a forearm vein into Vacutainers containing no anticoagulant immediately before and at 0.5, 1, 2, 3, 4, 6, 8, 24, and 32 (tetracycline) or 48 (doxycycline) h after dosing. Serum was separated and deep-frozen until assayed. Assays were done within 48 h of sampling.

Treatments. The tetracycline study immediately preceded the doxycycline study. All subjects received all treatments in both studies with one exception. One male subject vomited when taking doxycycline on an empty stomach. This subject was therefore replaced by another of similar age, weight, and height for the three doxycycline fasting treatments. Subjects received single 500-mg doses of tetracycline (hydrochloride) (Achromycin, lot 416-411, Lederle) as two 250-mg capsules or single 200-mg doses of doxycycline (hyclate) (Vibramycin, lot 51408, Pfizer) as two 100-mg capsules. Test meals were prepared and standardized as described previously (26). Each drug was administered as the following treatments: treatment 1, two capsules with 250 ml of water immediately after a standard high-carbohydrate meal; treatment 2, two capsules with 250 ml of water immediately after a standard high-fat meal; treatment 3, two capsules with 250 ml of water immediately after a standard high-protein meal; treatment 4, two capsules with 25 ml of water on an empty stomach; treatment 5, two capsules with 250 ml of water on an empty stomach; and treatment 6, the contents of two capsules dissolved in 250 ml of water taken on an empty stomach.

All subjects received the same treatment at the same time, and at least 2 weeks were allowed between each treatment. Capsules were swallowed whole.

Assay. Serum tetracycline and doxycycline concentrations were determined by the spectrofluorometric method of Kohn (17) as modified by Wilson and associates (27). Assays were carried out using 0.5 ml of serum, and volumes of all solutions and reagents used in the assay were suitably adjusted. Fluorescence was read on a Perkin-Elmer model MPF-4 instrument. The excitation wavelength was maintained at 395 nm, and emission was read at 525 nm. Both excitation and emission slits were set at 10 nm. Fluorescent response was linear over the concentration ranges of 0.1 to 5.0 μg/ml and 0.4 to 7.0 μg/ml for tetracycline and doxycycline, respectively. Standard solutions of both compounds were prepared and measured with each batch of unknowns to allow for slight instrument drift.

Interpretation of results. Individual serum antibiotic levels were fitted to equation 1, which is appropriate to the pharmacokinetic one-compartment open model, as described previously (25, 26; P. G. Welling et al., in press).

$$C = \frac{FD}{V}\left(\frac{k}{k-K}\right)\left(e^{-Kt} - e^{-kt}\right) \quad (1)$$

In this equation, C is the concentration of drug in serum at any time t after dosing, F is the fraction of the dose D that is ultimately absorbed into the circulation, V is the apparent distribution volume of antibiotic in the body, and k and K are first-order rate constants for drug absorption and elimination, respectively. Fitting of individual data sets to the equation was improved in many cases by incorporating a lag time, t_o, to represent the time elapsed between dosing and appearance of antibiotic in serum. Statistical comparisons were carried out as described previously (25, 26; P. G. Welling et al., in press).

RESULTS

Serum levels. Mean serum concentrations of the two tetracyclines, together with statistical comparisons between treatments, are given in Tables 1 and 2, and the data are summarized in Fig. 1 and 2. Similar serum profiles were obtained from all fasting treatments with both agents. Absorption was delayed slightly when capsules were administered with a small volume of water. This delay, reflected in the absorption rate constant and time of peak height (Tables 3 and 4), was significant ($P < 0.05$) for doxycycline but not for tetracycline.

Serum levels of tetracycline after the high-carbohydrate and high-fat test meals were reduced to about one-half those in fasted subjects. Serum levels were reduced further after the high-protein meal, but differences in serum levels between nonfasting treatments were significant only at 3 and 6 h.

Serum levels of doxycycline were reduced by approximately 20% in nonfasted subjects. Differences between fasting and nonfasting levels were significant during the first 4 h after dosing, but not at later times. Doxycycline serum levels after the high-protein meal appeared to be somewhat lower than other nonfasting levels during the first 4 h after dosing, but the differences were not significant.

Results of the pharmacokinetic analysis are summarized in Tables 3 and 4. The adequacy of the simple one-compartment open model to describe the serum level profiles is indicated by the high coefficients of determination, r^2. Despite the large differences in tetracycline serum levels in fasted and nonfasted subjects, there were no significant differences between treatments in absorption rate constants or times of peak serum levels. With doxycycline, however, significant differences in these parameters were observed in some cases between fasting and nonfasting subjects.

The major differences in the effects of food on both drugs were those associated with overall absorption efficiency. For tetracycline, peak serum levels, areas under serum level curves from the time of dosing until 2, 8, and 32 h and to infinite time, and FD/V values (the fraction of dose absorbed expressed as a concentration in its overall distribution volume) were all significantly greater in fasted than in nonfasted subjects. With doxycycline, however, despite a

TABLE 1. *Tetracycline serum levels (±1 standard deviation)*

Treatment	Serum levels								
	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	24 h	32 h
1. Carbohydrate	0.1 ± 0.1	0.3 ± 0.1	0.7 ± 0.4	2.2 ± 0.5	2.6 ± 0.8	1.9 ± 0.9	1.2 ± 0.6	0.3 ± 0.2	0 ± 0
2. Fat	0.2 ± 0.2	0.4 ± 0.2	0.9 ± 0.4	2.0 ± 0.2	2.3 ± 0.7	2.5 ± 0.9	1.3 ± 0.5	0.4 ± 0.1	0 ± 0
3. Protein	0.1 ± 0.2	0.3 ± 0.1	0.5 ± 0.4	1.3 ± 0.4	1.8 ± 1.1	1.5 ± 0.7	1.1 ± 0.6	0.3 ± 0.2	0.1 ± 0.1
4. Fasting, low volume	0.7 ± 0.9	2.4 ± 0.6	3.4 ± 0.4	3.9 ± 0.2	4.1 ± 0.2	3.9 ± 0.4	3.4 ± 0.2	0.8 ± 0.3	0.2 ± 0.2
5. Fasting, high volume	0.4 ± 0.3	1.6 ± 0.6	3.4 ± 0.4	4.1 ± 0.5	4.4 ± 0.3	3.6 ± 0.6	2.7 ± 1.1	0.7 ± 0.5	0.3 ± 0.2
6. Fasting, solution	0.6 ± 0.2	2.3 ± 0.9	3.8 ± 0.7	4.3 ± 0.5	4.4 ± 0.6	3.6 ± 0.8	2.8 ± 1.0	0.4 ± 0.2	0.3 ± 0.1
Paired *t* test[a]	5 > 1 6 > 1–3	4–6 > 1–3	4–6 > 1–3	1, 2 > 3 4–6 > 1–3	4–6 > 1–3	2 > 1, 3 4–6 > 1–3	4–6 > 1–3	NSD[b]	NSD

[a] Significant at $P < 0.05$.
[b] NSD, no significant differences.

TABLE 2. *Doxycycline serum levels (±1 standard deviation)*

Treatment	Serum levels								
	0.5 h	1 h	2 h	3 h	4 h	6 h	8 h	24 h	48 h
1. Carbohydrate	0.2 ± 0.3	0.6 ± 0.4	1.2 ± 0.6	3.0 ± 1.3	4.0 ± 1.1	3.7 ± 2.3	3.6 ± 2.5	1.2 ± 0.4	0.7 ± 0.4
2. Fat	0.2 ± 0.2	0.3 ± 0.4	1.3 ± 0.7	2.5 ± 1.1	3.5 ± 1.1	3.6 ± 1.1	3.0 ± 0.9	1.2 ± 0.2	0.4 ± 0.2
3. Protein	0.1 ± 0.2	0.4 ± 0.5	1.0 ± 0.7	1.7 ± 1.2	2.6 ± 1.1	3.8 ± 1.2	3.5 ± 0.9	1.7 ± 0.5	0.6 ± 0.2
4. Fasting, low volume	0.6 ± 0.5	1.7 ± 1.5	3.5 ± 2.2	5.0 ± 1.9	5.4 ± 1.1	4.8 ± 0.9	4.0 ± 0.9	2.2 ± 0.8	0.5 ± 0.3
5. Fasting, high volume	0.8 ± 0.8	2.3 ± 1.6	4.4 ± 1.8	4.9 ± 1.9	4.8 ± 1.9	3.6 ± 1.4	3.0 ± 1.2	1.5 ± 0.5	0.3 ± 0.3
6. Fasting, solution	1.0 ± 0.5	2.5 ± 1.4	5.1 ± 1.5	5.0 ± 1.6	4.7 ± 1.6	3.6 ± 1.2	2.9 ± 1.2	1.3 ± 0.3	0.8 ± 0.2
Paired *t* test[a]	4, 5 > 3 6 > 1–3	4 > 3 5, 6 > 1–3	4–6 > 1–3	4–6 > 1–3	1, 2, > 3 4 > 1–3 5 > 2, 3	NSD[b]	4 > 2, 5, 6	NSD	6 > 2, 5

[a, b] See Table 1.

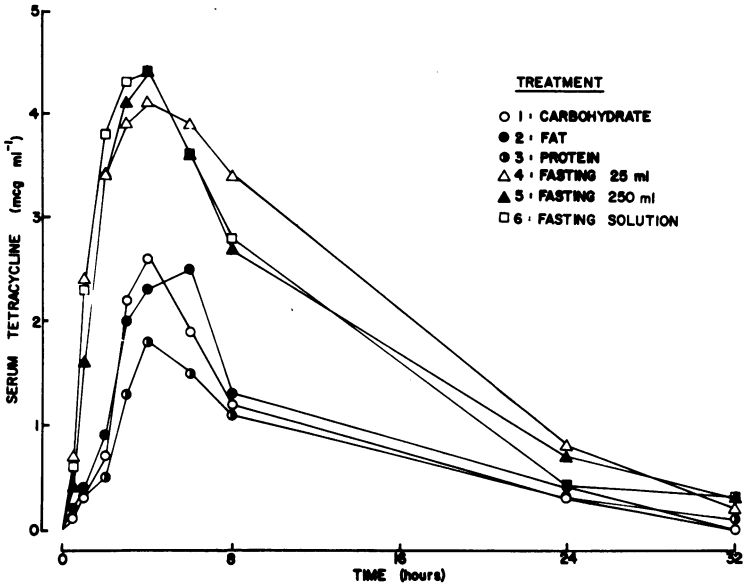

FIG. 1. *Average serum levels of tetracycline.*

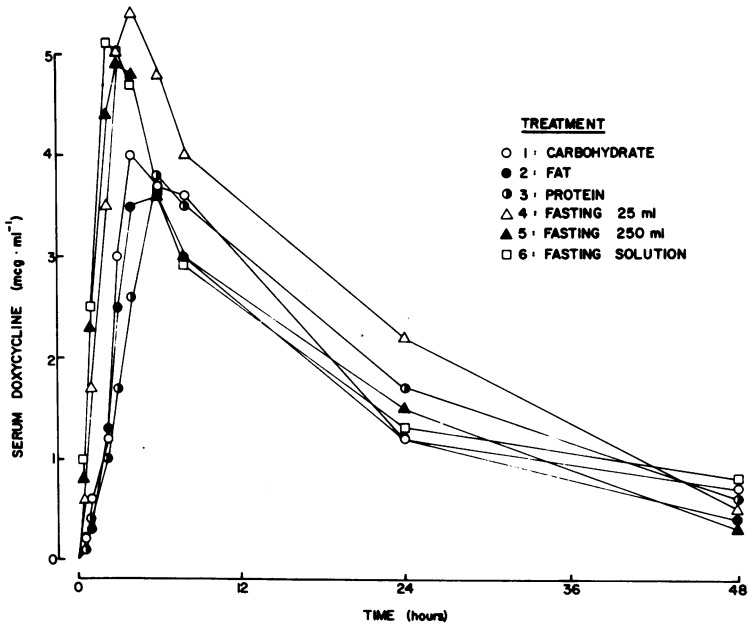

FIG. 2. *Average serum levels of doxycycline.*

tendency for these parameter values to be larger from the fasting treatments, differences in values between fasted and nonfasted treatments frequently failed to reach significant levels.

Serum levels, peak level values, times of peak levels, and serum half-lives in fasted subjects in this study were similar to previously reported values. Serum half-lives of doxycycline were somewhat shorter than those reported by some previous workers (11, 22), but were similar to those recently obtained by Ao and associates in normal individuals (1). The accuracy of some of the reported longer doxycycline half-lives has been questioned by Gibaldi (13).

TABLE 3. *Tetracycline pharmacokinetic parameters (±1 standard deviation)*

Treatment	Parameter												
	k (h^{-1})	$t_{1/2}$(abs) (h)	K (h^{-1})	$t_{1/2}$(elim) (h)	FD/V (μg/ml)	t_0 (h)	Areas (μg/ml × h)				r^{2c}	Peak ht (μg/ml)	Time of peak ht (h)
							0 → 2 h[a]	0 → 8 h[a]	0 → 32 h[a]	0 → ∞[b]			
1	0.47	1.6	0.13	5.6	3.4	0.5	0.7	11.9	24.4	27.0	0.90	2.6	3.8
	±0.16	±0.5	±0.03	±1.6	±1.2	±1.6	±0.2	±3.9	±9.8	±10.7	±0.04	±0.8	±0.4
2	0.49	1.9	0.11	6.2	3.6	0.45	0.9	12.8	28.3	31.7	0.94	2.7	4.7
	±0.33	±0.8	±0.01	±0.7	±1.1	±1.3	±0.3	±2.8	±6.2	±8.5	±0.04	±0.7	±1.5
3	0.50	1.8	0.10	7.2	2.5	0.5	0.5	9.0	23.5	25.5	0.92	2.0	4.5
	±0.76	±1.0	±0.02	±2.0	±1.2	±0.0	±0.4	±3.1	±10.0	±11.8	±0.05	±1.0	±1.2
4	0.52	1.6	0.11	8.1	6.4	0	3.2	27.0	66.5	74.7	0.99	4.1	4.2
	±0.33	±0.9	±0.02	±4.5	±1.3		±0.7	±1.0	±4.9	±18.9	±0.01	±0.2	±1.0
5	0.72	0.97	0.11	6.7	5.8	0.37	3.1	25.4	56.6	55.7	0.98	4.5	3.8
	±0.08	±0.12	±0.03	±1.5	±0.8	±0.7	±0.7	±3.3	±17.8	±12.5	±0.02	±0.3	±0.4
6	0.54	1.3	0.11	6.1	6.3	0	4.1	27.3	56.1	56.6	0.98	4.5	3.7
	±0.07	±0.2	±0.01	±0.6	±0.1		±1.0	±5.2	±14.7	±13.2	±0.01	±0.6	±0.5
Paired t test	NSD[d]	NSD	NSD	NSD	4–6 >1–3	1–3, 5 >4, 6	4–6 >1–3	4–6 >1–3	4–6 >1–3	4–6 >1–3	NSD	4–6 >1–3	NSD

[a] Calculated by trapezoidal rule.
[b] Calculated from FD/VK.
[c] $(\Sigma obs_2 - \Sigma dev_2)/\Sigma obs_2$.
NSD, No significant difference.

TABLE 4. *Doxycycline pharmacokinetic parameters (±1 standard deviation)*

Treatment	Parameter												
							Areas (μg/ml × h)						
	k (h^{-1})	$t_{1/2}$ (abs) (h)	K (h^{-1})	$t_{1/2}$ (elim) (h)	FD/V (μg/ml)	t_0 (h)	0 → 2 h[a]	0 → 8 h[a]	0 → 48[a]	0 → ∞[b]	r^{2c}	Peak ht (μg/ml)	Time of peak ht (h)
1	0.37	2.2	0.065	11.0	6.0	0.33	1.1	21.6	83.9	89.6	0.92	4.9	4.7
	±0.12	±1.0	±0.010	±2.2	±3.6	±0.26	±0.7	±8.9	±40.1	±48.8	±0.02	±2.1	±2.0
2	0.29	2.9	0.070	10.1	5.5	0.33	1.0	20.0	72.1	78.6	0.94	4.0	5.0
	±0.18	±1.2	±0.010	±1.8	±1.3	±0.41	±0.6	±7.0	±14.4	±17.2	±0.07	±1.1	±1.1
3	0.26	3.1	0.054	14.2	5.5	0.58	0.9	20.4	89.4	106.8	0.94	4.0	6.0
	±0.11	±1.3	±0.017	±5.3	±1.6	±0.49	±0.7	±8.7	±8.7	±37.6	±0.05	±0.9	±1.3
4	0.31	2.0	0.082	8.8	7.7	0	5.3	35.2	112.9	108.4	0.97	5.7	4.3
	±0.10	±0.9	±0.029	±2.9	±0.6		±1.3	±6.3	±26.9	±46.6	±0.01	±1.1	±1.4
5	0.78	1.0	0.067	11.0	5.8	0.08	4.4	28.9	87.4	85.3	0.96	5.1	3.2
	±0.35	±0.3	±0.020	±3.2	±2.3	±0.20	±2.1	±10.8	±30.2	±30.6	±0.02	±2.0	±1.0
6	1.03	0.85	0.062	12.6	5.7	0	5.2	31.1	90.3	90.4	0.95	5.2	2.7
	±0.48	±0.41	±0.024	±4.9	±2.5		±1.6	±8.8	±21.1	±16.5	±0.03	±1.5	±0.8
	5	1–3				1, 3							1–4
	>1–3	>5				>4, 6							>6
Paired t test	6	1–4	NSD[d]	NSD	4 >2,	3 > 5	4–6	4–6	4	NSD	NSD	4, 6	2–4
	>1–4	>6			3, 5, 6		>1–3	>1–3	>2, 6			>2, 3	>5
													3
													>4

[a–d] See Table 3.

DISCUSSION

The results obtained in this study show that, although the absorption of orally dosed doxycycline and tetracycline is impaired in the presence of food, the degree of impairment is far greater in the case of tetracycline. The small influence of food on doxycycline absorption is advantageous in view of the gastric irritation that may occur when this drug is taken on an empty stomach. Subjects in this study frequently reported transient nausea within 30 min of taking doxycycline in the fasting treatments, and one subject had to be withdrawn because of this. These symptoms did not occur when doxycycline was taken with food and were not observed at all with tetracycline.

The results also show that, for both drugs, inhibition of absorption is largely independent of the type of meal. It is interesting that the high-protein meal, which contained a higher proportion of heavy-metal ions, tended to produce somewhat lower serum levels of both tetracycline and doxycycline than did the other nonfasting treatments.

In other studies we demonstrated impaired absorption of amoxicillin trihydrate (P. G. Welling et al, in press) and, to a lesser extent, theophylline (25) when these drugs were administered in solid dosage forms with small accompanying water volumes. This may be attributed to their relatively low water solubility. Both doxycycline and tetracycline were administered as water-soluble salts in the present study, and changes in water volumes had only a small influence on their overall serum level profiles.

Several dosing and sampling methods have been used to measure the bioavailability of tetracycline drug products. Brice and Hammer (6) and Blair and associates (4) compared the bioavailability of various oxytetracycline products based on serum or blood level data collected through 6 h after single doses. Davis and associates (7) measured blood and urine tetracycline levels during a 96-h multiple-dosage regimen and concluded that single-dose studies using relatively short sampling periods may be inadequate for accurate bioavailability testing. Barr and associates (3), however, showed that results obtained from single-dose studies, using 10-h serum or 48-h urine sampling periods, accurately predicted tetracycline serum levels during multiple doses of various commercial products.

The present study utilized only single doses, but comparisons of data based on short and long postdosing intervals are instructive. Correlation coefficients between areas under serum level curves and also between 2-h, 8-h and peak serum levels and 0- to 32-h or 0- to 48-h areas are given in Table 5. With tetracycline, good correlations were obtained between all listed parameters, and it appears reasonable to suggest that the use of serum levels or areas under serum level curves measured at short postdosing time intervals provides a reliable estimate of tetracycline bioavailability characteristics. Agreement between the various parameters is not quite as good with doxycycline, but 8-h serum levels and 8-h areas correlate quite well with the 0- to 48-h areas.

Clinical significance. The in vitro MICs of most tetracyclines to susceptible bacteria range from 0.2 to 12.5 μg/ml (15, 23). Organisms with an MIC of 0.5 μg/ml or less are considered highly susceptible, those with an MIC of 0.5 to 2.5 μg/ml are considered moderately susceptible, and those with an MIC of 2.5 to 5 μg/ml are considered slightly susceptible. Doxycycline tends to be more active against many pathogens than tetracycline (22).

Based on our single-dose data, the mean tetracycline serum levels during a multiple-dosage regimen of 250 mg every 6 h would be approximately 4.5 μg/ml if the drug were dosed on an empty stomach (24). If the same regimen were followed but the doses were taken with meals, mean serum levels would drop to 2.4 μg/ml. The nonfasting regimen might thus result in insufficiently high circulating levels of antibiotic for activity against less susceptible organisms.

With doxycycline, the mean serum levels ob-

TABLE 5. *Correlations among areas under serum level curves and also between serum levels and areas from 0 to 48 h (doxycycline) and 32 h (tetracycline)*

Parameter	Correlation coefficient	
	Doxycycline	Tetracycline
Area 0 → 2 h vs. area 0 → 8 h	0.75	0.93
Area 0 → 2 h vs. area 0 → 48 (32) h	0.35	0.89
Area 0 → 8 h vs. area 0 → 48 (32) h	0.77	0.95
Peak serum level vs. area 0 → 48 (32) h	0.87	0.83
2-h serum level vs. area 0 → 48 (32) h	0.46	0.87
8-h serum level vs. area 0 → 48 (32) h	0.88	0.98

tained during a multiple-dosage regimen of 200 mg/day would be approximately 4.4 μg/ml if the drug were dosed on an empty stomach. If the doses were taken with meals this value would drop only slightly, to 4.0 μg/ml. This small reduction in serum levels is unlikely to cause therapeutic failures. Thus the reduction in serum levels due to food observed in this study is likely to be of clinical significance for tetracycline but not for doxycycline.

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