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Clindamycin Dose–Bioavailability Relationships

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Abstract □ Analyses of dose-related changes in pharmacokinetic variables indicating bioavailability and of dosage equivalence were performed on data from single-dose studies on three preparations of the antibiotic clindamycin [7(*S*)-chloro-7-deoxylincomycin]: clindamycin hydrochloride hard-filled capsules, clindamycin palmitate flavored granules, and clindamycin phosphate sterile solution. The variables studied were serum clindamycin bioactivity and parameters calculated from a single-compartment pharmacokinetic model. In general, the changes with dose were linear but not proportional and the pharmacokinetic model fit the data well. There were, however, some suggestions of nonlinear kinetics, particularly in the clindamycin hydrochloride study. Within the dose ranges (150–450 mg. clindamycin hydrochloride, 150–600 mg. clindamycin palmitate, and 300–600 mg. clindamycin phosphate), the average response to a dose could be predicted well. An equivalent dose analysis for the three clindamycin preparations offered some insight into their absorption and disposition characteristics and the relative bioavailability of clindamycin from them. A single equivalent dose could not be computed; there were different equivalent doses for peak serum concentration, area under the serum concentration–time curve, and other variables.

Keyphrases □ Clindamycin formulations—absorption, disposition, and relative bioavailability of hydrochloride capsules, palmitate flavored granules, and phosphate sterile solution □ Dose–bioavailability relationships—clindamycin hydrochloride capsules, clindamycin palmitate flavored granules, clindamycin phosphate sterile solution □ Bioavailability—absorption, disposition of clindamycin capsules, flavored granules, and sterile solution □ Pharmacokinetics—absorption, disposition, and relative bioavailability of three clindamycin formulations

Two problems frequently confront researchers testing new drugs: prediction of response to a particular dosage and equivalence of formulations. In the case of antibiotics, it is often assumed that the desired response, eradication of pathogens, is closely related to the concentration of drug in the serum and, therefore, that

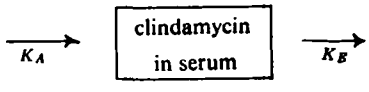
Table I—Subject Characteristics

Study Number	Compound and Dosage	Number of Men	Age (Years), Mean (Range)	Weight (kg.), Mean (Range)	Height (cm.), Mean (Range)
1	Clindamycin hydrochloride				
	150 mg.	10	36.4 (26.0–44.0)	80.0 (67.7–86.8)	182.1 (173.8–190.4)
	300 mg.	8	31.1 (22.0–46.0)	81.6 (70.9–95.0)	183.1 (173.8–198.2)
	450 mg.	8	35.4 (25.0–42.0)	82.5 (71.8–94.1)	181.3 (173.1–192.3)
2	Clindamycin palmitate				
	150 mg.	12	27.8 (23.0–35.0)	75.5 (61.4–91.4)	185.6 (176.9–193.6)
	225 mg. / 300 mg.	12	29.1 (22.0–42.0)	75.9 (65.9–93.6)	177.9 (143.6–191.0)
	600 mg.	6	30.0 (25.0–42.0)	70.6 (62.7–78.6)	176.7 (171.8–182.1)
3	Clindamycin phosphate				
	300 mg. / 450 mg. / 600 mg.	12	36.3 (25.0–48.0)	82.8 (69.1–105.0)	179.3 (172.4–193.6)

equal bioavailability implies therapeutic equivalence. Which measure(s) of drug absorption and distribution best reflects bioavailability remains to be established. This report considers several variables as indicators of bioavailability of three preparations of the antibiotic clindamycin[1] [7(*S*)-chloro-7-deoxylincomycin] undergoing clinical trials: (*a*) clindamycin hydrochloride hard-filled capsules; (*b*) a pediatric oral preparation of the 2-palmitate ester, clindamycin palmitate flavored granules; and (*c*) a parenteral preparation of the 2-phosphate ester, clindamycin phosphate sterile solution. The goal of administering any of the three is to attain therapeutically adequate concentrations of clindamycin bioactivity.

Wagner *et al.* (1) first described the clinical pharmacology of clindamycin hydrochloride, and their observations have been confirmed and extended by others (2–6). Clindamycin palmitate flavored granules, first prepared by Sinkula *et al.* (7), were shown in pharmacokinetic studies in adults (8) and children (9, 10) to be a satisfactory oral delivery agent for clindamycin. Results in clinical efficacy studies[2] in more than 1500 children with infectious diseases are confirmatory. The ester, which is inactive against bacteria *in vitro*, is readily hydrolyzed in the gut to microbiologically active clindamycin before absorption occurs. Preliminary studies did not reveal quantifiable amounts of the intact ester in human serum after a 300- or 600-mg. dose[3].

When clindamycin hydrochloride proved too irritating to use parenterally (11), the 2-phosphate ester was developed (12). Tolerance findings indicate that it is suitable for clinical use. However, to improve local tolerance the concentration of drug was halved from the 300 mg./ml. used in the first clinical pharmacology study reported here to 150 mg./ml., used in all subsequent studies. Microbiologically inactive 2-phosphate ester is absorbed intact after intramuscular injection. The kinetics of hydrolysis of the ester to active clindamycin will be dealt with in future publications.



Scheme I

In the three studies described here, healthy men were given single doses of 150, 300, and 450 mg.[4] clindamycin hydrochloride orally; 150, 225, 300, and 600 mg. clindamycin palmitate orally; or 300, 450, and 600 mg. clindamycin phosphate intramuscularly. Serum clindamycin levels were determined by bioassay, and the observations were subjected to pharmacokinetic analyses. In evaluating antibiotics, serum concentrations at various times after dosing, area under the serum concentration–time curve, peak serum level, and time of peak have all been considered clinically important by some workers. This paper considers these pharmacokinetic variables and others in assessing dose–bioavailability relations. The two aspects focused on are: (*a*) relationship between dose level and values of the pharmacokinetic variables for each compound, and (*b*) comparison of bioavailability of active clindamycin from the three compounds.

Urinary excretion of drug, sometimes used as an indicator of drug absorption, could not be estimated precisely for clindamycin in the studies reported here. Urine assays were run, but the bioactivity measured was due to a mixture of clindamycin and bioactive metabolites, one of which (*N*-demethylclindamycin) is more active and another (clindamycin sulfoxide) much less active than clindamycin itself. To report only the total amount of bioactivity excreted might perpetuate the misleading concept that the amount of bioactivity excreted represents the amount of drug excreted. Definitive studies of excretion of metabolites are not yet completed.

THEORETICAL

A single-compartment model (Scheme I) was used in studying serum clindamycin concentrations after all three clindamycin preparations, where K_A is a first-order rate constant for appearance of clindamycin in the blood (absorption) and K_B is a first-order rate constant for elimination from the blood. Both are expressed in liters

[1] Cleocin, The Upjohn Co.
[2] Case reports on file with The Upjohn Co.
[3] F. Sun and T. Brodasky, The Upjohn Co., personal communication.
[4] All dosages and concentrations expressed in terms of clindamycin base equivalents.

Table II—Dose-Bioavailability Relations after Clindamycin Hydrochloride[a]

Variable	Slope	Intercept	r^2	t-Statistic	Equivalent Dose, mg.	150 mg. Observed Mean[b]	150 mg. Predicted Mean[c]	300 mg. Observed Mean	300 mg. Predicted Mean	450 mg. Observed Mean	450 mg. Predicted Mean
Serum level, mcg./ml.:											
0.25 hr.	0.006	−0.60	0.21	2.54	195	0.48 ±0.69[d]	0.28	0.66 ±0.89	1.16	2.28 ±2.35	2.03
0.50 hr.	0.010	0.39	0.48	4.74	193	2.16 ±1.05	1.95	3.00 ±1.32	3.51	5.33 ±1.74	5.07
0.75 hr.	0.010	0.97	0.59	5.91	187	2.67 ±0.80	2.49	3.57 ±1.06	4.01	5.75 ±1.32	5.53
1.00 hr.	0.009	1.06	0.59	5.89	161	2.69 ±0.77	2.47	3.33 ±0.95	3.88	5.57 ±1.15	5.29
1.50 hr.	0.008	1.18	0.54	5.32	134	2.60 ±0.87	2.40	3.14 ±0.93	3.62	5.09 ±1.00	4.85
2.00 hr.	0.007	1.01	0.52	5.19	133	2.29 ±0.82	2.13	2.82 ±0.83	3.24	4.56 ±0.98	4.35
3.00 hr.	0.006	0.76	0.45	4.50	135	1.82 ±0.76	1.65	2.14 ±0.62	2.55	3.66 ±1.01	3.45
6.00 hr.	0.003	0.25	0.37	3.78	198	0.86 ±0.50	0.77	1.06 ±0.32	1.29	1.93 ±0.81	1.81
Model parameters:											
K_A	0.015	1.61	0.25	2.87	453	3.73 ±1.59	3.86	6.41 ±3.55	6.11	8.20 ±4.65	8.35
$A(^1/_2)$	N.R.	N.R.	0.15	<2	N.R.	0.22 ±0.09	N.R.	0.16 ±0.11	N.R.	0.13 ±0.09	N.R.
K_E	N.R.	N.R.	0.20	<2	N.R.	0.28 ±0.10	N.R.	0.22 ±0.05	N.R.	0.20 ±0.06	N.R.
$E(^1/_2)$	0.003	2.31	0.16	2.17	123	2.82 ±1.13	2.80	3.23 ±0.67	3.28	3.78 ±0.98	3.76
Estimated peak	0.009	1.17	0.61	6.13	174	2.84 ±0.65	2.56	3.44 ±0.87	3.94	5.58 ±1.26	5.33
Time of peak	N.R.	N.R.	0.12	<2	N.R.	1.06 ±0.37	N.R.	0.91 ±0.38	N.R.	0.76 ±0.31	N.R.
Area	0.063	3.64	0.43	4.29	139	14.88 ±7.80	13.18	18.49 ±6.14	22.73	34.40 ±12.55	32.28
Time lag	N.R.	N.R.	0.02	<2	N.R.	0.21 ±0.15	N.R.	0.22 ±0.05	N.R.	0.17 ±0.09	N.R.
Volume of distribution	0.106	33.54	0.43	4.29	153	43.90 ±7.40	49.40	78.90 ±15.90	65.27	74.30 ±14.20	81.10

[a] See text for explanation of terms. [b] Observed mean. [c] Mean predicted from model. [d] ± standard deviation.

per hour. The concentration of clindamycin in the serum as a function of time after dosing is described by the equation:

$$\text{concentration} = \frac{\text{dose } K_A}{V(K_E - K_A)}[\exp(-K_A t^*) - \exp(-K_E t^*)] \quad \text{(Eq. 1)}$$

where $t^* = t - t_0$; t is time measured in hours from dosing and t_0 is a time lag before measurable amounts of clindamycin can be observed in the serum. Dose is in milligrams, and V is the apparent volume of distribution in liters. In addition to being a volume factor, V also adjusts for the fraction of the dose absorbed; in this paper (dose/V) corresponds to the (FD/V) parameter of Wagner and Nelson (13). Parameters that can be calculated from this model include the absorption half-life $A(^1/_2) = (\ln 2)/K_A$ (in hours), the elimination half-life $E(^1/_2) = (\ln 2)/K_E$ (in hours), the peak serum concentration (in micrograms per milliliter), the time of peak (in hours), and the total area under the serum concentration–time curve (in micrograms per milliliter × hours). The use of this model in both single-dose and multidose studies of clindamycin hydrochloride was discussed elsewhere (6).

In this model, serum concentrations are related to dose in a linear manner. If the model holds over all doses, then serum concentrations at a given time should increase in the same proportion as do doses. Thus, if the dose is doubled, serum concentrations at a given time should double, as should the parameters directly dependent upon concentration (peak and area under the curve). However, rate constants, half-lives, time lag, time of peak, and volume should not change. Deviation from this behavior may provide information about the drug and different formulations; it may also indicate that the model does not give a complete description of the drug kinetics.

One way to compare bioavailability of the two formulations is to calculate the dose of one formulation ("equivalent dose") that will produce the same average value of a chosen variable as does a specified dose of the standard formulation. In this paper, 150 mg. clindamycin hydrochloride is used as the standard and, where feasible, the equivalent doses of palmitate and phosphate esters that will produce the same average values for serum concentrations and parameter estimates from the pharmacokinetic model are estimated. The composite means of pharmacokinetic variables found in six studies with 150 mg. clindamycin hydrochloride (6) were used as the reference values. Values obtained with clindamycin hydrochloride in Study 1 described here were also compared with the composite means, using the same method of inverse estimation.

Since for the chosen variables the dose–bioavailability relationship is assumed to be linear over the doses used for each formulation, the equation:

$$\text{value of pharmacokinetic variable} = \text{intercept} + (\text{slope} \times \text{dose}) \quad \text{(Eq. 2)}$$

was used. Thus, for a pharmacokinetic variable, the dose of the ester that is equivalent to 150 mg. clindamycin hydrochloride is given by the equation:

$$\text{equivalent dose} = \frac{P - I}{S} \quad \text{(Eq. 3)}$$

where P is the average value of the pharmacokinetic variable observed in subjects receiving 150 mg. clindamycin hydrochloride in the six studies, and I is the intercept and S is the slope of the linear dose–bioavailability relation computed for all the observed dose

Table III—Dose-Bioavailability Relations after Clindamycin Palmitate[a]

Variable	Slope	Intercept	r^2	t-Statistic	Equivalent Dose, mg.	150 mg. Observed Mean[b]	150 mg. Predicted Mean[c]	225 mg. Observed Mean	225 mg. Predicted Mean	300 mg. Observed Mean	300 mg. Predicted Mean	600 mg. Observed Mean	600 mg. Predicted Mean
Serum level, mcg./ml.:													
0.33 hr.	N.R.	N.R.	0.00	<2	N.R.	1.14 ±0.95[d]	N.R.	0.80 ±0.65	N.R.	1.22 ±0.97	N.R.	1.15 ±0.74	N.R.
0.67 hr.	0.003	1.40	0.14	2.54	370	1.77 ±0.84	1.85	1.94 ±0.84	2.07	2.58 ±1.29	2.30	3.04 ±1.52	3.18
1.00 hr.	0.004	1.13	0.32	4.35	345	1.70 ±0.60	1.80	2.11 ±0.26	2.13	2.63 ±1.00	2.47	3.70 ±1.77	3.80
1.50 hr.	0.005	0.98	0.40	5.20	306	1.70 ±0.55	1.71	2.04 ±0.64	2.07	2.48 ±0.86	2.43	3.86 ±1.66	3.89
2.00 hr.	0.005	0.91	0.43	5.47	206	1.66 ±0.57	1.64	1.93 ±0.57	2.01	2.46 ±0.84	2.38	3.83 ±1.59	3.85
3.00 hr.	0.004	0.83	0.47	5.90	185	1.43 ±0.52	1.46	1.71 ±0.53	1.77	2.20 ±0.61	2.08	3.28 ±1.18	3.34
6.00 hr.	0.002	0.37	0.43	5.48	232	0.76 ±0.31	0.73	0.87 ±0.34	0.90	1.08 ±0.38	1.08	1.80 ±0.70	1.79
12.00 hr.	—	—	—	—	—	0.00	—	0.00	—	0.26	—	0.62 ±0.23	—
Model parameters:													
K_A	N.R.	N.R.	0.07	<2	N.R.	14.25 ±14.38[d]	N.R.	7.17 ±9.39	N.R.	9.30 ±14.54	N.R.	2.00 ±1.07	N.R.
$A(^1/_2)$	N.R.	N.R.	0.04	<2	N.R.	0.24 ±0.41	N.R.	0.24 ±0.16	N.R.	0.31 ±0.50	N.R.	0.46 ±0.27	N.R.
K_B	N.R.	N.R.	0.00	<2	N.R.	0.23 ±0.09	N.R.	0.21 ±0.06	N.R.	0.24 ±0.08	N.R.	0.23 ±0.05	N.R.
$E(^1/_2)$	N.R.	N.R.	0.01	<2	N.R.	3.41 ±1.01	N.R.	3.52 ±1.10	N.R.	3.18 ±1.00	N.R.	3.18 ±0.66	N.R.
Estimated peak	0.005	1.35	0.36	4.71	278	2.02 ±0.64	2.05	2.32 ±0.67	2.40	2.87 ±0.99	2.74	4.08 ±1.63	4.14
Time of peak	N.R.	N.R.	0.09	<2	N.R.	0.96 ±0.71	N.R.	1.18 ±0.54	N.R.	1.09 ±0.74	N.R.	1.62 ±0.49	N.R.
Area	0.031	6.93	0.38	4.90	177	11.92 ±5.06	11.51	13.81 ±4.86	13.80	15.46 ±4.23	16.09	25.67 ±10.83	25.26
Time lag	N.R.	N.R.	0.01	<2	N.R.	0.26 ±0.15	N.R.	0.24 ±0.15	N.R.	0.27 ±0.78	N.R.	0.22 ±0.12	N.R.
Volume of distribution	0.113	55.39	0.18	2.95	−50	59.84 ±25.58	72.39	101.71 ±30.73	80.89	82.18 ±36.53	89.39	121.26 ±46.32	123.39

[a] See text for explanation of terms. [b] Observed mean. [c] Mean predicted from model. [d] ± standard deviation.

levels of that ester. This is called inverse estimation in the statistical literature (14).

EXPERIMENTAL

Design of Studies—Study 1 was described in detail (as Study 7) by DeHaan *et al.* (6). Results after the first 150-mg. dose were included in the six single-dose studies referred to previously.

The other two studies were carried out with prisoners as subjects[5]. In Study 2 the 12 men who took 150 mg. clindamycin palmitate also took 150 mg. clindamycin hydrochloride in a two-way crossover with a week between doses; data from the clindamycin hydrochloride part of the study were reported (as Study 3) previously (6). Another panel of 12 received the 225- and 300-mg. doses in a two-way crossover with a week between doses. In the 600-mg. phase of the palmitate study, six men were given clindamycin palmitate and another six received placebos (vehicle for clindamycin palmitate) as a tolerance control group.

Study 3 was a three-way crossover study in which each of 12 men received intramuscular injections of 300, 450, and 600 mg. clindamycin phosphate with a week between doses.

The volunteers were required to be within 20% of ideal body weight for height and build; to have no known GI, hepatic, or renal disease; and to have screening clinical laboratory values, physical examinations, and vital signs within normal limits. Table I summarizes subject characteristics.

Clindamycin hydrochloride hydrate (Lot 15,759-15) was given as 150-mg. hard-filled capsules, and clindamycin palmitate hydrochloride flavored granules (Lot 16,110-1) were given as a suspension reconstituted with distilled water to a concentration of 15 mg./ml. In both oral studies the subjects fasted (except for water *ad libitum*) overnight before the dose and for 3 hr. after the dose, and they drank 180 ml. (6 fl. oz.) water after the dose. Study 3 utilized clindamycin phosphate sterile solution containing 300 mg. clindamycin base equivalents/ml. (Lot 15,953); this lot did not contain the disodium edetate that was added to subsequent lots. Injections of 1.0, 1.5, or 2.0 ml. drug were made deep into the gluteal muscles, using a 3.8-cm. (1.5-in.) 22-gauge needle.

Microbiological Assay[6]—Serum specimens were obtained for microbiological assay at the times indicated in Tables II–IV, and the samples were frozen promptly and stored at −20°. To estimate clindamycin bioactivity (clindamycin plus bioactive metabolites), a cylinder-plate method was used. Sterile Pen Assay Seed Agar[7] was inoculated with the test organism, *Sarcina lutea* ATCC 9341. Primary standards were prepared in commercial pooled human serum[8], and secondary standards were prepared in the subject's own pretreatment serum specimen. Specimens were assayed undiluted and calculated *versus* their respective secondary standards, all specimens from an individual subject being assayed on the same day. Reported values of less than 0.9 mcg./ml. were extrapolated from the standard curve, and zero indicates less than 0.2 mcg./ml. Before assaying for free clindamycin activity in serum following clindamycin phosphate administration, phosphate buffer was added to the specimen immediately after it was thawed to halt hydrolysis of any clindamycin phosphate present. Wagner *et al.* (1) found that nearly all of the bioactivity in serum after clindamycin hydrochloride is due to clindamycin *per se*.

Tolerance Monitoring—*See Appendix.*

[5] In Jackson Experimental Clinic, State Prison of Southern Michigan, Jackson, Mich.

[6] The Microbiology Section of the Clinical Research Laboratory, The Upjohn Co., performed all bioassays.

[7] Difco.

[8] Hyland.

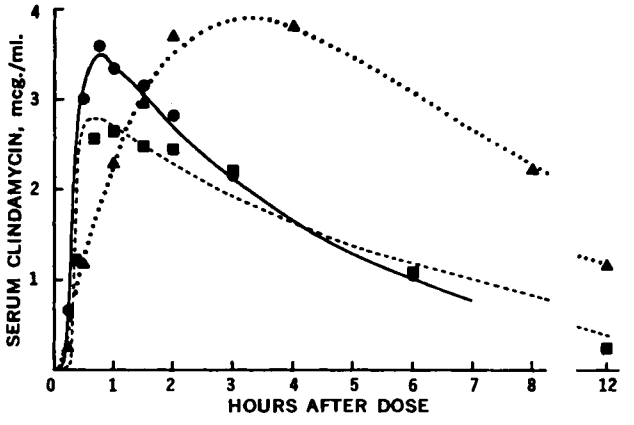


Figure 1—*Mean serum clindamycin (micrograms per milliliter) after a 300-mg. dose of three clindamycin preparations. Key: ●——●, clindamycin hydrochloride (eight men); ■- - -■, clindamycin palmitate (12 men); and ▲...▲, clindamycin phosphate intramuscularly (12 men).*

RESULTS AND DISCUSSION

Serum Levels—Mean serum clindamycin concentrations observed at the various sampling times are listed in Tables II–IV. Figure 1 illustrates the differences and similarities in the serum concentration–time curves following a 300-mg. dose of the three preparations.

Differential assay results in several clindamycin phosphate studies, including Study 3 described here, indicate that a substantial amount of unhydrolyzed ester appears in the serum shortly after intramuscular injection. In this study the ester reached a mean peak value between 1 and 2 mcg./ml. at 30 or 60 min. and virtually disappeared within 4 hr. Presumably the flattened, delayed peak in clindamycin bioactivity (compared with the oral dose curves) reflects hydrolysis of the ester to clindamycin in the serum, as well as various absorption and excretion factors.

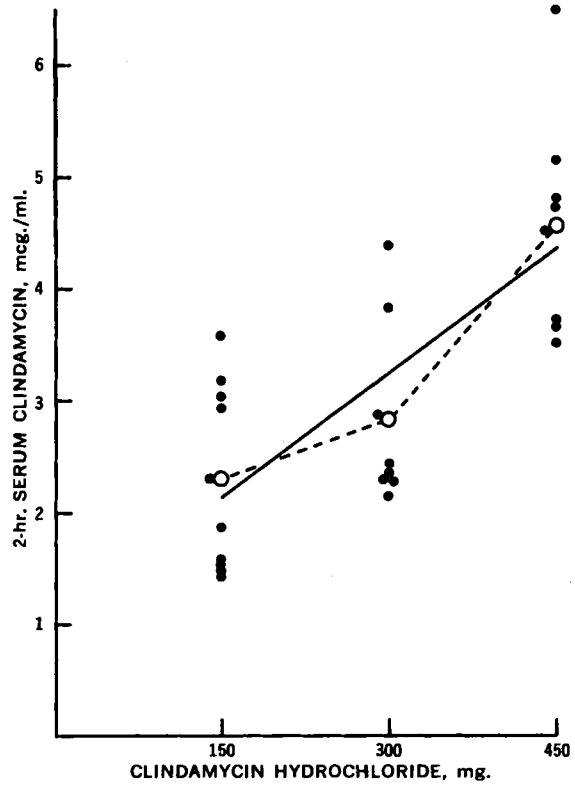


Figure 2—*Dose–bioavailability relation: 2-hr. serum clindamycin concentration after clindamycin hydrochloride. Key: ——, predicted means from linear model; O- - -O, observed means; and ●, individual values.*

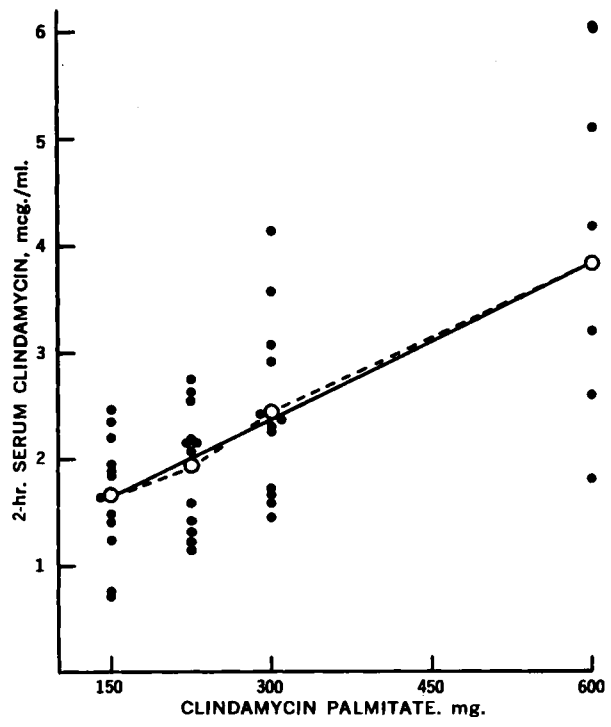


Figure 3—*Dose–bioavailability relation: 2-hr. serum clindamycin concentration after clindamycin palmitate. Key: ——, predicted means from linear model; O- - -O, observed means; and ●, individual values.*

Definitions and units for the estimated model parameters listed in Tables II–IV are given in the *Theoretical* section. The estimates were obtained by use of the nonlinear estimation program NONLIN (15).

Dose–Bioavailability Considerations—For all three formulations and all pharmacokinetic variables considered, where there was a change due to dose, the relation between dose and response was linear. Since at least three dose levels of the formulations were studied, a quadratic relation could be fitted to the data and, in fact, was calculated for all formulations and all variables; however, the resulting fit to the data was not significantly better than the linear fit. This linearity may hold only over the range of doses studied here. Since the intercept was in most cases nonzero, linearity would not hold for small doses and probably would not hold for very large doses.

For each variable (observed value or estimated parameter), a linear regression was computed with the dose as the independent variable and the value of the pharmacokinetic variable as the dependent variable. The strength of the relation was evaluated by a statistical test of the estimated slope; the t-statistic tests whether the slope is significantly different from zero. If the t-statistic was less than 2, that response was judged to be independent of dose [indicated by N.R. (no regression) in Tables II–IV].

Even though the mean values of the pharmacokinetic variables at each dose level fall on a line, there is so much variability about the means at each dose level that only a fraction of the total variability is due to changes in dose. The proportion of the variability of a pharmacokinetic variable that could be explained by change in dose is represented by r^2 (the square of r, the correlation coefficient). To express this proportion as a percent, multiply r^2 by 100. For example, as illustrated in Fig. 3, although the mean 2-hr. serum clindamycin levels at the four dose levels of clindamycin palmitate lie very close to a straight line, the individual values vary considerably about the mean. From Table III in the r^2 column for the 2-hr. serum concentration, it is apparent that only 43% of the total variation of the 2-hr. serum concentration is due to increasing dose levels.

Much of the overall variability in blood level studies is due to between-subject variability (16). Where the same panel of subjects

Table IV—Dose-Bioavailability Relations after Clindamycin Phosphate[a]

Variable	Slope	Intercept	r^2	R^2	t-Statistic	Equivalent Dose, mg.	300 mg. Observed Mean[b]	300 mg. Predicted Mean[c]	450 mg. Observed Mean	450 mg. Predicted Mean	600 mg. Observed Mean	600 mg. Predicted Mean
Serum level, mcg./ml.:												
0.25 hr.	—	—	—	—	—	—	0.23 ±0.49[d]	—	0.31 ±0.39	—	0.53 ±0.71	—
0.50 hr.	N.R.	N.R.	0.08	0.11	<2	N.R.	1.19 ±0.98	N.R.	1.40 ±0.60	N.R.	1.76 ±0.88	N.R.
1.00 hr.	0.002	1.61	0.11	0.20	2.03	450	2.29 ±0.98	2.28	2.59 ±0.54	2.61	2.96 ±0.87	2.95
1.50 hr.	0.004	1.69	0.24	0.40	3.31	140	2.96 ±1.14	2.96	3.59 ±0.50	3.60	4.23 ±1.08	4.23
2.00 hr.	0.005	2.23	0.26	0.45	3.49	−63	3.68 ±1.16	3.75	4.64 ±0.80	4.51	5.20 ±1.22	5.27
4.00 hr.	0.007	1.56	0.43	0.84	5.09	−27	3.79 ±1.03	3.91	5.32 ±1.07	5.09	6.15 ±1.30	6.26
8.00 hr.	0.006	0.29	0.41	0.84	4.88	43	2.22 ±0.65	2.35	3.63 ±1.12	3.38	4.28 ±1.23	4.40
12.00 hr.	0.004	−0.13	0.33	0.76	4.10	90	1.17 ±0.46	1.23	2.02 ±0.90	1.91	2.53 ±1.00	2.59
24.00 hr.	—	—	—	—	—	—	0.09 ±0.21	—	0.27 ±0.47	—	0.50 ±0.36	—
Model parameters:												
K_E	N.R.	N.R.	0.07	0.14	<2	N.R.	0.17 ±0.06[d]	N.R.	0.15 ±0.04	N.R.	0.14 ±0.04	N.R.
$E(^1/_2)$	N.R.	N.R.	0.06	0.10	<2	N.R.	4.50 ±1.57	N.R.	4.77 ±1.21	N.R.	5.32 ±1.29	N.R.
Estimated peak	0.007	1.96	0.43	0.80	5.04	111	4.06 ±1.09	4.18	5.53 ±0.98	5.29	6.29 ±1.17	6.41
Time of peak	0.002	2.06	0.13	0.28	2.29	−620	2.60 ±0.31	2.65	3.03 ±0.80	2.94	3.19 ±0.69	3.24
Area	0.101	5.22	0.40	0.85	4.75	71	37.68 ±13.07	38.92	58.73 ±17.42	55.76	71.38 ±21.20	72.61
Time lag	N.R.	N.R.	0.04	0.07	<2	N.R.	0.31 ±0.21	N.R.	0.34 ±0.25	N.R.	0.22 ±0.11	N.R.
Volume of distribution	N.R.	N.R.	0.09	0.25	<2	N.R.	60.07 ±21.52	N.R.	62.63 ±17.73	N.R.	75.20 ±21.20	N.R.

[a] See text for explanation of terms. [b] Observed mean. [c] Mean predicted from model. [d] ± standard deviation.

is used for all doses of a formulation, it is possible to remove this component. In Study 3 the same 12 subjects received the three dose levels in a crossover design. In Table IV, R^2 is the square of the correlation coefficient for the linear dose-bioavailability relations after the between-subject component of variance is removed. Consider, as an example, the 2-hr. serum concentrations. Of the total variability, only 26% is due to the different dose levels; but after removing the between-subject variability, 45% of the remaining variability is due to the different dose levels. Thus the small values of r^2 in Tables II–IV reflect between-subject variability as much as deviations from the linear dose–bioavailability relations.

Tables II–IV list the t-statistic, r^2, and mean observed value at each dose level. For those pharmacokinetic variables for which the regression was significant (t-statistic >2), the slope and intercept of the regression line and the mean of the pharmacokinetic variable predicted from the linear regression are also reported. By comparing the observed and predicted means at each dose level, it is possible to get some idea of how closely the means fit the computed linear relations. Space limitations prohibit illustrating all these relations, but the 2-hr. serum concentrations for the three preparations are shown in Figs. 2–4. The use of the 2-hr. serum concentrations to illustrate the methods used does not imply that these values have any special therapeutic importance.

Equivalence Considerations—As described in the *Theoretical* section, for appropriate variables the dose of clindamycin ester equivalent to a 150-mg. dose of clindamycin hydrochloride was determined, using the composite means from six studies in adults (6) as the standard of comparison. This comparison was also carried out with the data from Study 1 reported here to see how closely this study fit the overall results from six studies of 150 mg. clindamycin hydrochloride.

Figure 5 illustrates graphically how the equivalent dose was computed. The mean 2-hr. serum concentration is plotted against clindamycin palmitate dose. The arrowed line enters the graph at the composite mean of the 2-hr. serum concentrations observed in the six clindamycin hydrochloride studies (1.94 mcg./ml.). The clindamycin palmitate dose level (206 mg.) at which this arrowed line intercepts the regression line is the "equivalent dose"; this is the estimated dose of clindamycin palmitate that yields the same average value for the pharmacokinetic variable as does 150-mg. clindamycin hydrochloride. The equivalent dose could be computed only for those variables for which the regression with dose was significant (t-statistic >2); other variables are designated N.R. in the tables.

Clindamycin Hydrochloride (Table II)—The relation of the 2-hr. serum concentration to dose (Fig. 2) is representative of all the serum concentrations in that at all sampling times the mean serum level after the 300-mg. dose was less than predicted from the line fitted through all the data. Even though the means did not lie exactly on a straight line, as noted previously, the quadratic component of the regression line was not significant. This is because the variation of the individual observations about the means was greater than the deviations of the means from a straight line. In Study 1 the different dose levels were administered to different panels of subjects at different times. The deviation of the mean responses in the 300-mg. dose group cannot be explained.

At all serum sampling times, there was a highly significant relation between dose and serum level, as evidenced by the large values of the t-statistic. The slopes of the regression lines were quite similar. Because of between-subject variation in serum concentrations at each dose level, no more than 59% ($r^2 = 0.59$) of the variance at any sampling time could be ascribed to changes in dose. Serum concentrations increased only about half as much as dose; *i.e.*, when the dose increased by 100%, the mean serum levels increased by about 50%.

Three of the model parameters that should not be dose dependent, K_A, $E(^1/_2)$, and volume of distribution, did show a significant regression with dose (t-statistics 2.86, 2.17, and 4.29, respectively). As noted previously (6), because of the rapid absorption of clindamycin hydrochloride, it is difficult to obtain enough prepeak serum concentration values to make good estimates of K_A. In all of our clindamycin hydrochloride studies, estimates of K_A have

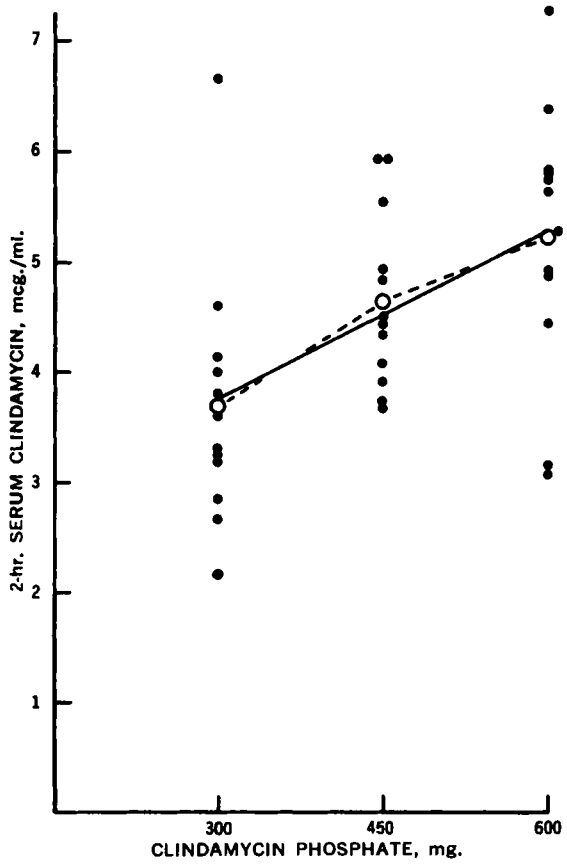


Figure 4—*Dose-bioavailability relation: 2-hr. serum clindamycin concentration after clindamycin phosphate. Key: ——, predicted means from linear model; O- - -O, observed means; and ●, individual values.*

had large standard deviations; K_E is much easier to estimate and has had much smaller standard deviations. While $E(^1/_2)$ tended to increase with dose level for the first dose of clindamycin hydrochloride, after a postequilibrium dose on a *q6h* regimen, $E(^1/_2)$ values did not differ significantly, having mean values of 3.58, 3.12, and 3.32 hr. with 150-, 300-, and 450-mg. regimens, respectively (6). The changes in K_A, $E(^1/_2)$, and volume with changes in the first dose are unexplained but could reflect inappropriateness of the model. Compartmental models of drug kinetics are based on assumptions of linear kinetics. There are several possible causes of nonlinear kinetics; DiSanto and Wagner (17) showed that if one of these, tissue binding, is significant, then the use of a compartmental model will lead to the erroneous conclusion that some of the kinetic parameters change with dose.

The two model parameters that should increase with dose, estimated peak and area under the serum concentration–time curve, did so but, like the serum levels, they did not increase in the same proportion as did dose.

The computed equivalent doses in Table II compared Study 1 with the composite results in six studies of clindamycin hydrochloride. All of these equivalent doses should be close to 150 mg., of course, and any deviation indicates that in some respect this study is different from the average results. Absorption was slower in this study, as reflected in higher equivalent doses at early sampling times and lower ones at later sampling times. That the average total absorption in this study was similar to the overall experience is indicated by the equivalent doses to attain the area under the curve and estimated peak (139 and 174 mg., respectively). The equivalent dose was 153 mg. for volume of distribution.

Clindamycin Palmitate (Table III)—The relation between dose and 2-hr. serum level (Fig. 3) is representative of all the clindamycin palmitate variables. Mean values for the four doses lie very close to the regression line computed from all the data. Despite this good fit, variability within each treatment group was great enough that difference in dose accounted for less than 50% of the variation.

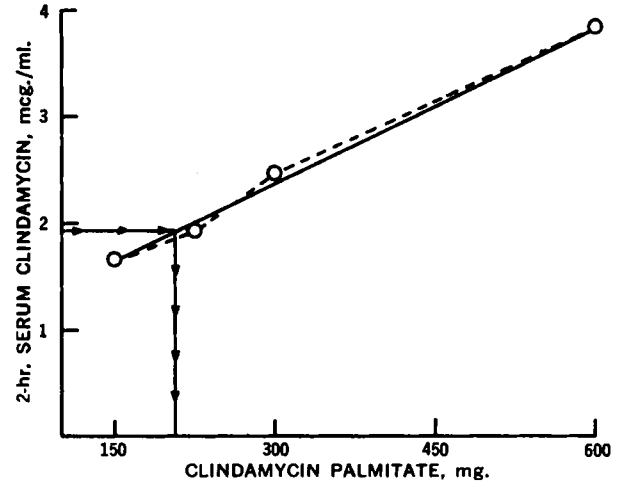


Figure 5—*Estimated dose of clindamycin palmitate required to produce 2-hr. serum clindamycin bioactivity equivalent to that produced by 150 mg. clindamycin hydrochloride in six studies. Key: ——, linear dose–response (predicted means); and O- - -O, observed mean responses. Equivalent dose = 206 mg. clindamycin palmitate.*

Most of the model parameters showed the expected linear relation with dose; rate constants, half-lives, time of peak, and time lag were all independent of dose, while peak and area were dose dependent. Volume, however, did increase significantly with dose (t-statistic, 2.95). Until more information about the distribution and metabolism of clindamycin and about the correctness of the model is available, any explanation for this remains speculative. As noted previously, the volume term in the model includes F, the fraction of dose absorbed. In the 225/300-mg. crossover group, the volume estimate was greater after the lower dose than after the higher dose.

The equivalent doses calculated for clindamycin palmitate illustrate that it is absorbed more slowly than is clindamycin hydrochloride. Equivalent doses are more than double 150 mg. at early serum sampling times but only about one-third larger than 150 mg. at later times. The lower peak levels are reflected in an equivalent dose of 278 mg. to achieve the same peak. However, the equivalent dose (177 mg.) computed for area under the serum curve suggests that total absorption of clindamycin is about the same after the two preparations.

Estimating equivalent doses was a primary purpose in designing Study 2, and the information proved helpful in predicting appropriate dosages for clinical trials with this compound.

Clindamycin Phosphate (Table IV)—Although area under the serum concentration curve almost doubled with a doubling of clindamycin phosphate dose, serum concentrations increased only by about 50% when the dose was doubled. Again the linear dose–bioavailability model, although it fits the serum concentration–time curves very well, dose not completely describe the kinetics of the drug. Although time of peak and time lag had statistically significant dose–bioavailability relations, the estimated equivalent doses are meaningless. Since estimation of absorption of the intramuscular dose is confounded by estimation of rate of hydrolysis of the ester to clindamycin, the absorption rate constant K_A and half-life $A(^1/_2)$ were not included in this analysis.

The delayed peak and flatter, higher serum clindamycin curve after intramuscular clindamycin phosphate injection are reflected in the calculated equivalent doses. As expected from inspection of the curves, calculation of equivalent doses for serum levels at individual sampling times did not yield useful information. However, the equivalent dose for area under the serum concentration–time curve suggests that nearly twice as much clindamycin is absorbed into the circulation from clindamycin phosphate given intramuscularly as from clindamycin hydrochloride given orally.

CONCLUSIONS

For clindamycin hydrochloride, clindamycin palmitate, and clindamycin phosphate, the dose–bioavailability relations for serum

clindamycin bioactivity are linear but not proportional. Means of the pharmacokinetic variables for the different dose levels lie on (or nearly on) a straight line, but the response does not double when the dose is doubled.

Within the dose ranges in the three studies described, the *average* effect of a dose can be predicted well. An individual's serum concentration cannot be predicted as precisely as the average; in no case in these studies did the regression of serum level with dose account for more than 60% of the total variability. In those situations where the between-subject variation could be removed, the regression of serum levels with dose accounts for as much as 84% of the remaining variability.

Analysis of the dose–bioavailability relations is one check on the validity of the one-compartment model as a model of clindamycin absorption and elimination. In general, those model parameters that should be dose related had significant regressions and those that should not change with dose had nonsignificant regressions. The exceptions, especially in the study of clindamycin hydrochloride, suggest that perhaps there is some nonlinearity in the kinetics of clindamycin.

Attempts to compute equivalent doses of the three preparations showed that it is not meaningful to talk about a single equivalent dose, even for compounds producing serum concentration curves as similar as those after clindamycin hydrochloride and clindamycin palmitate. The equivalent doses will be different for peak, area, *etc.* An equivalent dose analysis does provide some understanding of the similarities and differences of formulations.

APPENDIX

Tolerance Monitoring—There were no serious side effects or indications of toxicity in any of the studies. Tolerance of multiple dosing with clindamycin hydrochloride has been described elsewhere (6), but tolerance findings in Studies 2 and 3 have not. The following clinical laboratory determinations[9] were performed during screening and before and after dosing in both studies, except where indicated otherwise: complete blood count, complete urinalysis, serum alkaline phosphatase, serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum bilirubin, serum creatinine (Study 2), blood urea nitrogen, and serum creatine phosphokinase (CPK) (Study 3). In Study 2, two subjects developed mildly abnormal SGOT values (normal = <45 K units) after dosing with clindamycin palmitate. One, whose SGPT also became mildly abnormal, was found to have a history of heavy alcohol consumption and slightly elevated SGPT values (although his screening and pretreatment values were normal). The other subject, who had an extremely high CPK but normal SGPT, admitted indulging in strenuous activity; these findings indicated muscle as the source of SGOT elevation in this case. In Study 3, SGOT typically rose after intramuscular injection, along with CPK; SGPT, however, scarcely changed, suggesting muscle trauma as one source of the SGOT increase.

Vital signs (blood pressure, pulse, temperature, and respiration) were recorded before and after each dose. Physical examinations, performed during screening, were repeated after dosing, and in Study 3 audiometric examinations were conducted before and after dosing. Subjects were questioned about systemic side effects. In Study 2, one subject developed signs of a urinary tract infection. Symptoms admitted on repeated questioning were loose or watery stools in three, headache in six, nausea in two, vomiting in one, gas in two, rectal itching in one, and bad taste (1 hr. after dosing) in two. All were transient and most were mild, but one subject had moderate vomiting and loose stools after the 225-mg. dose and then nausea and watery stools after the 300-mg. dose a week later. In the placebo-controlled 600-mg. trial, one subject developed transient dizziness and nausea after drug and one had nausea after placebo. In Study 3, changes in stools (softer, more frequent, or loose stools or diarrhea) were reported in six, rectal itching in four, abdominal pain in one, heartburn and gas in one, and itching of back and buttocks in one. Audiometric evaluations showed no drug effect.

In Study 3 repeated subjective and objective evaluations of tolerance at the intramuscular injection sites indicated that the drug caused more discomfort than saline placebo. However, this was less severe and shorter lived than that reported after intramuscular clindamycin hydrochloride (11).

[9] All determinations were performed by the Clinical Research Laboratory.

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