Pharmacokinetic Evaluation of a Drug Interaction between Kaolin–Pectin and Clindamycin

K. S. ALBERT ˣ, K. A. DeSANTE, R. D. WELCH, and A. R. DiSANTO

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Abstract □ The effect of a kaolin–pectin antidiarrheal suspension on the bioavailability of orally administered clindamycin was evaluated by model-dependent pharmacokinetic techniques. Each subject's serum clindamycin concentration–time data in the absence of the kaolin–pectin suspension were fitted to a one-compartment open model with first-order absorption and lag time. The resulting disposition parameters were used to construct individual Wagner–Nelson absorption profiles, expressed as the cumulative relative fraction of clindamycin absorbed *versus* time following combined antidiarrheal–antibiotic therapy. For each subject, absorption persisted to varying degrees through 14 hr. On the average, the half-time for absorption was prolonged 20-fold (from about 16 min to more than 300 min). In contrast, extrapolation of the individual time courses of relative absorption to infinity revealed that the antidiarrheal had no effect on the extent of clindamycin absorption.

Keyphrases □ Kaolin–pectin suspension—effect on bioavailability of orally administered clindamycin in humans □ Clindamycin—orally administered, effect of kaolin–pectin suspension on bioavailability in humans □ Bioavailability—orally administered clindamycin, effect of kaolin–pectin suspension in humans □ Antidiarrheals—kaolin–pectin suspension, effect of bioavailability of orally administered clindamycin in humans □ Antibacterials—clindamycin, orally administered, effect of kaolin–pectin suspension on bioavailability in humans

That an antidiarrheal suspension containing kaolin and pectin[1] can irreversibly adsorb coadministered drugs *in vivo*, resulting in decreased bioavailability, was first documented by Wagner (1, 2). When a single oral dose of lincomycin was administered together with a dose of a kaolin–pectin suspension, the resulting serum antibiotic levels were reduced to one-tenth those obtained when the antibiotic was given alone (1, 2). Subsequent studies showed that concomitant kaolin–pectin and drug administration decreased the bioavailability of tetracycline (3, 4) and digoxin (5–7) but not of ampicillin (3) and warfarin[2], indicating that the drug interaction potential of the antidiarrheal was not absolute.

This report describes the effects of a kaolin–pectin suspension on the bioavailability of orally administered clindamycin when both products were given concomitantly. Although the antidiarrheal dramatically reduced the clindamycin absorption rate, it had no effect on the extent of drug absorption.

EXPERIMENTAL

Sixteen normal, nonobese adult volunteers, whose average age was 29 years (range of 23–51 years) and whose average weight was 69 kg (range of 57–94 kg), exhibited normal vital signs and selected laboratory parameters and were without any evidence of cardiac, renal, or GI abnormalities. The subjects did not receive any medication for 7 days, any antibacterial agents for 15 days, and any long-acting antibacterial medication (such as penicillin G benzathine) for 30 days prior to the study. During the study, volunteers received only the medication prescribed, with 7 days separating each administered treatment.

Subjects were fasted (food and beverage) from 10:00 pm the night before their allocated treatment to 4 hr after their medication. Smoking was permitted only if it was the subject's usual custom. Volunteers did not engage in strenuous and athletic activities during the days of drug administration.

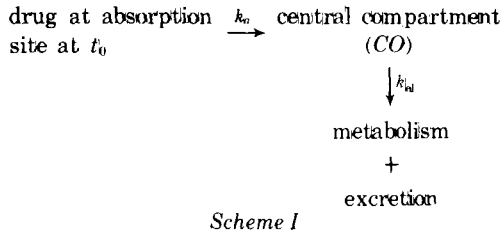
Each subject received a 150-mg dose of clindamycin capsules[3] with and without the kaolin–pectin suspension[4] (Treatments A and B, respectively) in crossover fashion (Table I). Serum samples were harvested at 0, 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, and 14.0 hr after the drug was given and frozen until assayed microbiologically for clindamycin-like activity (8).

RESULTS

Model-Independent Approach—The effect of the kaolin–pectin suspension on average serum clindamycin levels when both products were given concomitantly is summarized in Table II. At all sampling times except the 6-hr time point, there was a highly significant difference between treatment means. Furthermore, the average of individual peak serum antibiotic concentrations was reduced by 61%, with a concomitant delay in time to peak from 1.01 to 2.34 hr. Since the terminal slope of the serum concentration–time curve following the kaolin–pectin treatment appeared to be less steep for all subjects than when antibiotic was given alone, these results suggested that either the disposition of clindamycin was perturbed or the absorption of clindamycin was prolonged after coadministration of the antidiarrheal. Based on other drug interaction studies (1–7), however, the latter possibility seemed more plausible.

Table II also shows that the average area under the clindamycin serum–time curve through 14 hr (AUC) was reduced by 23% in the presence of the kaolin–pectin suspension. Attempts to estimate relative bioavailability by extrapolating individual AUC values to infinity were unsuccessful because of the erratic temporal change in clindamycin-like activity for Treatment A beyond the peak. Therefore, model-dependent pharmacokinetic techniques were utilized to assess the effect of the antidiarrheal on serum clindamycin concentrations.

Model-Dependent Approach—*Estimation of Pharmacokinetic Parameters for Treatment B*—The kinetics of absorption and disposition of clindamycin can be represented by a one-compartment open model with first-order absorption and lag time (possibly associated with stomach emptying) as shown in Scheme I:



Scheme I

where t_0 is lag time; k_a and k_{el} are the first-order rate constants for the designated processes; and CO is equivalent to FD/V, where F is the fraction of the dose, D, absorbed and V is the apparent volume of distribution for the central compartment including blood serum.

Model parameters estimated from individual serum concentration curves following Treatment B (clindamycin alone) by the technique described in the *Appendix* are shown in Table III. Good fits of the data to the model were obtained in all cases, as judged by low coefficients of

[1] Kaopectate (18% kaolin and 0.4% pectin), The Upjohn Co., Kalamazoo, MI 49001.

[2] The Upjohn Co., Kalamazoo, MI 49001, unpublished data.

[3] Cleocin Hydrochloride capsules, 150 mg, The Upjohn Co., Kalamazoo, MI 49001.

[4] Kaopectate Concentrate (27% kaolin and 0.6% pectin), The Upjohn Co., Kalamazoo, MI 49001.

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Table I—Dosage Schedule and Treatments [a]

Group	Subjects in Group	Treatment for Phase I	Treatment for Phase II
1	1–8	A	B
2	9–16	B	A

[a] Treatment A, 90 ml of Kaopectate Concentrate (Upjohn, lot 902CX) followed immediately by one Cleocin Hydrochloride 150-mg capsule (Upjohn, lot 033PA) administered orally with 90 ml of water; and Treatment B, one Cleocin Hydrochloride 150-mg capsule (Upjohn, lot 033PA) administered orally with 180 ml of water.

variation of the estimates and high correlation coefficients (r_1 and r_2^2) of observed *versus* model-predicted serum concentrations (see *Appendix* for further discussion). The mean parameter estimates reported here were in excellent agreement with previously reported average values (9, 10).

Estimation of Cumulative Relative Fraction Absorbed—On the presumption that the kaolin–pectin suspension had no effect on the disposition of clindamycin, the cumulative fraction of the dose absorbed of Treatment A relative to Treatment B, $[A^A(t)/V]/F^BD$, is given by (11):

$$\frac{A^A(t)}{V}\Big/F^BD = \frac{C^A(t) + k_{el}\int_0^t C^A(t)\,dt}{CO} \qquad \text{(Eq. 1)}$$

where $C^A(t)$ is the observed serum concentration following Treatment A, the integral is estimated by the trapezoidal rule, and k_{el} and CO are the parameter estimates from Treatment B (Table III).

Individual time courses of relative oral absorption constructed with the aid of Eq. 1 are shown in Table IV; the average data are depicted graphically in Fig. 1. Among individuals, relative absorption persisted to varying degrees through the 14th hr. On the average, at least 86% of the dose relative to Treatment B was absorbed within 14 hr following kaolin–pectin and clindamycin administration, the fractional value of which tested statistically significantly different from unity.

An attempt was made to estimate the relative fraction absorbed at infinite time by constructing a plot of the reciprocal of the cumulative relative fraction absorbed *versus* the reciprocal of time, fitting the points to an exponential curve, and determining the ordinate value at 1/time

Table II—Effect of the Kaolin–Pectin Suspension on Serum Clindamycin Levels

Parameter	Treatment Mean[a] A	Treatment Mean[a] B	Significance Level of Treatment Differences
Serum clindamycin level, μg/ml, at:			
0.00 hr	0.00	0.00	N.S.[b]
0.33 hr	0.41	1.13	$p < 0.025$
0.67 hr	0.74	2.34	$p < 0.0001$
1.0 hr	0.73	2.48	$p < 0.0001$
1.5 hr	0.71	2.13	$p < 0.0001$
2.0 hr	0.67	1.81	$p < 0.0001$
2.5 hr	0.66	1.53	$p < 0.0001$
3.0 hr	0.66	1.38	$p < 0.0001$
4.0 hr	0.64	1.12	$p < 0.0001$
5.0 hr	0.71	0.88	$p < 0.025$
6.0 hr	0.74	0.70	N.S.
8.0 hr	0.64	0.45	$p < 0.010$
10.0 hr	0.50	0.23	$p < 0.001$
12.0 hr	0.39	0.11	$p < 0.0005$
14.0 hr	0.30	0.06	$p < 0.0005$
Average of individual peak serum levels, μg/ml	1.06	2.77	$p < 0.0001$
Average time of individual peaks, hr	2.37	1.01	$p < 0.05$
Area under clindamycin serum–time curve through 14 hr, μg/ml × hr	8.05	10.5	$p < 0.0005$

[a] Treatment A, clindamycin and kaolin–pectin; and Treatment B, clindamycin alone. [b] Not significant.

Table III—Final Parameter Estimates for Treatment B (Clindamycin Alone) following NONLIN Fit to One-Compartment Model [a]

Subject	k_a, hr^{-1}	k_{el}, hr^{-1}	CO, μg/ml	Lag Time, hr
1	28.2	0.409	4.08	0
2	60[b]	0.333	3.54	0
3	9.94	0.263	1.91	0
4	3.82	0.270	4.39	0
5	1.67	0.315	1.93	0
6	1.14	0.270	2.90	0.0600
7	4.88	0.324	1.96	0
8	1.73	0.196	2.56	0.186
9	2.32	0.250	3.47	0
10	3.81	0.225	3.13	0.276
11	1.49	0.348	5.23	0
12	1.99	0.279	2.21	0
13	4.36	0.244	3.12	0.0696
14	6.11	0.303	3.30	0.285
15	2.82	0.256	3.49	0
16	2.46	0.370	2.69	0
Mean	5.12	0.291	3.12	0.0548
SD	6.78	0.0562	0.932	0.100

[a] Points weighted equally. [b] Excluded from mean estimate.

= 0[5]. Individual subject values are given in Table V. The average ratio, $F^A/F^B = 1.08$, which was not statistically significantly different from unity, indicates that the kaolin–pectin suspension had no effect on the extent of clindamycin absorption.

Estimation of Time for Half-Absorption—The time for half-absorption of clindamycin ($t_{1/2}^{abs}$) for Treatment B (clindamycin alone) can be calculated using:

$$(t_{1/2}^{abs})^B = 0.693/k_a \qquad \text{(Eq. 2)}$$

where k_a is the absorption rate constant listed in Table III for each subject. As shown in the *Appendix*, this value corresponds to the time when $A(t) = \frac{1}{2}A_\infty$, where $A(t)$ is the amount of drug absorbed at any given time, t, and A_∞ is the total amount of drug absorbed, FD. For Treatment A where relative bioavailability was estimated, $(t_{1/2}^{abs})^A$ may

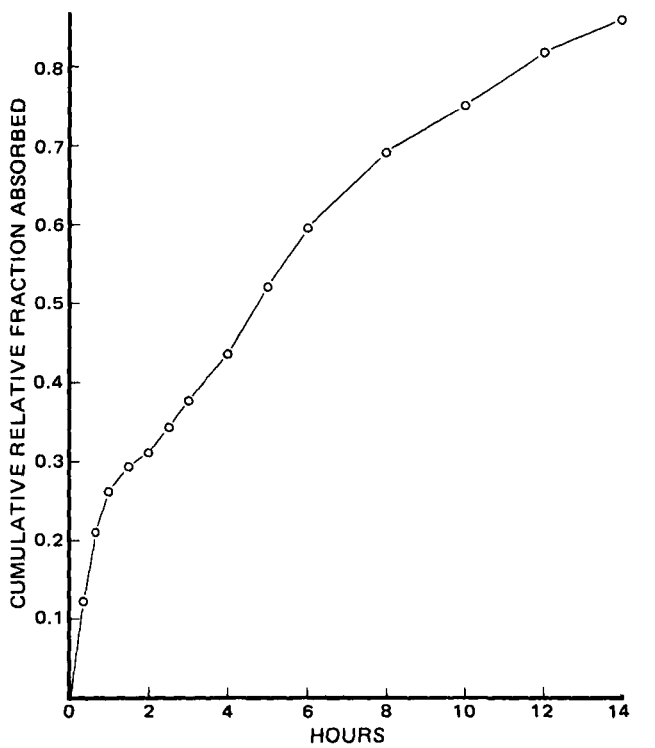

Figure 1—*Profile of the average time course of relative oral absorption for clindamycin.*

[5] As 1/time → 0, $1/[A^A(t)/V]/F^BD \to 0$, corresponding to $[A^A(t)/V]/F^BD \to \infty$. The range in r^2 was between 0.97 and 1.00.

Table IV—Relative Absorption Profiles of Clindamycin following Coadministration of the Kaolin–Pectin Suspension and Clindamycin

Subject	Cumulative Relative Fraction Absorbed[a]													
	0.33	0.67	1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	8.0	10.0	12.0	14.0
1	0	0.254	0.279	0.359	0.321	0.358	0.390	0.433	0.506	0.589	0.730	0.810	0.867	0.929
2	0.459	0.493	0.447	0.490	0.452	0.467	0.463	0.470	0.484	0.507	0.567	0.505	0.505	0.505
3	0	0.408	0.455	0.535	0.552	0.559	0.594	0.636	0.732	0.814	0.969	1.07	1.13	1.20
4	0.133	0.482	0.419	0.417	0.446	0.435	0.472	0.519	0.623	0.771	0.916	1.01	1.09	1.14
5	0	0	0	0	0	0.129	0.209	0.306	0.517	0.713	0.770	0.811	0.833	—
6	0.183	0.238	0.241	0.246	0.243	0.242	0.282	0.315	0.413	0.485	0.609	0.698	0.760	0.804
7	0	0	0.209	0.252	0.253	0.265	0.297	0.387	0.452	0.504	0.606	0.665	0.737	0.803
8	0	0	0.278	0.316	0.327	0.341	0.350	0.383	0.419	0.432	0.465	0.489	0.515	—
9	0.460	0.459	0.462	0.500	0.558	0.556	0.564	0.623	0.753	0.837	0.894	0.917	0.939	0.941
10	0	0	0	0	0	0.152	0.212	0.364	0.595	0.757	0.900	0.975	1.01	1.08
11	0	0.299	0.306	0.280	0.299	0.324	0.346	0.372	0.432	0.489	0.564	0.613	0.667	0.708
12	0	0	0	0	0.102	0.144	0.180	0.287	0.399	0.458	0.598	0.699	0.774	0.806
13	0	0.108	0.142	0.202	0.263	0.319	0.406	0.437	0.489	0.539	0.599	0.696	0.760	0.767
14	0.317	0.392	0.429	0.472	0.484	0.493	0.514	0.555	0.614	0.647	0.743	0.832	0.913	0.983
15	0.423	0.443	0.416	0.450	0.512	0.517	0.529	0.562	0.583	0.627	0.675	0.727	0.771	0.808
16	0	0.184	0.144	0.165	0.186	0.224	0.244	0.313	0.375	0.405	0.446	0.506	—	0.570
Mean[b]	0.123	0.235	0.264	0.293	0.312	0.345	0.378	0.435	0.524	0.598	0.690	0.751	0.818	0.860
SD	0.184	0.196	0.169	0.183	0.181	0.147	0.134	0.114	0.116	0.143	0.162	0.180	0.182	0.201

[a] Estimated by Eq. 1. [b] All mean values were statistically significantly different from unity as judged by the t-statistic, $t_{n-1} = (\bar{x} - 1)/(x_i - \bar{x})^2/[n(n-1)]$.

be interpolated from individual graphs of the cumulative relative fraction absorbed *versus* time data (Table IV) where $[A^A(t)/V]/F^BD = \frac{1}{2}F^A/F^B$. Individual values for $t_{1/2}^{abs}$ for both treatments are given in Table V. In every case, $t_{1/2}^{abs}$ was dramatically prolonged in the presence of the kaolin–pectin suspension. On the average, the time for half-absorption increased 20-fold, from about 16 min to more than 300 min.

DISCUSSION

The influence of the kaolin–pectin suspension on the bioavailability of orally administered clindamycin when both products were given concomitantly was evaluated by model-dependent pharmacokinetic techniques. On the assumption that the disposition of the antibiotic was unaltered by the kaolin–pectin suspension, it was found that the antidiarrheal had no effect on the extent of clindamycin absorption, but it markedly reduced its absorption rate. Hence, continuing absorption through 14 hr most likely accounted for the prolonged serum levels exhibited by clindamycin when coadministered with the antidiarrheal.

Structurally, clindamycin differs from lincomycin only at the 7-position because of the (*S*)-chloro substitution of the (*R*)-hydroxyl group of lincomycin. In terms of a drug interaction with the kaolin–pectin suspension, however, lincomycin appeared to be adsorbed irreversibly to components of the antidiarrheal, as judged by its 90% reduction in relative bioavailability (1, 2). In marked contrast, the continuing absorption of clindamycin beyond the last sampling time suggests that this antibiotic was desorbed from components of the antidiarrheal mixture such that its relative bioavailability was unaltered. Thus, 7-chloro substitution of the hydroxyl group of lincomycin dramatically influenced the *in vivo* behavior of the parent compound. This aspect of the study, as well as mechanistic considerations in general, is currently under investigation and will be reported subsequently.

Table V—Effect of the Kaolin–Pectin Suspension on the Rate and Extent of Clindamycin Absorption

Subject	Half-Time for Absorption, min		Relative Extent of Absorption, F^A/F^B
	Treatment A	Treatment B	
1	414	1.47	1.30
2	—	—	0.505
3	336	4.18	1.56
4	375	10.9	1.59
5	291	24.9	0.976
6	462	34.5	1.18
7	390	8.52	1.06
8	104	24.1	0.581
9	92.4	17.9	1.01
10	328	10.9	1.34
11	322	27.9	0.909
12	510	20.9	1.24
13	288	9.54	0.959
14	432	6.78	1.41
15	101	14.7	0.943
16	260	16.9	0.671
Mean	314[a]	15.6[a]	1.08[b]
% *SD*	41.5	60.4	30.0

[a] Statistically significantly different from one another by ANOVA. [b] Not statistically significantly different from unity by t test.

APPENDIX

Fit of Data to Model—Individual sets of serum concentration data following Treatment B (clindamycin alone) were fitted to the integrated equation describing the one-compartment open model with first-order absorption and lag time, *i.e.*:

$$C(t) = (CO)\left[\frac{k_a}{k_a - k_{el}}\right] e^{-k_{el}(t-t_0)} - e^{-k_a(t-t_0)} \qquad \text{(Eq. A1)}$$

where CO is equivalent to FD/V, F being the fraction of dose, D, that is absorbed and V being the volume of distribution of the central compartment which includes blood serum; k_a and k_{el} are the first-order absorption and elimination rate constants, respectively; t is clock time; and t_0 is lag time.

The nonlinear least-squares computer program NONLIN (12) was employed to estimate the parameters CO, k_a, k_{el}, and t_0; initial estimates were obtained with the program CSTRIP (13). The least-squares estimates of the parameters were obtained by minimizing the weighted sum of deviation squared, *i.e.*:

$$\sum_{i=1}^{n} w_i(\hat{C}_i - C_i)^2 \qquad \text{(Eq. A2)}$$

where w_i is the weighting factor taken to be equal to 1.0 in this case, $\hat{C}_i$ is the estimated concentration, and C_i is the observed concentration at time t_i.

Criteria used to assess the adequacy of the fit of the data to the model were: (*a*) r_1, the correlation coefficient for the linear regression of the model predicted *versus* the observed plasma concentration; (*b*) r_2^2, the coefficient of determination equivalent to the difference between the sum of observed concentrations squared and the sum of the deviations squared, divided by the sum of observed concentrations squared, *i.e.*, $[(\Sigma^2_{obs} - \Sigma^2_{dev})/\Sigma^2_{obs}]$; (*c*) the magnitudes of the coefficients of variation (CV%) of the estimated parameters; and (*d*) the lack of trends or regions of poor fit. Individual values for r_1, r_2^2, and CV% indicated that excellent fits were obtained in all cases[6].

Estimation of $t_{1/2}^{abs}$—As shown by Wagner and Nelson (11), the amount of drug absorbed having entered the volume of distribution V up to time t is given by:

$$\frac{A(t)}{V} = C(t) + k_{el}\int_0^t C(t)\,dt \qquad \text{(Eq. A3)}$$

The maximum value of the function is:

$$\frac{A_\infty}{V} = k_{el}\int_0^\infty C(t)\,dt \qquad \text{(Eq. A4)}$$

[6] Data available from the authors on request.

Since $A_\infty/V = FD/V$, the fraction absorbed is given by (11):

$$\frac{A(t)}{V}\Big/\frac{FD}{V} = \frac{C(t) + k_{el}\int_0^t C(t)\,dt}{k_{el}\int_0^\infty C(t)\,dt} \qquad \text{(Eq. A5)}$$

If two or more treatments are being compared at equal doses and if the assumption is made that disposition is invariant among treatments, the cumulative fraction absorbed of Treatment X relative to Treatment S can be expressed as:

$$\frac{A^x(t)}{F^sD} = \frac{C^x(t) + k_{el}\int_0^t C^x(t)\,dt}{CO^s} \qquad \text{(Eq. A6)}$$

where k_{el} is the elimination rate constant obtained from Treatment S; $CO^s = F^sD/V$, which is equivalent to $k_{el}\int_0^\infty C^s(t)\,dt$; and the superscripts refer to the designated treatments. At $t = \infty$, the asymptotic value of Eq. A6 is F^x/F^s. Therefore, the time for half-absorption relative to Treatment S, $(t_{1/2}^{abs})^x$, is the time when $A^x(t)/F^sD = \frac{1}{2}F^x/F^s$.

For Treatment S, if the assumption of first-order absorption is made:

$$\frac{A^s(t)}{V} = \frac{A_\infty{}^s}{V}(1 - e^{-k_a t}) \qquad \text{(Eq. A7)}$$

When $t = (t_{1/2}^{abs})^s$:

$$\frac{A^s(t)}{V} = \frac{1}{2}\frac{A_\infty{}^s}{V} \qquad \text{(Eq. A8)}$$

and:

$$e^{-k_a(t_{1/2}^{abs})^s} = 0.5 \qquad \text{(Eq. A9)}$$

where:

$$(t_{1/2}^{abs})^s = 0.693/k_a \qquad \text{(Eq. A10)}$$

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Influence of Kaolin–Pectin Suspension on Digoxin Bioavailability

K. S. ALBERT *x, J. W. AYRES ‡, A. R. DiSANTO *, D. J. WEIDLER ‡, E. SAKMAR ‡, M. R. HALLMARK ‡, R. G. STOLL *§, K. A. DeSANTE *, and J. G. WAGNER ‡

Received December 20, 1977, from **The Upjohn Company, Kalamazoo, MI 49001*, and ‡*The Upjohn Center for Clinical Pharmacology, University of Michigan, Ann Arbor, MI 48109.* Accepted for publication March 20, 1978. §Present address: Arnar-Stone Laboratories, Mt. Prospect, Ill.

Abstract □ The effect of a kaolin–pectin suspension on the bioavailability of orally administered digoxin was evaluated when both drugs were given concomitantly and when their time of administration was separated by 2 hr. Coadministration of the antidiarrheal with the cardiac glycoside delayed absorption of the latter and, at the same time, decreased by 62% the amount of drug absorbed. Intersubject variation in digoxin bioavailability also was increased more than twofold. When the kaolin–pectin suspension was given 2 hr before the cardiac glycoside, the digoxin absorption rate was not affected, although its relative extent of absorption was reduced by about 20%. In contrast, when the antidiarrheal was given 2 hr after digoxin, neither the rate nor the extent of absorption of the cardiac glycoside was perturbed. No change in the intersubject variability in digoxin bioavailability was noted whether the antidiarrheal was given 2 hr before or 2 hr after the cardiac glycoside.

Keyphrases □ Digoxin—GI absorption and bioavailability, effect of kaolin–pectin suspension in humans □ Kaolin–pectin suspension—effect on GI absorption and bioavailability of digoxin in humans □ Absorption, GI—digoxin, effect of kaolin–pectin suspension in humans □ Bioavailability—digoxin, effect of kaolin–pectin suspension in humans □ Cardiotonic agents—digoxin, GI absorption and bioavailability, effect of kaolin–pectin suspension in humans □ Antidiarrheals—kaolin–pectin suspension, effect on GI absorption and bioavailability of digoxin in humans

The decreased bioavailability of digoxin due to coadministration of an antidiarrheal suspension containing 18% kaolin and 0.4% pectin[1] was first reported by Binnion (1) after observing ineffective blood levels of cardiac glycoside in a patient who had taken the antidiarrheal at the same time as digoxin. Brown and Juhl (2) subsequently verified Binnion's findings in a crossover study employing 10 normal volunteers. When 60 ml of kaolin–pectin was given with 0.75 mg of digoxin, the area under the serum digoxin concentration–time curve through 8 hr was decreased by 41% while 6-day urinary recovery of digoxin was reduced by 42% relative to digoxin alone (2). Furthermore, terminal half-lives based on urinary excretion following the two

[1] Kaopectate, The Upjohn Co., Kalamazoo, MI 49001.

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