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

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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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Table I—Effect of the Kaolin–Pectin Suspension on Serum Digoxin Levels following Concomitant Administration of Both Drugs

Parameter	Treatment Mean[a] A	Treatment Mean[a] B	Significance Level of Treatment Differences[b]
Serum digoxin level, ng/ml, at:			
0.25 hr	0.00	0.34	N.S.[c]
0.50 hr	0.02	0.90	$p < 0.001$
0.75 hr	0.10	1.25	$p < 0.0001$
1.0 hr	0.19	1.20	$p < 0.0001$
1.5 hr	0.25	0.98	$p < 0.0001$
3.0 hr	0.15	0.64	$p < 0.0001$
5.0 hr	0.17	0.51	$p < 0.010$
7.0 hr	0.13	0.31	$p < 0.001$
9.0 hr	0.13	0.25	$p = 0.001$
12.0 hr	0.12	0.23	$p < 0.001$
16.0 hr	0.11	0.21	$p < 0.001$
24.0 hr	0.12	0.23	$p < 0.010$
36.0 hr	0.07	0.15	$p < 0.025$
48.0 hr	0.07	0.14	$p < 0.05$
AUC through 48 hr, ng/ml × hr	4.98	12.48	$p = 0.0001$
Average of individual peak serum levels, ng/ml	0.33	1.45	$p < 0.0001$
Time of individual peak serum levels, hr	3.16	0.86	$p < 0.010$

[a] Treatment A, digoxin and kaolin–pectin; and Treatment B, digoxin alone. [b] Based on results of analysis of variance. [c] Not significant.

Table II—Individual Estimates of Relative Absorption of Digoxin following Coadministration with the Kaolin–Pectin Suspension

Subject[a]	*AUC* through 48 hr, ng/ml × hr[b] A	*AUC* through 48 hr, ng/ml × hr[b] B	F^A/F^B [c]
1	13.2	13.2	1.00
2	3.74	17.1	0.219
3	1.88	9.33	0.202
4	3.35	12.1	0.277
5	1.16	12.3	0.094
6	10.5	19.2	0.547
7	4.73	12.5	0.378
8	2.50	10.8	0.231
10	1.30	6.64	0.196
11	4.72	12.0	0.393
12	7.76	12.2	0.636
Average	4.98	12.5	0.379
SD[d], %	78.8	27.1	69.0

[a] Subject 9 did not complete the study. [b] Treatment A, digoxin and kaolin–pectin; and Treatment B, digoxin alone. [c] Relative bioavailability calculated as the ratio of the *AUC* through 48 hr (see text for discussion). [d] $(SD/\bar{X}) \times 100$.

Table III—Effect of Concomitant Administration of Kaolin–Pectin Suspension on the Treatment Variability of Digoxin

Parameter	Intersubject Treatment Variability[a] A Low	A High	B Low	B High	*SD*, %[b] A	*SD*, %[b] B
Peak concentration, ng/ml	0.10	0.82	0.82	1.98	69.7	23.3
Time to peak, hr	0.75	7.0	0.50	0.50	75.8	31.6
AUC through 48 hr, ng/ml × hr	1.30	13.2	6.64	17.1	78.5	27.0

[a] Treatment A, digoxin and kaolin–pectin; and Treatment B, digoxin alone. [b] $(SD/\bar{X}) \times 100$.

treatments were similar, suggesting that the interaction probably affected only absorption and not disposition. Brown and Juhl (2) speculated that the decreased digoxin bioavailability could not be related entirely to physical adsorption to kaolin–pectin or to an alteration in gut transit time by the antidiarrheal.

This report describes the effect of a more concentrated antidiarrheal, containing 27% kaolin and 0.6% pectin[2], on the bioavailability of orally administered digoxin when both drugs were given concomitantly (Study 1) and when the antidiarrheal was given 2 hr before and 2 hr after the cardiac glycoside (Study 2). Although coadministration of both drugs markedly decreased the rate and extent of digoxin absorption, the interaction could be essentially circumvented by giving the medication at separated time intervals.

EXPERIMENTAL

Normal, nonobese adult volunteers exhibited normal vital signs and selected laboratory parameters and had no evidence of cardiac, renal, and GI abnormalities. Each subject underwent a complete physical examination before acceptance. Subjects did not receive any medication for 7 days or any enzyme-inducing drugs for 30 days before the study. During each study, subjects received only the medication prescribed, with 14 days separating each administered treatment.

Subjects were required to fast (food and beverage) from 10:00 pm the night before their allocated treatment until 4 hr after the medication. Except in Study 2, where meals were standardized, food and beverages were permitted *ad libitum* after the fasting period. Smoking was only permitted if it was the subject's usual custom. Volunteers did not engage in strenuous and athletic activities during the days of drug administration.

Blood was drawn at selected time intervals after each specified treatment. Serum was harvested from all blood during Study 1; plasma[3] was collected during Study 2. Twenty-four-hour urine specimens also were collected for Study 2. All samples were frozen immediately and kept frozen until assayed for digoxin by radioimmunoassay (3).

Study 1—Treatments A and B were randomly administered to 11 subjects whose average age was 29.7 years (range of 24–39 years) and whose average weight was 80.7 kg (range of 63.5–98.8 kg[4]).

Treatment A—Two 0.25-mg digoxin compressed tablets[5] and 90 ml of the kaolin–pectin suspension[6] were administered at zero time. The antidiarrheal mixture was administered first, with 90 ml of water being used to rinse the dispensing container and aid in swallowing the digoxin tablets.

Treatment B—Two 0.25-mg digoxin compressed tablets[5] were administered with 180 ml of water at zero time.

Serum samples were collected at 0, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 5.0, 7.0, 9.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hr after dosing.

Study 2—Treatments A–C were randomly administered to 15 subjects whose average age was 27.3 years (range of 21–34 years) and whose average weight was 73.5 kg (range of 64.0–86.2 kg).

Treatment A—Two 0.25-mg digoxin compressed tablets[5] were administered at zero time with 180 ml of water.

Treatment B—Ninety milliliters of the kaolin–pectin suspension[7] administered 2 hr before zero time, followed immediately by 90 ml of water to rinse the dispensing container. Then two 0.25-mg digoxin compressed tablets[5] were administered at zero time with 180 ml of water.

Treatment C—Two 0.25-mg digoxin compressed tablets[5] were administered at zero time. Then 90 ml of the kaolin–pectin suspension[7] was administered 2 hr after zero time, followed immediately by 90 ml of water to rinse the dispensing container.

[2] Kaopectate Concentrate, The Upjohn Co., Kalamazoo, MI 49001.
[3] Vacutainers, Becton-Dickinson No. 477, containing dry-filled edetate disodium as an anticoagulant.
[4] Twelve subjects began the study, but one subject dropped out after Phase I.
[5] Lanoxin, lot 776-0, supplied by Burroughs Wellcome, Research Triangle Park, N.C.
[6] Kaopectate Concentrate, lot 402CX, The Upjohn Co., Kalamazoo, MI 49001.
[7] Kaopectate Concentrate, lot 333A3L, The Upjohn Co., Kalamazoo, MI 49001.

Table IV—Effect of the Kaolin–Pectin Suspension on Plasma Digoxin Levels following a Dosing Interval of 2 hr between Drugs

Parameter	Treatment Average[a] A	B	C	Level of Significance	Significance Level of Treatment Differences[b] B *versus* A	C *versus* A	B *versus* C
Plasma digoxin level, ng/ml, at:							
0.25 hr	0.31	0.18	0.33	N.S.[c]	–	–	–
0.5 hr	1.05	0.81	1.08	N.S.	–	–	–
0.75 hr	1.50	1.23	1.57	N.S.	–	–	–
1.0 hr	1.53	1.40	1.70	N.S.	–	–	–
1.5 hr	1.31	1.06	1.23	N.S.	–	–	–
3.0 hr	0.73	0.58	0.64	$p < 0.025$	+	–	–
5.0 hr	0.48	0.42	0.39	$p < 0.025$	–	+	–
7.0 hr	0.39	0.33	0.31	$p < 0.005$	+	+	–
9.0 hr	0.34	0.32	0.32	N.S.	–	–	–
12.0 hr	0.29	0.24	0.23	$p < 0.01$	+	+	–
24.0 hr	0.26	0.23	0.22	$p < 0.05$	–	+	–
48.0 hr	0.18	0.15	0.16	N.S.	–	–	–
72.0 hr	0.13	0.11	0.11	$p < 0.025$	+	–	–
96.0 hr	0.08	0.07	0.07	N.S.	–	–	–
Average of individual peak plasma levels, ng/ml	1.71	1.53	1.81	N.S.	–	–	–
Time of individual peak plasma levels, hr	1.02	0.93	0.88	N.S.	–	–	–
AUC through 96 hr, ng/ml × hr	21.8	18.4	18.8	$p < 0.01$	+	+	–
Amount excreted in urine through 24 hr, μg	85.6	70.4	87.1	N.S.	–	–	–
Elimination rate constant, hr^{-1}	0.018	0.020	0.020	N.S.	–	–	–
Half-life, hr	43.8	40.5	43.5	N.S.	–	–	–
Renal clearance, ml/min	144	136	165	N.S.	–	–	–

[a] Treatment A, digoxin alone; Treatment B, kaolin–pectin 2 hr before digoxin; and Treatment C, kaolin–pectin 2 hr after digoxin. [b] Tested only at the 0.05 level using Tukey's allowable difference, where (+) = $p \leq 0.05$ and (–) = $p > 0.05$. [c] Not significant.

To ensure adequate urine output, subjects were required to drink 360 ml of water upon arising in the morning.

Plasma samples were harvested at 0, 0.25, 0.50, 0.75, 1.0, 1.5, 3.0, 5.0, 7.0, 9.0, 12.0, 24.0, 48.0, 72.0, and 96.0 hr after drug administration. Urine specimens were collected for 24 hr before each treatment to serve as a control (−24–0 hr) and for the next 24 hr postdosing (0–24 hr).

RESULTS

Study 1—Administration of the kaolin–pectin suspension concomitantly with digoxin markedly reduced average serum levels of the cardiac glycoside at all sampling times (Table I and Fig. 1). The average of individual peak serum digoxin concentrations was depressed by 77% with a corresponding delay in the average time to peak (Table I).

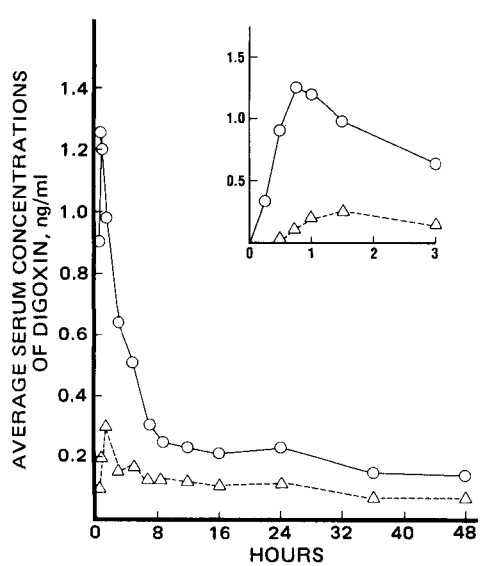

Figure 1—*Effect of the kaolin–pectin suspension on serum digoxin levels following concomitant administration of both drugs. Insert shows expanded 0–3-hr data. Key: ○, digoxin alone; and △, digoxin plus kaolin–pectin.*

These results suggested that the antidiarrheal mixture decreased the absorption rate of digoxin. In addition, average areas under the serum digoxin concentration–time curve through 48 hr were reduced from 12.5 to 4.98 ng/ml × hr, indicative of a 62% decrease in the relative amount of drug absorbed (Table II)[8]. Table III illustrates that more than a twofold increase in the intersubject treatment variability in digoxin bioavailability also resulted when the cardiac glycoside was given with the antidiarrheal.

Study 2—The effect of the kaolin–pectin suspension on plasma digoxin concentrations when the dosing of both products was separated by 2 hr is summarized in Table IV and Fig. 2. Through the first 1.5 hr, no significant differences among treatment average plasma levels were found. Since the average of individual peak plasma digoxin levels of 1.71, 1.53, and 1.81 ng/ml following Treatments A, B, and C, respectively, or their corresponding times to peak of 1.02, 0.93, and 0.88 hr, respectively, did not test significantly differently, these results suggested that the ad-

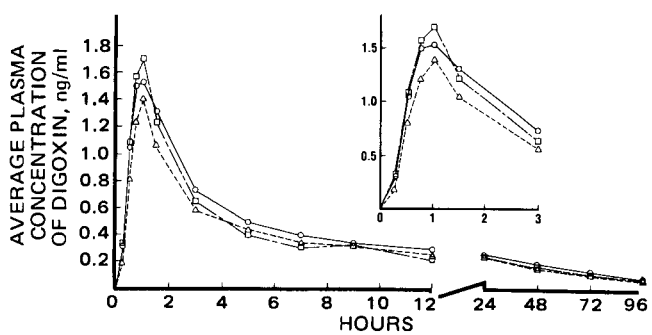

Figure 2—*Effect of the kaolin–pectin suspension on plasma digoxin levels following a dosing interval of 2 hr between drugs. Insert shows expanded 0–3-hr data. Key: ○, digoxin alone; △, kaolin–pectin 2 hr before digoxin; and □, kaolin–pectin 2 hr after digoxin.*

[8] It was impossible to estimate the terminal slope for all subjects since blood was not collected for a long enough time. Hence, the *AUC* through 48 hr was used to estimate relative bioavailability.

Table V—Individual Estimates of Relative Absorption of Digoxin when Given before or after the Kaolin–Pectin Suspension [a]

Subject	$\dot{V}_{cl,r}$, ml/min [b]			AUC_∞, ng/ml × hr [c]			Bioavailability Ratios [d] F^B/F^A			F^C/F^A		
	A	B	C	A	B	C	I	II	III	I	II	III
1	208	127	145	27.1	26.1	24.2	0.709	0.588	0.963	0.710	0.623	0.893
2	156	143	188	26.7	28.9	20.8	1.04	0.992	1.08	0.859	0.939	0.779
3	178	134	174	18.2	15.0	19.0	0.750	0.620	0.824	1.04	1.02	1.04
4	98.1	186	172	31.2	27.6	19.7	1.18	1.68	0.885	0.806	1.11	0.631
5	153	106	146	24.8	24.8	22.1	0.860	0.613	1.00	0.873	0.850	0.891
6	140	120	143	25.0	20.0	23.1	0.752	0.686	0.800	0.932	0.944	0.924
7	92.4	178	157	31.5	25.6	30.2	1.08	1.57	0.813	1.19	1.63	0.959
8	155	150	279	22.8	24.5	26.0	1.06	1.04	1.08	1.53	2.05	1.14
9	146	63.7	195	39.1	21.4	18.5	0.336	0.239	0.547	0.582	0.632	0.473
10	181	158	192	22.4	29.0	19.4	1.22	1.13	1.30	0.892	0.919	0.866
11	113	120	95.5	32.4	26.2	36.5	0.831	0.859	0.809	1.05	0.952	1.13
12	125	130	197	27.3	9.05	18.4	0.337	0.345	0.332	0.833	1.06	0.674
13	117	134	143	26.3	28.5	25.5	0.845	0.902	0.787	0.784	0.861	0.704
14	95.1	141	86.9	22.6	15.7	25.2	0.781	1.03	0.695	1.09	1.02	1.12
15	211	146	167	21.7	15.0	25.3	0.574	0.478	0.691	1.03	0.923	1.17
Mean,	144	136	165	27.2	22.5	23.6	0.824	0.857	0.840	0.947	1.04	0.892
SD, % [e]							32.7	47.5	27.7	23.8	34.8	23.4
t-Value							2.54	1.37	2.65	1.37	0.380	1.98
Significance level							$p < 0.05$	$p > 0.10$	$p < 0.02$	$p > 0.10$	$p > 0.25$	$p > 0.10$

[a] Treatment A, digoxin alone; Treatment B, kaolin–pectin 2 hr before digoxin; and Treatment C, kaolin–pectin 2 hr after digoxin. [b] Renal clearance calculated as the ratio of the amount of digoxin excreted in the urine in 24 hr to the AUC through 24 hr. [c] Area through infinity estimated by trapezoidal rule through 96 hr and classical extrapolation techniques beyond 96 hr. [d] Assumption I, nonrenal clearance is constant; Assumption II, renal and nonrenal clearances change proportionally; and Assumption III, plasma clearance is constant. [e] $(SD/\bar{X}) \times 100$.

ministration of the kaolin–pectin suspension either 2 hr before or 2 hr after digoxin had no effect on the absorption rate of the cardiac glycoside. In contrast, mean areas under the plasma digoxin concentration–time curve through 96 hr were significantly depressed relative to Treatment A by 16% for Treatment B and 14% for Treatment C (Table IV). These results parallel the significant differences among treatment average plasma levels beyond 1.5 hr that were observed.

Table IV also gives treatment average elimination half-lives, renal clearances, and 24-hr urinary recoveries of digoxin. The kaolin–pectin suspension did not perturb these parameters, suggesting that the antidiarrheal had no effect on the mean renal elimination of digoxin.

Observed plasma levels and urinary recovery of digoxin are functions not only of the drug absorption and renal elimination rates, as already delineated, but also of the extent of drug absorption and the effects of the kaolin–pectin suspension on absorption. An estimate of this influence can be made utilizing the model-independent method of Kwan and Till (4). This technique, which uses plasma level and urinary recovery data together, is based on the determination of renal clearance and assumptions regarding the constancy of nonrenal clearance among treatments.

Individual assessments of relative absorption, with the assumptions that nonrenal clearance for a given subject was constant and that individual values for nonrenal clearance varied in proportion to observed changes in renal clearance (4), are given in Table V. Included for comparison are individual relative bioavailability estimates based on the assumption of constant plasma clearance. This assumption ignores observed differences in renal clearance on the premise that the nonrenal components of plasma clearance are compensating. Equations appropriate to the methods, as applied here, are given in the *Appendix*.

When the kaolin–pectin suspension was given 2 hr before digoxin, the average ratio F^B/F^A of about 0.8 was significantly less than unity with the assumption that nonrenal clearance was either constant (Assumption I) or compensating (Assumption III) (Table V). When renal and nonrenal clearances change in proportion to one another (Assumption II), 10 out of 15 subjects had ratios less than 1.0. These results suggested that when the antidiarrheal dose preceded the cardiac glycoside dose, absorption was reduced by about 20% (Table V). In contrast, when the kaolin–pectin suspension was administered 2 hr after digoxin, absorption was not appreciably perturbed, as evidenced by the average ratio F^C/F^A not being different from 1.0 regardless of which assumption was utilized.

The effect of the antidiarrheal mixture on the intersubject treatment variability in the bioavailability of digoxin is summarized in Table VI. The ranges of coefficients of variation of the tested parameters were similar among the three treatments, suggesting no change in the treatment variability of digoxin whether the kaolin–pectin suspension was given 2 hr before or 2 hr after the cardiac glycoside.

DISCUSSION

When both drugs were given concomitantly, the digoxin absorption rate was delayed and, based on 48-hr areas under the concentration–time curve, the relative extent of digoxin absorption was reduced by 62%. In contrast, the interaction was virtually eliminated by giving the antidiarrheal 2 hr after the cardiac glycoside; administration of the kaolin–pectin suspension 2 hr before the cardiac glycoside did not perturb the rate of digoxin absorption, although the relative extent of its absorption was reduced by about 20%.

Apparently, a 2-hr dosing interval, within the parameters of rational therapy, exists for the kaolin–pectin suspension and oral digoxin administration, particularly since digoxin is given chronically once a day.

Table VI—Effect of Kaolin–Pectin Suspension on the Treatment Variability of Digoxin following a Dosing Interval of 2 hr between Drugs

Parameter	Intersubject Treatment Variability [a] A Low	A High	B Low	B High	C Low	C High	SD, % [b] A	B	C
Peak concentration, ng/ml	1.04	2.57	0.83	2.86	0.89	2.29	28.6	34.0	24.1
Time to peak, hr	0.50	1.50	0.50	1.50	0.50	1.00	32.8	31.2	18.1
AUC through 96 hr, ng/ml × hr	16.4	29.2	8.57	2.50	12.9	22.7	19.6	25.3	14.1
24-hr urinary recovery, μg	65.5	119	50.5	109	62.5	145	19.2	17.8	13.1
Half-life, hr	14.9	69.7	12.8	77.4	11.1	81.9	31.4	41.3	42.5
Renal clearance, ml/min	92.4	211	63.7	186	95.5	279	26.5	21.5	27.5

[a] Treatment A, digoxin alone; Treatment B, kaolin–pectin 2 hr before digoxin; and Treatment C, kaolin–pectin 2 hr after digoxin. [b] $(SD/\bar{X}) \times 100$.

Since the half-life of the cardiac glycoside is about 40 hr, accumulation occurs. Therefore, the effect of the antidiarrheal mixture on a given dose of digoxin with respect to steady state would be considerably less than that reported herein after a single dose. The influence of the kaolin–pectin suspension on steady-state plasma digoxin levels is under investigation.

The decreased digoxin bioavailability after coadministration with the kaolin–pectin suspension appears to be related to a mechanism involving physical adsorption. This conclusion is supported by *in vitro* experiments that show that the antidiarrheal mixture removes digoxin from solution[9]. The mechanism probably also involves differences in gut transit time between digoxin and the kaolin–pectin suspension, with the latter persisting for a longer time in the GI tract. This hypothesis is consistent with the observation that when the antidiarrheal was administered before the cardiac glycoside, an interaction occurred; no such interaction was noted, however, when the antidiarrheal was given after the cardiac glycoside. Hence, mechanisms involving physical absorption and alterations in gut transit time appear to explain the interaction of the kaolin–pectin suspension with digoxin, a conclusion not totally supported by others (2).

APPENDIX

In accordance with the model-independent method of Kwan and Till (4), the following equation was derived to estimate relative bioavailability under the assumption of constant nonrenal clearance:

$$\frac{F^x}{F^s} = \frac{AUC_\infty{}^x}{AUC_\infty{}^s} - \frac{AUC_\infty{}^x}{D^x}(\dot{V}^s_{cl,r} - \dot{V}^x_{cl,r}) \qquad \text{(Eq. A1)}$$

where F is the fraction of the dose, D, that reaches the general circulation unchanged; $\dot{V}_{cl,r}$ is renal clearance; AUC_∞ is the area under the plasma concentration–time curve through infinity; and the superscripts x and s refer to test treatment and standard treatment, respectively.

For the case of nonrenal clearance changing in proportion to observed changes in renal clearance:

$$\frac{F^x}{F^s} = \frac{AUC_\infty{}^x}{AUC_\infty{}^s}\left(\frac{\dot{V}^x_{cl,r}}{\dot{V}^s_{cl,r}}\right) \qquad \text{(Eq. A2)}$$

With the assumption of constant plasma clearance:

$$\frac{F^x}{F^s} = \frac{AUC_\infty{}^x}{AUC_\infty{}^s} \qquad \text{(Eq. A3)}$$

This equation ignores observed changes in renal clearance by assuming that nonrenal clearance compensates.

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

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Pentobarbital Absorption from Capsules and Suppositories in Humans

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Abstract □ Serum pentobarbital levels following administration of the sodium salt as a 100-mg capsule orally and as two 120-mg suppository formulations (A and B) rectally were measured. From these data and previously determined kinetic constants after intravenous administration, the absorption rates and bioavailability of pentobarbital from each dosage form were determined. All three dosage forms were 100% absorbed. Peak serum pentobarbital levels occurred at 1, 4, and 10 hr for the capsule, Suppository A, and Suppository B, respectively. *In vitro* studies agreed with the serum data in that Suppository A released drug in an *in vitro* aqueous pH 7.4 system at a much greater rate than Suppository B. The capsule and Suppository A both appeared to be absorbed by simple first-order processes; however, Suppository B had a complex absorption pattern, which was modeled using sequential zero-order and first-order absorption.

Keyphrases □ Pentobarbital—absorption rates and bioavailability from capsules and suppositories in humans □ Absorption rates—pentobarbital from capsules and suppositories in humans □ Bioavailability—pentobarbital from capsules and suppositories in humans □ Hypnotic-sedatives—pentobarbital, absorption rates and bioavailability from capsules and suppositories in humans

Studies in rats on the oral absorption of phenobarbital demonstrated that food decreases the rate but not the extent of absorption (1). This delayed but complete absorption markedly influenced the pharmacological responses observed. In humans, the absorption rate of orally administered pentobarbital was decreased in the presence of food (2). It can be expected that the alteration of absorption of barbiturates into the blood by any factor (*e.g.*, food, dosage formulation, or route of administration) will influence desired pharmacological responses.

This investigation compares the rectal and oral absorption of pentobarbital in human subjects and evaluates two different suppository vehicles to determine the influence of formulation on the rectal absorption of pentobarbital.

EXPERIMENTAL

Chemicals—The following drug products were used: pentobarbital sodium capsules[1] containing 100 mg of pentobarbital sodium; pentobarbital suppositories, A and B[2], prepared with two different vehicles, containing 120 mg of pentobarbital sodium[2]; and mephobarbital NF. All chemicals were reagent grade. Suppository A contained a synthetic base, and Suppository B contained a cocoa butter–spermaceti base.

[1] Nembutal Sodium, lot 09-091, Abbott Laboratories.

[2] Supplied by Abbott Laboratories.

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