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[9] The Upjohn Co., Kalamazoo, MI 49001, unpublished data.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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Table I—Serum Pentobarbital Levels (Micrograms per Milliliter) following Oral Administration of Pentobarbital Sodium 100-mg Capsules

Hour	Subject										
	PIM	BG	RB	GB	TB	LM	HS	KD	SD	RM	Mean + *SD*
0.5	1.57	0.76	1.28	1.63	1.13	0.54	1.57	0.96	0.67	1.07	1.12 ± 0.39
1.0	(1.60)[a]	0.87	1.18	1.69	1.50	0.42	2.71	1.19	1.39	1.17	1.37 ± 0.60
1.5	1.66	0.57	1.12	0.50	1.46	1.46	1.49	0.99	1.45	1.13	1.18 ± 0.40
2.5	1.36	0.52	0.59	0.64	1.08	0.94	1.23	1.00	1.09	0.84	0.93 ± 0.28
4.0	1.13	0.70	0.52	0.75	0.77	(0.90)	0.94	0.74	1.08	0.73	0.83 ± 0.19
6.0	0.75	0.71	0.50	(0.74)	0.66	0.89	0.88	0.57	0.33	0.68	0.67 ± 0.17
8.0	(0.70)	0.22	0.44	0.74	0.63	0.56	1.24	0.72	0.51	1.08	0.68 ± 0.30
24.0	0.67	0.43	0.33	(0.70)	0.49	0.36	0.79	0.70	0.73	0.70	0.59 ± 0.17

[a] Parentheses equal approximate value.

Table II—Serum Pentobarbital Levels (Micrograms per Milliliter) following Rectal Administration of Pentobarbital Sodium 120-mg Suppositories

Hour	Subject						
	LN	GB	BG	RB	RM	LM	Mean + *SD*
				Suppository A			
0.5	0.221	0.109	0.295	0.346	0.310	0.300	0.263 ± 0.086
1.0	0.354	0.319	0.612	0.714	0.620	0.614	0.537 ± 0.162
1.5	0.566	0.596	0.714	0.968	0.661	0.679	0.696 ± 0.143
2.5	0.643	1.097	0.932	1.062	0.838	0.903	0.897 ± 0.164
4.0	0.820	1.280	1.015	0.956	0.897	0.932	0.982 ± 0.159
6.0	0.968	1.050	0.991	0.938	0.785	0.950	0.947 ± 0.089
8.0	1.121	0.932	0.944	0.885	0.720	0.897	0.915 ± 0.129
10.0	1.027		0.773			0.767	0.861 ± 0.148
12.0			0.743			0.749	(0.746)[a]
				Suppository B			
0.5	N.M.[b]	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.
1.0	N.M.	0.171	N.M.	0.087	N.M.	N.M.	(0.043)
1.5	0.048	0.230	0.039	0.133	0.083	0.056	0.099 ± 0.072
2.5	0.071	0.566	0.139	0.173	0.230	0.182	0.227 ± 0.174
4.0	0.483	0.661	0.291	0.225	0.679	0.444	0.464 ± 0.185
6.0	0.814	1.056	0.749	0.560	0.791	0.649	0.770 ± 0.169
8.0	0.897	1.156	1.103	0.944	0.784	0.826	0.952 ± 0.149
10.0		1.133		1.056	0.867		1.019 ± 0.232
12.0		0.944		0.9991	0.761		0.899 ± 0.121

[a] Parentheses equal approximate value. [b] Not measurable.

Selection of Subjects—*Oral Study*—The 10 healthy male volunteers were 21 years or older and ranged in weight from 69.0 to 89.5 kg. Five of these volunteers participated in the suppository study.

Suppository Studies—The six healthy male volunteers were 21 years or older and ranged in weight from 69.0 to 89.5 kg. These volunteers had not consumed any drug substances for at least 1 week prior to the study. These subjects had participated in a previous study of intravenous pentobarbital pharmacokinetics. The intravenous, oral capsule, and rectal suppository studies all were conducted within 10 months.

Study Design—*Oral Study*—The 10 subjects fasted overnight and were given a single oral capsule containing 100 mg of pentobarbital sodium. No food or water, other than that taken with the capsule, was allowed until the 3rd experimental hr. Venous blood specimens (15 ml) were collected before dosing and at 0.5, 1.0, 1.5, 2.5, 4.0, 6.0, and 8.0 hr following capsule administration.

Suppository Studies—The six subjects were randomly divided into two groups of three subjects.In the first part of the crossover study, Group I volunteers were given Suppository A and Group II volunteers were given Suppository B. One week later, in the second part of the crossover study, the test was repeated and medications were reversed.

The studies began in the early morning following an overnight fast. Each subject was given a breakfast consisting of orange juice, two eggs, two slices of bacon, two slices of toast, and coffee with cream and sugar. After breakfast, each subject was given an enema. One suppository was administered 1 hr postenema. The subjects were not confined to bed, but strenuous activity was prohibited. The suppositories were retained by all subjects. Experimental timing began with suppository administration. Venous blood specimens (15 ml) were collected before dosing and at 0.5,

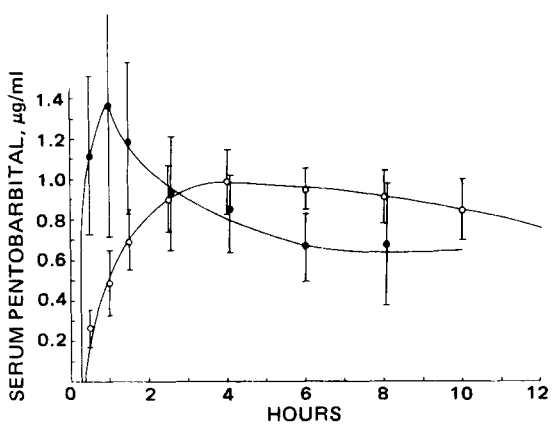


Figure 1—*Serum pentobarbital levels with standard deviations following oral administration to 10 subjects of 100 mg of pentobarbital sodium by capsule (○) and following rectal administration to six subjects of 120 mg by Suppository A (●).*

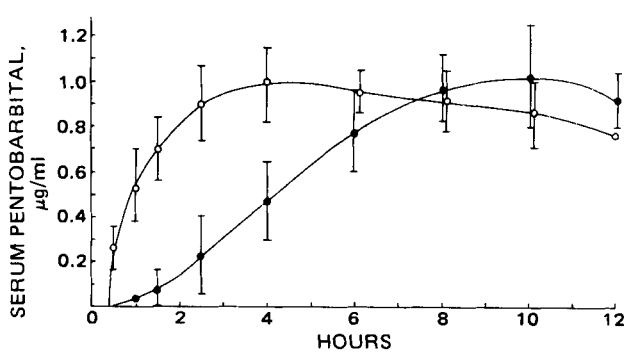
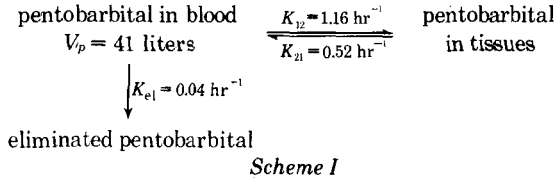


Figure 2—*Serum pentobarbital levels with standard deviations following rectal administration to six subjects of 100 mg by Suppository A (○) and Suppository B (●).*



Scheme I

1.0, 1.5, 4.0, 6.0, and 8.0 hr following suppository administration in the first part of the crossover. Analysis of the samples collected indicated that further samples should be taken. In the second part of the crossover, samples also were taken at 10.0 and 12.0 hr.

Assay of Serum Pentobarbital—The concentration of unmetabolized pentobarbital in serum was determined by GLC as previously described (2).

***In Vitro* Release Studies**—The apparatus used in the *in vitro* studies consisted of a 38-mm o.d. × 10-cm glass tube centered in a 600-ml beaker and immersed 5.08 cm (2 in.) below the fluid surface. A 500-ml volume of pH 7.5 buffer at 50° was used. Sealed to the bottom of the tube was a 12-mesh stainless steel screen to allow for more uniform agitation. After the fluid reached the desired temperature, a suppository was placed in the tube, and the fluid was stirred with a 2.54-cm magnetic bar at 100 rpm.

Samples were taken every 5 min for the first 30 min and at 45, 60, and 90 min. These samples were diluted 1:6 with 1.5% ammonium hydroxide and assayed by UV spectroscopy at 240 nm.

RESULTS AND DISCUSSION

Serum pentobarbital levels following oral administration of 100 mg of pentobarbital sodium by capsule and rectal administration of 120 mg by Suppositories A and B are shown in Tables I and II and Figs. 1 and 2.

In a previous study (2) of five subjects, the average serum pentobarbital levels were determined following a 50-mg iv dose. From these data, the constants for pentobarbital distribution and elimination were calculated (2). The model employed and the appropriate constants are shown in Scheme I. The mean total clearance rate of pentobarbital was 1.64 liters/hr or 27.33 ml/min in these subjects.

Serum levels following oral administration of a 50-mg pentobarbital sodium capsule also were obtained after an overnight fast in the previous study (2). It was estimated that 100% of the 50-mg oral dose was absorbed. A time lag of 0.30 hr occurred prior to the onset of absorption, the absorption half-life was 0.35 hr (k_a = 2.00 hr^{-1}), and peak serum levels occurred 1.0 hr after dosing.

The absorption rate constant, k_a, for the 100-mg pentobarbital sodium capsule in the present investigation was calculated according to Loo and Riegelman (3) using the mean serum level data from the present investigation and the mean rate constants after intravenous administration from the previous study as already described. Mean data were employed since kinetic constants following intravenous administration were not available for all subjects. [Also, results from the previous study (2) indicated the same outcome when average data were used as compared to average parameters from individual data.] The k_a calculated by this method was 2.0 hr^{-1} with a lag time of 0.30 hr.

A comparison of the area under the curve (*AUC*) with the *AUC* from previously reported intravenous data in the same subjects (2) indicated 100% absorption from the 100-mg capsule. The theoretical line for these data shown in Fig. 1 was calculated using the mean rate constants from the previous study and the absorption rate constant of 2.0 hr^{-1}. From the good approximation of the data using these rate constants, it appears that

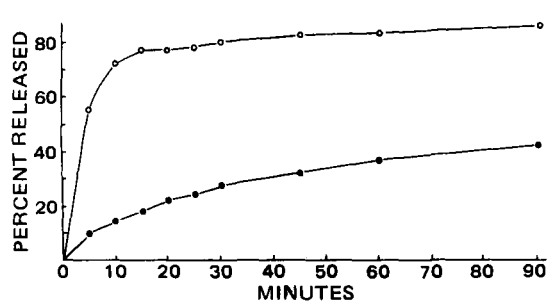


Figure 3—In vitro *dissolution of Suppository A* (○) *and Suppository B* (●) *in an aqueous pH 7.4 system.*

Table III—Absorption Characteristics of Pentobarbital Sodium from Oral and Rectal Dosage Forms

Formulation	Time of Peak Concentration, hr	Lag Time, hr	$t_{1/2}$, hr	*AUC*/Dose[a], hr/liter	F^b
50.0-mg Capsule[c]	1.0	0.3	0.35	0.630	1.11
100-mg Capsule	1.0	0.3	0.35	0.25	1.05
Suppository A	4.0	0.4	1.70	0.669	1.15
Suppository B	9–10	0.5	—[d]	0.767	1.33

[a] Values represent the mean of subjects who received all dosage forms and an intravenous injection (data from Ref. 2). [b] $(AUC_{form} \cdot dose_{iv}/AUC_{iv} \cdot dose_{form})$; intravenous data from Ref. 2. [c] Taken from Ref. 2. [d] Complex absorption pattern; see text.

no significant changes in parameters had occurred since the previous study.

Serum levels in six subjects following rectal administration of Suppositories A and B are shown in Table II and Figs. 1 and 2. The *AUC* for both suppositories was calculated from the mean data with the trapezoidal rule up to the last data point. The *AUC* from the last data point to infinity was estimated by dividing the plasma concentration at the last time point by the mean value of the slope of the elimination phase of the intravenous data (2). A comparison of these calculated *AUC* values with the *AUC* after intravenous administration, when corrected for difference in the doses, indicated that both suppositories were approximately 100% absorbed.

The data also were analyzed according to the method of Loo and Riegelman (3). However, the absorption of pentobarbital following administration of Suppository A was appreciably faster than that of Suppository B. Suppository A showed a peak serum level 4 hr after administration, and the absorption half-life was calculated to be 1.7 hr (k_a = 0.40 hr^{-1}). Suppository B showed a peak serum level approximately 9 or 10 hr after administration, and the serum curve could be fitted only when a complex absorption pattern [involving zero-order (k_0 = 0.07 μg/ml/hr) and first-order (k_1 = 0.35 hr^{-1}) processes] was assumed. The complex absorption pattern is most likely a result of the release characteristics of Suppository B.

Other models involving mixed zero- and first-order, pure first-order, and pure zero-order absorption processes were tested. However, none resulted in a better fit of the data. Without further data, no conclusions about the release and absorption rates from Suppository B can be made other than that the overall process was not simple first order.

The absorption characteristics for the oral and rectal dosage forms are shown in Table III. Table III and Fig. 1 illustrate that, although pentobarbital was efficiently absorbed after rectal administration, even the better formulation was absorbed more slowly than when the drug was administered by oral capsule.

The results of pharmacokinetic calculations from serum levels following administration of pentobarbital sodium indicate that:

1. The rate and extent of oral absorption following administration of 50- and 100-mg capsules are similar. The absorption half-life in each case was 0.35 hr, and each dose was totally absorbed.

2. Pentobarbital absorption after administration of rectal suppositories was influenced dramatically by product formulation. Both suppository products studied allowed total absorption of pentobarbital, but Suppository A give a peak serum level 4 hr after administration whereas Suppository B gave a peak serum level 9–10 hr after administration.

3. Oral absorption of pentobarbital sodium was faster than rectal absorption from the suppositories studied. As shown in Fig. 3, *in vitro* studies agreed with absorption estimates following suppository administration in that Suppository A released pentobarbital at a much faster rate than Suppository B in an *in vitro* aqueous pH 7.4 system.

Thus, the route of pentobarbital sodium administration as well as product formulation may markedly influence the rate of absorption and, consequently, the serum level–time profile. *In vitro* release characteristics may be helpful as a guide in formulation of pentobarbital suppositories with optimal absorption properties. Based on previous studies, these effects may influence pharmacological responses seen in patients.

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