Bioavailability of Digoxin Capsules and Tablets: Effect of Coadministered Fluid Volume

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Abstract □ The effect of different coadministered fluid (water) volumes on the consistency of digoxin absorption was studied in 16 male volunteers. Each volunteer received four single-dose treatments (two 0.25-mg digoxin tablets with 30- and 240-mL of water and two 0.2-mg digoxin capsules with 30- and 240-mL of water). Digoxin present in serum and urine samples collected for 48 h after dosing was quantified by RIA. Treatments were compared by evaluating the following model-independent pharmacokinetic parameters: maximum serum concentration (C_{max}); time of maximum serum concentration (t_{max}); area under the serum concentration-time curve for 0–12 h (AUC_{0-12}); cumulative urinary excretion for 0–48 h (CUE_{48}). No significant differences were found between dosage form (tablets *versus* capsules) and coadministered water volume (30 mL *versus* 240 mL) for any of the parameters. For both fluid volumes the AUC_{0-12} and C_{max} were significantly larger ($p < 0.01$) and the t_{max} significantly shorter ($p < 0.01$) for the capsules than for the tablets. The volume of coadministered water had no effect on the amount of digoxin absorbed from either dosage form.

Keyphrases □ Digoxin—bioavailability, coadministered fluid volume □ Fluid volume—bioavailability of digoxin

The bioavailability of orally administered drugs may be affected by a number of factors, including dosage form, physicochemical properties of the drug, first-pass extraction by the liver, interactions prior to absorption between the drug and substances in the GI tract, and certain diseases involving the GI tract. One factor which may affect oral bioavailability, that has received little attention, is the potential influence of coadministered fluid volume on drug absorption. In fact, a commonly accepted notion is that drugs are absorbed more rapidly from concentrated than from dilute solutions (1). However, some studies in experimental animals and humans dispute this point. Ferguson (2) studied the toxicity of a variety of organic and inorganic compounds following oral doses to fasted rats. Equal doses of dissolved compounds were given in increasing water volumes equivalent to 1.25, 2.5, and 5.0% of body weight. The toxicity of all compounds, expressed in terms of median lethal dose (LD_{50}), increased with increasing dilution, indicating that absorption was more rapid and/or more complete from dilute solutions. General mechanisms that have been suggested for increased drug absorption from dilute oral solutions are (*a*) more rapid stomach emptying due to the greater volume and (*b*) relative hypotonicity of the solutions, with consequent exposure of the solute to a greater intestinal surface area (3).

The influence of fluid volume on bioavailability of drugs in humans has been studied with erythromycin stearate (4), ampicillin trihydrate (5), amoxicillin trihydrate (5), theophylline (6), doxycycline hyclate (7), tetracycline hydrochloride (7), and propoxyphene hydrochloride (8). In general, these studies of passively absorbed drugs indicate that the volume of fluid coadministered with a drug of poor water solubility may significantly affect the rate and/or extent of its absorption. The bioavailability of drugs with good water solubility, on the other hand, is relatively unaffected by a change in fluid volume.

Digoxin is a compound that is poorly soluble in water [0.095 mg/mL (9)]. Because of this, concern has been expressed that absorption from a tablet may be affected by administration

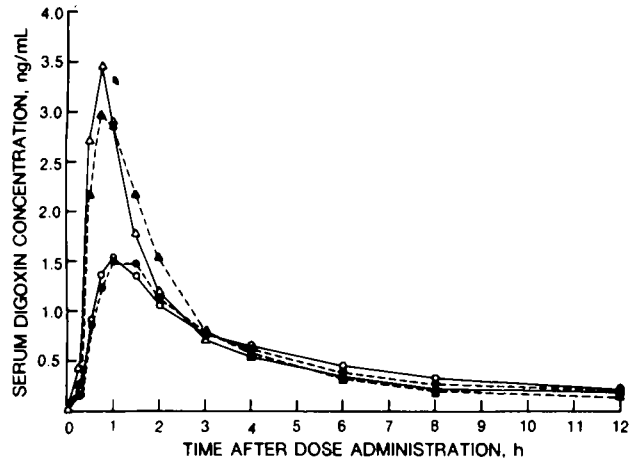

Figure 1—*Mean serum digoxin concentration–time curves during the first 12 h following oral administration. Key: (●) tablets + 30 mL; (○) tablets + 240 mL; (▲) capsules + 30 mL; (△) capsules + 240 mL.*

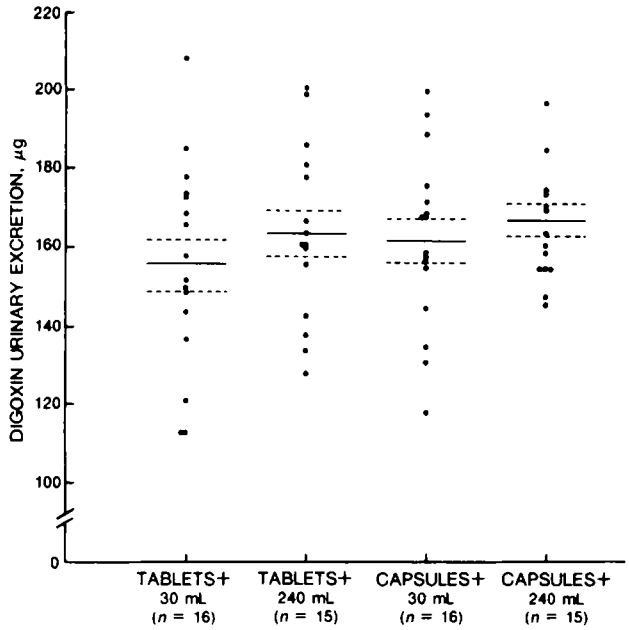

Figure 2—*Cumulative urinary excretion of digoxin during the first 48 h following digoxin administration. Key: (—) mean; (- - -) ± SE.*

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Table I—Area Under the Serum Concentration–Time Curves 0–12 h (ng·h/mL)

Volunteer	Tablets + 30 mL	Tablets + 240 mL	Capsules + 30 mL	Capsules + 240 mL
1	3.34	6.29	5.92	5.72
2	2.86	4.73	6.93	8.02
3	5.61	6.45	8.05	6.25
4	10.96	6.91	10.58	10.35
5	6.02	7.43	7.82	8.26
6	7.25	6.85	8.25	8.27
7	5.97	5.67	10.14	5.02
8	3.83	5.53	5.74	7.48
9	5.73	10.98	9.25	11.51
10	8.75	6.06	9.94	10.58
11	4.76	4.34	8.77	8.21
12	5.75	7.93	5.69	6.07
13	6.39	6.86	5.86	4.64
14	7.71	6.49	8.61	10.14
15	10.31	9.79	8.00	9.07
16	5.60	5.45	7.37	6.54
Mean	6.30	6.74	7.93	7.88
SD	2.27	1.71	1.60	2.08

with different fluid (water) volumes. If this concern was justified, differences in fluid volumes may have had a significant influence on the results of previously published bioavailability studies. Also, many patients take their medications with varying amounts of fluid, ranging from a small ("gulp") to a glassful of water. The difference in patterns of administration could be associated with inconsistency in the amount of digoxin absorbed from tablets during clinical use.

A solid dosage form (capsule) in which the digoxin is already in solution is now available. Theoretically, absorption from this capsule should not be affected by different water volumes and may be more consistent than tablet doses. Thus, a study was conducted to compare the influence of fluid volume on the consistency of digoxin absorption from these two dosage forms when given in bioequivalent doses[1]. This was accomplished by administering digoxin tablets and a digoxin formulation as a solution in soft gelatin capsules [90–100% absorbed (10–12)] with 30 mL and 240 mL of water to healthy volunteers in a crossover study.

EXPERIMENTAL SECTION

Clinical Study—Sixteen healthy male volunteers [23–33 years old (mean 25.1) and 61.2–83.0 kg (mean 72.2)] entered and completed the study. All volunteers were in good health (physical examination, clinical laboratory studies, and an electrocardiogram). Information about the purpose of the study and the procedures to be performed was provided to each volunteer. Each signed an informed consent form (approved by the Institutional Review Board) and participated in the study for approximately 8 weeks.

The volunteers fasted from midnight prior to dosing until 4 h following treatment administration. Volunteers were given 120 mL of water at least 1 h before dosing on the morning of each test day to provide adequate hydration after overnight fluid restriction.

Dosing for each treatment occurred at 8 a.m., and blood and urine collections were made over the next 48 h. Blood samples (5 mL) were obtained by standard venipuncture techniques in vacuum tubes without additives at the following times: just prior to dosing (0 h), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 h after dose administration. These samples were allowed to clot and immediately centrifuged; the serum was separated and stored at −20°C until the time of analysis.

Urine was collected prior to drug administration (blank specimen), 0–24 h, and 24–48 h after drug administration. At the end of each interval the samples were thoroughly mixed, the volumes measured and recorded, and aliquots were removed and frozen until analysis.

Following dose administration the volunteers were ambulatory; however, no strenuous or abnormal physical activity was permitted. A standardized light lunch was served 4 h after dosing.

[1] Lanoxicaps package insert; Burroughs Wellcome Co., Research Triangle Park, N.C., June 1982.

Table II—Cumulative Urinary Digoxin Excretion (μg/48 h)

Volunteer	Tablets + 30 mL	Tablets + 240 mL	Capsules + 30 mL	Capsules + 240 mL
1	143.0	—[a]	167.0	159.0
2	148.5	200.0	199.5	163.0
3	207.5	160.0	167.5	154.5
4	173.5	178.0	154.5	146.0
5	151.5	199.0	157.5	196.5
6	172.5	127.5	145.0	155.0
7	177.5	160.0	194.0	195.5
8	168.0	167.0	188.5	184.5
9	120.5	160.5	117.5	173.5
10	149.0	163.5	158.0	170.0
11	112.5	137.5	131.0	160.5
12	136.5	133.0	156.5	147.0
13	165.5	185.5	176.0	170.0
14	185.0	180.0	172.0	174.5
15	157.5	155.5	169.0	154.5
16	113.0	142.5	135.0	—[a]
Mean	155.1	163.3	161.8	166.9
SD	26.4	22.4	22.5	15.9

[a] Incomplete urine collection.

Study Design—The treatments listed below were administered using an open, single-dose, four-way complete crossover (Latin square) design:

1. Two 0.25-mg digoxin tablets[2] with 30 mL of water (tablets + 30 mL).
2. Two 0.25-mg digoxin tablets[2] with 240 mL of water (tablets + 240 mL).
3. Two 0.2-mg capsules[3] of digoxin solution with 30 mL of water (capsules + 30 mL).
4. Two 0.2-mg capsules[3] of digoxin solution with 240 mL of water (capsules + 240 mL).

The sixteen volunteers were randomly assigned to four groups for treatment administration. A 2-week washout period followed each treatment.

Sample Analysis—Digoxin concentration in each serum sample was quantified in duplicate by RIA using a double-antibody slurry and ^{125}I-digoxin (available in kit form)[4]. The procedure was identical to that outlined[4] except that the order of double antibody and ^{125}I-digoxin was reversed. Urine samples were also determined in duplicate by RIA (13). The sensitivities of the serum and urine assays were both 0.1 ng/mL.

Pharmacokinetic and Statistical Analyses—The following parameters were determined from the serum concentration–time curves for each volunteer for each treatment: observed maximum serum concentration (C_{max}), time of observed maximum serum concentration (t_{max}), and the area under the serum concentration–time curve (AUC). Additionally, the cumulative urinary excretions of digoxin during the first 48 h after dose were determined (CUE_{48}). These parameters were analyzed using an ANOVA for a crossover design[5]. Individual contrasts were made using the least significant difference.

RESULTS

The doses of digoxin tablets and capsules used in this study are recognized as bioequivalent in both the official product labeling[1] and elsewhere (14, 15). Thus, all comparisons were made without adjusting for the actual differences in the doses administered (0.5 mg for tablets *versus* 0.4 mg for capsules).

Figure 1 graphically presents the serum digoxin concentration–time profiles (0–12 h) for the four treatments, and Fig. 2 presents the cumulative urinary excretions for the first 48 h after dose administration. For purposes of comparing relative bioavailability, the CUE_{48} was used. The AUC_{0-12}, C_{max}, and t_{max} were used for additional descriptive and clinical comparisons. AUC_{0-12} was used instead of AUC_{0-48} because the majority of the serum concentrations after 12 h following single-dose administration were below the level of assay sensitivity.

Tables I and II list the individual values for area under the serum concentration–time curves (ng · h/mL) and cumulative urinary digoxin excretions (μg/48 h). During the study, two urine collections were reported as incomplete by the respective volunteers. Table III gives the summary statistics for the pharmacokinetic parameters (*i.e.*, AUC_{0-12}, C_{max}, t_{max}, and CUE_{48}) determined in this study. Table IV summarizes the statistical analyses (ANOVA) of pharmacokinetic parameters based on the means of serum digoxin concentration and cumulative urinary excretion data.

[2] Lanoxin tablets 0.25 mg, Lot 0G2780 (dissolution rate of 80.9% in 60 min); Burroughs Wellcome Co.

[3] Lanoxicaps 0.2 mg, Lot 0G2778, Burroughs Wellcome Co.

[4] Dac-Cel Digoxin Kit; Wellcome Diagnostics Division, Burroughs Wellcome Co.

[5] User's Guide Statistical Analysis System, 1979; SAS Institute, Cary, N.C.

Table III—Pharmacokinetic Summary Statistics[a] for the Four Treatments

Parameter	Tablets + 30 mL	Tablets + 240 mL	Capsules + 30 mL	Capsules + 240 mL
AUC_{0-12}, ng·h/mL	6.30 ± 2.27	6.74 ± 1.71	7.93 ± 1.60	7.88 ± 2.08
C_{max}, ng/mL	1.84 ± 0.56	1.71 ± 0.37	3.87 ± 1.04	3.67 ± 0.72
t_{max}, h	1.22 ± 0.40	1.00 ± 0.34	0.95 ± 0.45	0.69 ± 0.17
CUE_{48}, μg[c]	155.1 ± 26.4	163.3 ± 22.4[b]	161.8 ± 22.5	166.9 ± 15.9[b]

[a] Mean of 16 values ± *SD*. [b] Mean of 15 values ± *SD*. [c] Cumulative urinary excretion.

Table IV—Pharmacokinetic Parameters and Urinary Excretion Data ANOVA

Comparison	Statistic	AUC_{0-12}, ng·h/mL	C_{max}, ng/mL	t_{max}, h	CUE_{48}, μg[a]
30 mL *versus* 240 mL with Capsules	p[b]	N.S.[d]	N.S.	0.03	N.S.
	Power[c]	0.84	0.78	0.36	1.00
30 mL *versus* 240 mL with Tablets	p	N.S.	N.S.	0.07	N.S.
	Power	0.84	0.78	0.36	1.00
Capsules *versus* Tablets	p	<0.01	<0.01	<0.01	N.S.
	Power	0.99	0.97	0.61	1.00
Dosage Form × Volume Interaction	p	N.S.	N.S.	N.S.	N.S.
	Power	0.55	0.49	0.20	0.95

[a] Cumulative urinary excretion. [b] Two-sided test. [c] Power to detect a difference equal to 20% of the overall mean with $\alpha = 0.05$. [d] Not significant.

Table V—Comparison of Drug Solubilities[a]

Drug	Solubility[b]	Dose Administered	Theoretical Volume of Water Required to Solubilize Dose
Ampicillin trihydrate	6.7 mg/mL (21)	500 mg (5)	74.6 mL
Amoxicillin trihydrate	2.5 mg/mL (21)	500 mg (5)	200.0 mL
Doxycycline hyclate	333.3 mg/mL (21)	200 mg (7)	0.6 mL
Erythromycin stearate	≤0.1 mg/mL (21)	500 mg (4)	≥5000 mL
Propoxyphene hydrochloride	3333.3 mg/mL (21)	130 mg (8)	0.4 mL
Tetracycline hydrochloride	100 mg/mL (21)	500 mg (7)	5.0 mL
Theophylline	8.3 mg/mL (21)	260 mg (6)	31.3 mL
Digoxin	0.095 mg/mL (9)	0.5 mg Tablet[c]	5.3 mL
		0.4 mg Capsule[c]	4.2 mL

[a] For drugs administered in previous studies that evaluated effect of coadministered fluid volume. [b] In water at room temperature. [c] Doses used in present study.

Based on CUE_{48}, there were no significant differences found between dosage form (tablets *versus* capsules) and coadministered water volume (30 mL *versus* 240 mL). Mean CUE_{48} values were 155.1 and 163.3 μg for the tablets with 30 mL and 240 mL of water, respectively. Mean CUE_{48} values for capsules with 30 mL and 240 mL of water were 161.8 and 166.9 μg, respectively. Both fluid volumes showed significantly larger ($p < 0.01$) AUC_{0-12}, and C_{max} values for capsules than tablets. The t_{max} was significantly shorter ($p < 0.01$) for the capsules than for the tablets. Also, capsules administered with 240 mL of water had a significantly shorter t_{max} ($p < 0.05$) than capsules administered with 30 mL of water (0.69 *versus* 0.95 h, respectively). There were no significant interactions between dosage form (tablets *versus* capsules) and coadministered water volume (30 mL *versus* 240 mL) for AUC_{0-12}, C_{max}, t_{max}, and CUE_{48}.

Figure 3 illustrates the between-subject variability in cumulative urinary excretion for the treatments. The *CV* values ranged from 9.5% for capsules administered with 240 mL of water to 17.0% for the tablets administered with 30 mL of water. The two other treatments (capsules + 30 mL and tablets + 240 mL) showed similar *CV* values of 13.9 and 13.7%, respectively.

DISCUSSION

Results of previous studies that evaluated the effect of coadministered fluid volume on bioavailability vary and depend largely on the compound tested. Erythromycin stearate was administered to fasting normal volunteers in single 500-mg doses with 20 mL or 250 mL of water. The results showed that reduction in fluid volume significantly decreased erythromycin serum levels, probably due to the low aqueous solubility of erythromycin stearate (4). Amoxicillin trihydrate (5) and theophylline (6) also show decreased serum levels when administered with smaller fluid volumes.

In some instances, the coadministered fluid volume has minimal or no effect on the bioavailability of the drug tested. Such was the case with doxycycline and tetracycline (water-soluble salts); little effect on the overall serum level-time profiles was seen when each preparation was administered with 25 mL or 250 mL of water (7). Ampicillin trihydrate bioavailability was slightly affected by changes in coadministered fluid volume (5). Although plasma propoxyphene levels have been shown to be lower with a 500 ml volume of water *versus* 250 ml when the drug is given as a capsule, the difference was significant only at the 6-h sampling time (8).

In this study, a comparison of mean CUE_{48} values across both coadministered fluid volume and dosage forms revealed no statistically significant differences. The power to detect a difference of 20% in means for these comparisons with $\alpha = 0.05$ was between 0.95 and 1.00. A comparison of the other pharmacokinetic parameters revealed no significant interactions between dosage form (tablets *versus* capsules) and volume (30 *versus* 240 mL of water). Capsules had significantly larger AUC_{0-12} and C_{max} values and a significantly shorter (earlier) t_{max} than tablets ($p < 0.01$). Interestingly, a significantly shorter t_{max} was observed when the capsules were administered with 240 mL of water than when they were taken with 30 mL of water ($p =$

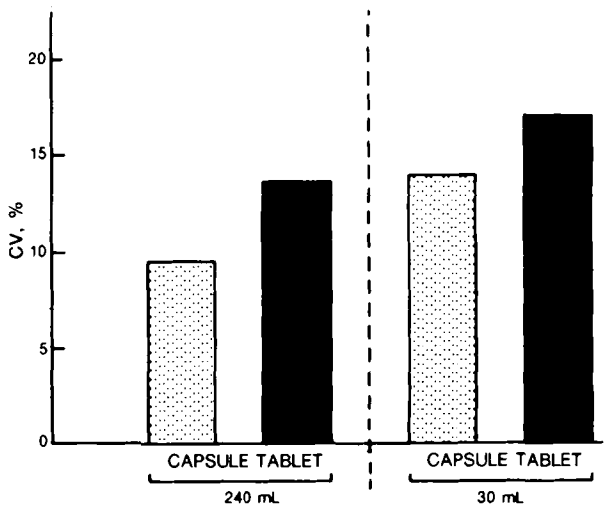

Figure 3—*Between-subject variability in cumulative urinary excretion of digoxin for capsules and tablets (expressed as* CV).

0.03). The larger C_{max} and shorter t_{max} with the capsules *versus* tablets indicate a more rapid absorption rate of the capsule dosage form. Our findings also confirm the results of previous comparative studies, which demonstrate the equivalence of bioavailability of the 0.2-mg capsule and 0.25-mg tablet doses (14, 15).

While no significant differences in the amount of digoxin absorbed were noted based on CUE_{48}, it is interesting to note from Fig. 3 that a smaller *CV* is seen with the capsule than the tablet for both the 240 mL (9.5 *versus* 13.7%) and the 30 mL (13.7 *versus* 17.0%) volumes of water.

Digoxin bioavailability studies (15–20) have used different coadministered volumes of water (100–240 mL). If the results of our study had indicated a difference in bioavailability with different volumes of water, some of the findings of these studies could be questioned. However, since we found no difference in bioavailability with a small *versus* a large amount of fluid, this variable does not have an important influence on digoxin absorption in normal individuals.

A review of drug solubility and volume-related variability in drug absorption is interesting. Table V presents a comparison of the solubilities and doses of drugs that have been administered in previous studies with designs similar to the present study. These data show that concerns over alterations in bioavailability of a drug due to coadministered fluids should not only take into account the solubility of the drug, but also the dose of the respective drug administered. A case in point is digoxin with a solubility of 0.095 mg/mL, one of the lowest values listed. However, because the therapeutic dose is small, only a small volume of water is theoretically required to solubilize the dose in the GI tract.

The results of this study indicate that, in normal volunteers, there are no differences in total digoxin absorption (for either the tablet or capsule forms), when digoxin is administered with relatively small or large volumes of fluid. Such pharmaceutical information is useful in identifying drugs or drug preparations which may or may not be influenced by differences in coadministered fluid volume.

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Pharmacokinetics of Fostedil, a New Calcium Antagonist, in Beagle Dogs Following Oral and Intravenous Administration

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Received August 8, 1983, from the *Drug Metabolism Department, Pharmaceutical Products Division, Abbott Laboratories, North Chicago, IL 60064.* Accepted for publication November 28, 1983.

Abstract □ Twelve adult beagle dogs received both an oral and intravenous dose (12 mg/kg) of fostedil in a cross-over design. The plasma levels and urinary excretion of intact fostedil were measured, and the pharmacokinetic parameters of the drug were defined. The results indicate that fostedil was at least 68% bioavailable after an oral dose given as a suspension or solution. The terminal half-life was about 7–8 h. The *in vitro* protein binding, at concentrations of 0.1–100 μg/mL, ranged from 95 to 97%. The binding was not concentration dependent, and saturation of the binding sites was not apparent at concentrations up to 100 μg/mL. Excretion of unchanged drug from the kidneys accounted for only a small percentage of drug clearance.

Keyphrases □ Fostedil—pharmacokinetics, dogs □ Pharmacokinetics—fostedil, dogs □ Blocking agent—calcium entry, fostedil, pharmacokinetics, dogs

Fostedil (I) (diethyl{[4-(2-benzothiazolyl)phenyl]methyl}-phosphonate) is a new calcium entry blocking compound[1] (1–4). This study was designed to determine the pharmacokinetics of fostedil in beagle dogs after intravenous and oral administration.

[1] This compound is being studied under a joint license agreement between Abbott Laboratories, North Chicago, Ill., and Kanebo, Ltd., Japan, and has been reported in the literature as KB-944.

EXPERIMENTAL SECTION

Animals—Five male and seven female adult beagle dogs (8.5–13.0 kg) were randomly divided into three groups of four dogs per group. The groups were dosed at 12 mg/kg, once with an oral solution, an oral suspension, an oral

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