Bioavailability of Digoxin in a New Soluble Pharmaceutical Formulation in Capsules

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Abstract □ The *in vitro* dissolution and the bioavailability of two pharmaceutical formulations of digoxin were compared, one being a common commercial tablet form and the other a solution of the glycoside in soft gelatin capsules. Digoxin capsules dissolved more readily *in vitro* and showed higher bioavailability than digoxin tablets in both dogs and humans. In dogs, the capsules and tablets were compared with an elixir of digoxin, which possesses complete bioavailability. The better bioavailability of digoxin capsules as compared with tablets may be explained by the fact that this formulation contains the cardiac glycoside in a solution.

Keyphrases □ Digoxin—*in vitro* dissolution and bioavailability, commercial tablets and soft gelatin capsules, dogs and humans □ Dissolution, *in vitro*—digoxin, commercial tablets and soft gelatin capsules compared □ Bioavailability—digoxin, commercial tablets and soft gelatin capsules compared, dogs and humans □ Cardiotonic agents—digoxin, *in vitro* dissolution and bioavailability, commercial tablets and soft gelatin capsules compared, dogs and humans □ Dosage forms—digoxin tablets and soft gelatin capsules, *in vitro* dissolution and bioavailability, dogs and humans

Several investigators (1–8) have reported marked differences in the bioavailability of digoxin tablets among different products of the glycoside or different batches of the same product. In addition, a lack of digoxin content uniformity was observed in the same tablet preparations, varying from 28 to 148% (9). To control this problem, the Food and Drug Administration standardized an analytical monitoring program (10) to ensure that individual tablets of digoxin do not differ significantly in glycoside content.

The best bioavailability of digoxin is achieved when the glycoside is administered in a solution or in the form of an elixir (11, 12). This paper reports a comparative study of the composition, *in vitro* dissolution, and bioavailability in dogs and humans of two pharmaceutical formulations of digoxin, a commercial tablet[1] and soft gelatin capsules containing the glycoside in a dissolved form[2].

EXPERIMENTAL

Digoxin Tablets and Capsules—Both capsules and tablets contained 250 μg of the glycoside and were from the same batch. The capsules also contained 1.500 mg of *N,N*-dimethylacetamide and 139.250 mg of polyethylene glycol 400.

Tablets and capsules were assayed for glycoside content according to Italian F.U. 1972 (13). The capsules contained 102% ± 0.35 (*SE*) of glycoside; this value is marginally higher than the 97% ± 0.35 (*SE*) found in the tablets.

Dissolution Rate—The dissolution rate of both tablets and capsules of digoxin was investigated *in vitro* according to the "paddle water" (distilled water) and "paddle acid" [0.6% (v/v) HCl] methods (14). Five hundred milliliters of distilled water or 0.6% HCl and a digoxin tablet or capsule were placed in a 1000-ml flask, thermostated at 37°, and stirred at 50 ± 2 rpm. After 15 or 60 min, a sample was taken from the flask. Digoxin was extracted and determined by the spectrophotofluorometric method. Evaluation of dissolution rates was made using the Student *t* test for independent data (Table I).

Bioavailability in Dogs—Four mongrel dogs, 16–18 kg, received the digoxin tablets during a single trial, followed 10 days later by the capsules and 10 days later by a digoxin elixir.

All dogs received 250 μg of the glycoside in each of the three formulations. The digoxin elixir contained 50 μg/ml of the glycoside in propylene glycol–95% ethanol–water [10:2.5:112.5 (v/v/v)]. Venous blood samples were taken from each dog at 0, 7.5, 15, 30, 45, 60, 90, 120, and 240 min. Plasma digoxin levels were determined by the radioimmunoassay method of Smith *et al.* (15)[3].

The statistical comparison of results was processed using an analysis of variance for all three preparations, followed by a Tukey test for specific pairs (Table II).

Bioavailability in Humans—The investigation was carried out on six healthy volunteers (58–82 kg and 36–70 years of age). Each subject received two digoxin capsules (500 μg) and two digoxin tablets (500 μg). The two administrations were carried out with a crossover design at an interval of 10 days.

The statistical comparison of capsules and tablets was made using the Student *t* test for paired observations.

Venous blood samples were taken from each patient at 0, 15, 30, 45, 60, 120, and 240 min. Plasma digoxin levels were determined as described previously.

Blood samples in both dogs and human subjects were taken over 4 hr, on the basis of reported observations (16–18). These reports concluded that areas under the plasma level–time curves (*AUC*) correlate well for the first 5 hr with areas obtained after longer sampling times, indicating that extended sampling may not be necessary for digoxin studies.

RESULTS

With the paddle water method, both digoxin tablets and capsules dissolved almost entirely in 15 min. Standard errors with digoxin tablets were two to three times higher than with digoxin capsules. With the paddle acid method, the degree of dissolution of digoxin tablets after 15 min was about 70% of the values obtained in the same time with capsules ($p < 0.001$); after 60 min, both the capsules and tablets dissolved almost entirely and to a similar degree (Table I).

In the dog, the digoxin solution showed the best bioavailability in terms of plasma levels of the glycoside, followed by the capsules and tablets (Table II). Average peak times were the earliest (22 min) with the solution, followed by the capsules (45 min) and tablets (52 min). A difference of $p < 0.05$ existed between the solution and capsules, and a difference of $p < 0.01$ existed between the solution and tablets. A comparison between the capsules and tablets gave a statistically insignificant p value. Peak concentrations were highest with the solution, followed by the capsules and tablets. For the solution–tablet comparison, $p < 0.01$; tablet–capsule and solution–capsule comparisons did not give any statistically significant p value.

The area under the plasma level–time curve, evaluated by the trapezoidal rule from 0 to 240 min, showed the highest value with the solution, followed by the capsules and tablets. A statistical comparison gave the following values: solution–capsules and solution–tablets, $p < 0.01$. Tablet–capsule comparisons did not give a statistically significant p. The differences found in bioavailability between the capsules and solution of digoxin might be explained in part by the much higher concentration in the capsules than in the solution.

In human subjects, the best bioavailability was found with the capsules, which is in accord with previous findings with dogs. The peak times were longer with the tablets than with the capsules ($p > 0.05$), the peak con-

[1] Lanoxin, lot 4 B 16.
[2] Eudigox, lot 2019, Simes S.p.A.
[3] Kits for radioimmunoassay determination were supplied by Sorin S.p.A., Saluggia, Italy.

Table I—Dissolution Rate of Digoxin Tablets[a] and Capsules[a] in Paddle Water and in Paddle Acid Methods after 15 and 60 min[b]

	15 min		60 min	
	Digoxin Tablets	Digoxin Capsules	Digoxin Tablets	Digoxin Capsules
Paddle water method	88.33 ± 4.39[b]	91.50 ± 1.43	89.50 ± 5.05	95.67 ± 2.64
Paddle acid method	64.83 ± 3.62[c]	93.50 ± 3.14[c]	95.50 ± 1.86	95.17 ± 2.10

[a] $n = 6$. [b] Mean values ± *SE* in percent of digoxin dissolved. [c] $p < 0.001$ for the comparison of 64.83 with 93.50. The p value was evaluated with the Student t test.

Table II—Peak Plasma Concentration, Peak Time, and *AUC* in Four Dogs after Administration of Digoxin Solution (250 μg), Digoxin Capsules (250 μg), and Digoxin Tablets (250 μg)

	Peak Plasma Concentration, ng/ml			Peak Time, min			*AUC*, ng/ml/min		
Dog	Solution	Capsules	Tablets	Solution	Capsules	Tablets	Solution	Capsules	Tablets
1	4.5	2.9	1.4	30	60	45	592	267	167
2	5.0	4.4	1.6	30	45	60	508	273	219
3	3.8	3.2	2.5	15	30	45	461	324	262
4	3.2	2.3	1.8	15	45	60	340	209	180
Mean ± *SE*	4.1 ±0.4	3.2 ±0.4	1.8 ±0.2	22 ±4	45 ±6	52 ±4	475 ±53	268 ±23	207 ±21
Analysis of variance									
F ratio		9.847			9.750			15.689	
p		<0.01			<0.01			<0.01	
p value obtained with Tukey method									
Solution *versus* capsules		>0.05			<0.05			<0.01	
Solution *versus* tablets		<0.01			<0.01			<0.01	
Capsules *versus* tablets		>0.05			>0.05			>0.05	

centration was higher with the capsules (4.5 ng/ml) than with the tablets (2.2 ng/ml) ($p < 0.02$), and the *AUC* was higher with the capsules than the tablets ($p < 0.05$) (Table III).

DISCUSSION

The area under the plasma level–time curve is a useful parameter and allows the relative bioavailability of the oral formulation of a drug to be evaluated as a percentage related to an intravenous or oral solution of the same drug.

According to this method, several investigators (16, 17, 19) obtained a relative bioavailability of the tablets (of the same commercial type as those investigated here) of around 56–58%, assuming 100% values after intravenous solution, and of around 70%, assuming 100% values after oral solution.

From these data on the dog, it is possible to calculate a relative bioavailability of 56.5% for capsules and 44% for tablets. These values are a little lower than those obtained previously (16, 17, 19). However, dogs may absorb digoxin at a different rate from humans. In effect, the mean peak time with capsules was 45 min in dogs and 72 min in humans; with tablets, it was 52 min in dogs and 95 min in humans. For human subjects, all three parameters (peak plasma concentration, peak time, and *AUC*) agree with the data on the dog concerning the better bioavailability with the capsules than with the tablets.

Table III—Peak Plasma Concentration, Peak Time, and *AUC* in Six Human Volunteers after Administration of Digoxin Capsules (500 μg) and Digoxin Tablets (500 μg)

	Peak Plasma Concentration, ng/ml		Peak Time, min		*AUC*, ng/ml/min	
Subject	Capsules	Tablets	Capsules	Tablets	Capsules	Tablets
1	5.4	1.7	45	45	534	224
2	4.8	1.0	45	120	861	90
3	2.9	2.5	120	120	279	270
4	6.3	2.6	60	120	622	234
5	4.7	3.2	45	45	496	283
6	3.2	2.5	120	120	570	255
Mean	4.5	2.2	72	95	560	226
± *SE*	±0.5	±0.3	±15	±16	±77	±29
p[a]	<0.02		>0.05		<0.05	

[a] Evaluated with the Student t test for paired observations.

The problem of drug bioavailability as a whole is serious. Digoxin possesses an unfavorable therapeutic index, which requires optimum absorption from an oral pharmaceutical preparation. A digoxin product with poor or incomplete absorption could cause a poor or incomplete effect on myocardial contractility. However, it is undesirable to adjust dosage of an incompletely absorbed digoxin product because it may be associated with individual variability in enteral absorption related principally to the GI transit rate. It is also undesirable to adjust dosage in patients being treated with other drugs (*e.g.*, metoclopramide) (20). None of the digoxin tablet preparations available possesses total bioavailability, as does the solution or elixir (11, 12). The preparation of digoxin in soft gelatin capsules, containing a solution of the drug, dissolved faster *in vitro* and possessed better bioavailability in the dog and human subjects than did the preparation in tablets.

Some clinical trials (21–23) showed an earlier, more intense, and longer lasting effect with digoxin capsules than with tablets in terms of heart rate and polycardiographic measurements in both healthy subjects and in patients suffering from heart failure, thus confirming the greater efficacy of the capsules.

These data, obtained from both human subjects and dogs, agree with the recent results of Mallis *et al.* (24). They found better bioavailability with a digoxin solution in capsules than with tablets in human subjects. The results of this investigation also demonstrate that dogs are a valid model for testing experimental digoxin formulations.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 27, 1975, from the *Institute of Biological Chemistry, School of Medicine, State University, 20100 Milan, Italy.*

Accepted for publication March 16, 1976.

The authors thank Simes S.p.A. for providing Eudigox capsules and Dr. Gandolfi of Sorin S.p.A. for providing kits for digoxin radioimmunoassay.

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Cardiovascular and Neuromuscular Effects of Dimethyl Sulfoxide in Anesthetized Rabbits

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Abstract □ In rabbits anesthetized with pentobarbital, the carotid arterial blood pressure and bilateral contractions of the gastrocnemius muscles due to electrical stimulation of the sciatic nerves were recorded. Intravenous administration of up to 1 ml of dimethyl sulfoxide/kg caused profound hypotension and eventually failure of neuromuscular transmission. Caution must be used in considering dimethyl sulfoxide as a solvent for drug administration.

Keyphrases □ Dimethyl sulfoxide—intravenous administration, cardiovascular and neuromuscular effects, anesthetized rabbits □ Toxicity—dimethyl sulfoxide, intravenous administration, anesthetized rabbits □ Cardiovascular system—effects of intravenous administration of dimethyl sulfoxide, anesthetized rabbits □ Nerve impulse transmission—effects of intravenous administration of dimethyl sulfoxide, anesthetized rabbits

Previous reports demonstrated that dimethyl sulfoxide (I) has blocking activity at the neuromuscular junction *in vitro*. These studies ranged from depression of the guinea pig phrenic nerve diaphragm (1) to partial reversal of tubocurarine blockade in the frog sartorius nerve-muscle preparation (2) to a shift in the dose–response curve with acetylcholine in the chicken biventer cervicis muscular preparation (3). *In vivo* reports of the effects of I include the slow infusion of a 40% solution intravenously in unanesthetized rabbits; this dose (19.2 g/kg) resulted in a 12-mm Hg rise in arterial blood pressure and then bradycardia, which continued until death at 92 min (4). In unanesthetized cats, the LD_{50} for I was approximately 4 g/kg (5), but it was less than 0.4 g/kg in anesthetized cats (6). These findings imply that central nervous system (CNS) depression would have an appreciable effect on the toxicity caused by I.

EXPERIMENTAL

The present experiments were occasioned by the need to have a solvent for some bisquaternary ammonium water-insoluble compounds. Since the compounds were found to have sufficient solubility in I, its effect in one biological preparation to be used for the evaluation of the activity of the bisquaternary compounds was studied.

Albino rabbits, 2.2–2.5 kg, were anesthetized with pentobarbital sodium, 30 mg/kg, administered into the marginal ear vein. The right carotid artery and jugular vein were cannulated to permit the recording of the blood pressure *via* a pressure transducer and the administration of drugs, respectively. The trachea was cannulated, and the respiratory activity was monitored with a transducer connected to a polygraph. The sciatic nerve of each leg was cut proximally, and the distal stump was placed on an electrode connected to a stimulator. The Achilles tendon was cut at its insertion and attached to a transducer. The right leg was stimulated with supramaximal voltage at 1 Hz, and the left leg was stimulated at 0.1 Hz. Doses of I, 0.1, 0.5, and 1.0 ml/kg iv, were given.

RESULTS AND DISCUSSION

The lowest dose caused the diastolic blood pressure to decrease initially about 25 mm Hg. It returned to the control level within 25 min. There was an associated decrease of 50% in the force of contraction of the leg being stimulated at the faster rate. There was no appreciable change in the response occurring on the side being stimulated at the slower rate or in respiration.

When the 0.5-ml/kg dose of I was administered, there was a rapid decrease of 55 mm Hg in diastolic pressure, which returned to the control level within 1 min. Subsequently, there was a second decrease of 35 mm Hg in pressure, which was maximal at 3 min and returned to the control