Bioavailability of Digoxin in a New Soluble Pharmaceutical Formulation in Capsules

P. GHIRARDI*, G. CATENAZZO*, O. MANTERO*, G. C. MEROTTI, and A. MARZO

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, dogs and humans □ Bioavailability—digoxin, commercial tablets and soft gelatin capsules compared, dogs and humans □ Cardiogenic 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 tablet1 and soft gelatin capsules containing the glycoside in a dissolved form2.

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 μg of N,N-dimethylacetamide and 139.250 μg 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°C, 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–45% ethanol–water (102:5:112.5 (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).5

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, 90, 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 and tablets (45 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-

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1 Lansin, lot 4 B 16.
2 Rotigox, lot 2015, Simes S.p.A.
5 Kits for radioimmunoassay determination were supplied by Sorin S.p.A., Saluggia, Italy.
Table I—Dissolution Rate of Digoxin Tablets and Capsules in Paddle Water and in Paddle Acid Methods after 15 and 60 min

<table>
<thead>
<tr>
<th>Paddle Water Method</th>
<th>15 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin Tablets</td>
<td>88.33 ± 4.39^b</td>
<td>91.50 ± 1.43</td>
</tr>
<tr>
<td>Digoxin Capsules</td>
<td>89.50 ± 5.05</td>
<td>95.67 ± 2.64</td>
</tr>
<tr>
<td>Paddle Acid Method</td>
<td>64.83 ± 3.62^c</td>
<td>93.50 ± 3.14^c</td>
</tr>
<tr>
<td>Digoxin Tablets</td>
<td>95.50 ± 1.86</td>
<td>95.17 ± 2.10</td>
</tr>
<tr>
<td>Digoxin Capsules</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^a = 6, ^b Mean ± SE in percent of digoxin dissolved. ^c p < .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)

<table>
<thead>
<tr>
<th>Dog</th>
<th>Peak Plasma Concentration, ng/ml</th>
<th>Peak Time, min</th>
<th>AUC, ng/ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solution</td>
<td>Capsules</td>
<td>Tablets</td>
</tr>
<tr>
<td>1</td>
<td>4.5</td>
<td>2.9</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>4.4</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>3.8</td>
<td>2.2</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>3.2</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Mean</td>
<td>±0.4</td>
<td>±0.4</td>
<td>±0.2</td>
</tr>
</tbody>
</table>

Analysis of variance F ratio = 9.847
p value obtained with Tukey method
Solution versus capsules > 0.05
Solution versus tablets < 0.01
Capsules versus tablets > 0.05

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.

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 Gl 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.

REFERENCES
(2) P. F. Binnion and M. McDermott, Lancet, 2, 592 (1972).

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

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)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Peak Plasma Concentration, ng/ml</th>
<th>Peak Time, min</th>
<th>AUC, ng/ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capsules</td>
<td>Tablets</td>
<td>Capsules</td>
</tr>
<tr>
<td>1</td>
<td>5.4</td>
<td>1.7</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>4.8</td>
<td>1.0</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>2.9</td>
<td>2.5</td>
<td>2.6</td>
</tr>
<tr>
<td>4</td>
<td>6.3</td>
<td>2.6</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>4.7</td>
<td>3.2</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>3.2</td>
<td>2.5</td>
<td>120</td>
</tr>
<tr>
<td>Mean</td>
<td>4.5</td>
<td>2.2</td>
<td>72</td>
</tr>
<tr>
<td>± SE</td>
<td>±0.3</td>
<td>±1.5</td>
<td>±1.6</td>
</tr>
</tbody>
</table>

^p^2 < 0.02, ^*^ > 0.05, ^**^ < 0.05

^*^ Evaluated with the Student t test for paired observations.


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