Deposition and Disappearance of Digitalis from the Tissues of the Rat, Rabbit, and Dog after Parenteral Injection

By Meyer Friedman, M.D., Shirley St. George, Ph.D., René Bine, Jr., M.D., Sanford O. Byers, Ph.D., and Catharine Bland, A.B.

Digitoxin administered to the rat, rabbit, or dog has no specific avidity for heart muscle. The quantity recovered from this organ at any time was no greater than from liver or kidney, while these organs continued to contain the glycoside for a much longer period of time.

The digitalis glycosides have proved themselves so efficacious in the treatment of various cardiac disorders that it is frequently forgotten that, nevertheless, there is little exact knowledge about either the pharmacologic or physiologic properties of these substances. For example, the exact quantitative aspects of the processes by which digitalis glycosides are (1) absorbed from the gastrointestinal system, (2) carried in the blood stream, (3) enter various tissues and organs, and (4) are disposed of by these same tissues, are in the main unknown. Likewise, the means by which these drugs effect their benign changes in a deranged cardiovascular system still remain to be understood.

Undoubtedly one of the chief difficulties attendant on an investigation of the fate of digitalis glycosides in the body has been the absence of a tool sufficiently sensitive to measure their concentration in various tissues. Thus, although some approximations have been made concerning the fate of these substances in the mammalian body, the data allowing them have been obtained too often from experiments in which huge amounts of the drug have been given. Or else data have been gathered from experiments in which isolated preparations have been perfused with moderately dilute solutions of glycoside or digitalis. It can be understood that neither type of experiment is ideal, either from a physiologic or pharmacologic viewpoint.

Recently, however, by the use of the embryonic duck heart preparation we have been able to follow the initial deposition and later, the rate of disappearance of digitoxin from the tissues of various intact animals after parenteral injection of the drug. The present article gives the results of this study.

Methods

A. Rat. Samples of the heart, liver, kidney, lung, muscle, spleen, and brain were removed from groups of rats, immediately, 1, 3, 6, 10, 12, and 16 hours after intravenous injection of digitoxin (1 μg. per gram of body weight). Samples of the brain also were removed from groups of rats 24 and 48 hours after injection of digitoxin. One gram quantities of each sample then were analyzed for their digitoxin content according to previously described methods.1 In this manner, the fate of digitoxin in various tissues of the intact, normal rat could be followed.

B. Rabbit. Samples of heart, liver, kidney, and lung of rabbits were obtained immediately, and one hour after the injection of digitoxin (0.5 μg. per gram of body weight). They were analyzed for digitoxin exactly as the rat tissues had been. It was found in preliminary studies that known amounts of added digitoxin could be removed completely from the tissues studied. A second series of rabbits was injected with 0.2 μg. of digitoxin per gram of body weight and the tissues were obtained and analyzed immediately, one half, one, and three hours after injection.

C. Dog. Samples of the heart, liver, kidney, and lung were obtained immediately, 1, 2, 4, 8, 16, 24, and 48 hours after the injection of digitoxin (0.2 μg. per gram of body weight). Analyses of these tissues for digitoxin content were similar to those done on the rat and rabbit tissues.

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DEPOSITION AND DISAPPEARANCE OF DIGITOXIN FROM TISSUES

### Table 1.—Deposition and Disappearance of Digitoxin from Tissues of the Rat, Rabbit, and Dog

<table>
<thead>
<tr>
<th>Time after Injection (Hrs.)</th>
<th>No. Exps.</th>
<th>Digitoxin (µg.) per Gram</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart</td>
<td>Liver</td>
</tr>
<tr>
<td>Rat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>2.0 (1.0-2.5)†</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>1.85 (0.5-2.5)</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0.40 (0.2-0.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>0.30 (0.2-0.5)</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>0.05 (0.05-0.10)</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>N.D. (0.05-0.05)</td>
</tr>
<tr>
<td>16</td>
<td>5</td>
<td>N.D.</td>
</tr>
<tr>
<td>24</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>48</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Rabbit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>3.4 (2.5-4.2)</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>0.3 (0.2-0.45)</td>
</tr>
<tr>
<td>Dog</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>0.20 (0.20-0.20)</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>0.30 (0.2-0.45)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0.20 (0.2-0.2)</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>N.D.</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>N.D.</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>N.D.</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>48</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

* Non-detectable
† Range of Values

Results

A. The Deposition and Disappearance of Digitoxin from the Tissue of Various Animals

1. The Rat. As table 1 illustrates, the liver of the rat contained digitoxin at a concentration far exceeding that of the heart or any other organ. This predilection of the drug for the liver, moreover, continued for a considerable period of time. Certainly the glycoside displayed no especial affinity for the heart. This last fact also was demonstrated by the observa-
tion that both the kidney and lung contained either as much or more digitoxin than the heart. Skeletal muscle and spleen on the other hand, contained less digitoxin than the heart.

Unlike the other tissues studied, brain apparently received little digitoxin until about three hours after its injection, but then (see table 1) it continued to exhibit the drug long after it could not be detected in any other organ. This last observation suggests that the rate of transfer of the glycoside both into or out of brain tissue is exceedingly sluggish. In other words, the brain is the last tissue to accept digitoxin and the last to give it up.

Ten hours after the injection of digitoxin, although all tissues of the rat still contained the drug, its concentration in any tissue was very slight except in the liver which still contained 1.2 µg. per gram. Twelve hours after injection, even the liver contained very little (0.05 µg. per gram) and none was detectable in the remaining viscera. Digitoxin at 16 hours, could be detected only in the brain.

2. The Rabbit. Similar to the rat heart, the rabbit heart also did not appear to concentrate digitoxin in any extraordinary fashion. (See table 1.) Thus, the heart was not found to contain significantly larger amounts of digitoxin immediately after injection than the kidney or the lung. Actually the liver, as had been noted in the study of rat tissues, contained more digitoxin than the heart. Moreover, one hour after injection, the kidney as well as the liver was found usually to contain more digitoxin than the heart. No digitoxin was detectable in the brain.

The fate of digitoxin in the tissues of the rabbit could be determined one hour after the injection of 0.5 µg. per gram but not after this period of time because the animals died shortly after an hour as a result of the effects of the drug. When a series of 13 rabbits was given only 0.2 µg. of digitoxin per gram of body weight, the heart again was found to contain approximately the same amount of digitoxin (0.5 µg. per gram) immediately after injection as was found in the lung and kidney. Moreover, 30 minutes after injection, the heart contained only 0.1 µg. of digitoxin per gram compared to a concentration of 0.3 µg. per gram in the liver and kidney. At the end of one hour, only the kidney was found to contain a small amount of digitoxin (0.1 µg. per gram). At the end of three hours, the kidney also failed to exhibit any detectable digitoxin.

3. The Dog. Digitoxin after its intravenous injection into the dog was found to have no predilection for cardiac tissue. (See table 1.) Immediately after the injection of 0.2 µg. of digitoxin per gram of body weight, most of the organs contained about the same amount of drug (0.2 µg. to 0.4 µg. per gram). The heart, however, appeared to retain its digitoxin longer. Thus, one hour after injection, more digitoxin was found in the heart (0.3 µg.) than in the liver (0.2 µg.), or lung (0.10 µg.). (See table 1.) However, even at this time there was very much less in the heart than in the kidney (1.5 µg.). Two hours after the injection only the heart and the kidney exhibited digitoxin. From this period on, up to 24 hours, digitoxin was found only in the kidney and in diminishing amounts in this organ.

DISCUSSION

The present study indicates that digitoxin appeared capable of entering each tissue of the rat and other species assayed. Its tardiness in entering and leaving the brain of the rat and its absence in the rabbit brain (one hour after injection) might have been expected for apparently the blood brain barrier is not too easily trespassed in either direction by steroids.

If digitoxin, however, enters most tissues there is little evidence from the results of our analyses that it has extraordinary avidity for cardiac tissue, as has been reported. Thus, in the rat, rabbit, and dog, the amount of digitoxin deposited in the heart immediately after its injection appears to be about the same as that deposited in the lung or kidney. Moreover, the heart of the rat and rabbit did not appear to retain excess digitoxin any longer than other tissues. Only the dog’s heart appears to retain digitoxin slightly longer than such tissues as the lung and liver.

On the other hand, there was considerable evidence in the present studies that digitoxin is found in greatest concentration in those organs which excrete the drug. Thus, the liver
of the rat (which has been found capable of excreting digitoxin) was found to contain, 10 hours after injection of digitoxin, over 20 times as much of the drug as the heart. On the other hand, the dog excretes significant amounts of digitoxin in his urine, and his kidney accordingly was found to contain five times as much digitoxin as his heart, two hours after parenteral administration.

The present studies offer little information concerning the possible destruction of digitoxin in various tissues of the animal body. In other words, the disappearance of the drug from various tissues could be due to its escape back into the blood and its excretion by the liver, intestine, or kidney. Recently, however, Sjöerdema and Fischer concluded that their perfused heart preparation broke down 30 to 40 per cent of the digitoxin it absorbed, all in a period of 5 to 20 minutes. It should be mentioned, however, that their basis for this assumption was their inability to extract the entire amount of digitoxin calculated to have been absorbed by their perfused heart. It has been our experience, however, that chloroform extraction of any tissue homogenate for its content of digitoxin may be incomplete if the amount of the drug in the homogenate is minute.

If various tissues do have the power to destroy digitoxin, it is probably a process intimately attuned to the amount of the drug presented to the tissue. Thus, when small amounts of the drug are presented to various organs as is probably the case in man, the process of destruction must be exceedingly slow or limited. Otherwise, the prolonged persistence of the drug in the body and its gradual renal excretion over a period of several weeks becomes inexplicable. On the other hand, if moderately large amounts are administered as in the present experiment, considerable destruction in certain tissues might be expected to take place. This last possibility, however, remains to be demonstrated.

Summary

1. The amount of deposition and consequent rate of disappearance of digitoxin from various tissues of the rat, rabbit, and dog after parenteral administration of the drug were studied.

2. No special predilection was shown by digitoxin for deposition in the cardiac tissue of any animal studied although the heart of the dog retained digitoxin longer than did some of its other organs. Even in this animal, however, the kidney contained detectable amounts of digitoxin far longer than the heart.

3. Concentration of digitoxin appeared to occur in the body organ(s) chiefly involved in its excretion. Thus, it was found in highest concentration in the liver of the rat and in the kidney of the dog.

4. Digitoxin disappeared slowly from the tissues of the rat and dog but rather rapidly from the tissues of rabbit.

5. The possible fate of digitoxin in the animal and human body was discussed in the light of the above observations.

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