The Rate of Disappearance of Lanatoside C. and Digitoxin from the Blood of Rats

By René Bine, Jr., M.D. and Meyer Friedman, M.D.

With the technical assistance of Catherine Bland, A.B.

By means of the embryonic duck heart preparation, both lanatoside C. and digitoxin could be detected and quantitatively measured in the sera of rats after parenteral administration of both drugs. A study of the behavior of the two glycosides in blood indicated that a striking difference existed in the respective rates of disappearance of both drugs from the bloodstream.

The RAPID disappearance of lanatoside C. from the blood stream of human subjects who had received 1.2 mg. of the drug by intravenous injection already has been reported by us. It also was thought desirable to determine the rate of disappearance of the same drug and of digitoxin from the blood of rats after the latter had received either of the two drugs by intravenous injection. The results of such a study are herein reported.

From The Mount Zion Hospital, The Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif.

This work was aided by grants from The Life Insurance Medical Research Fund, The United States Public Health Service, and the Sandoz Chemical Works.

To aid was granted the Sandoz Chemical Company, for Cardiovascular Research, San Francisco, Calif. Also the technical assistance of CATHERINE BLAND, A.B.

Normal male, adult, albino rats (average wt.: 125 grams) were employed in the study. One series of rats (73) was given lanatoside C., 1.0 µg per Gm. of body weight, by vein. Single blood samples (2.0 to 3.0 cc.) then were obtained from these rats 1, 3, 5, 10, 15, 20, 30, and 60 minutes after the introduction of the drug. Each sample was allowed to clot, then centrifuged, the serum removed and stored in the refrigerator for twenty-four hours. The serum samples then were assayed for their lanatoside C. content by the employment of embryonic duck hearts, as previously described.

Another comparable series of rats (179) was given digitoxin (Sandoz), 1.0 µg per Gm. of body weight, by vein. Blood samples were obtained 5, 20, 30, and 60 minutes; also at 2, 4, 6, 8, 12, 16, and 24 hours after injection. These were treated and assayed exactly as described above.

### Methods

Normal male, adult, albino rats (average wt.: 125 grams) were employed in the study. One series of rats (73) was given lanatoside C., 1.0 µg per Gm. of body weight, by vein. Single blood samples (2.0 to 3.0 cc.) then were obtained from these rats 1, 3, 5, 10, 15, 20, 30, and 60 minutes after the introduction of the drug. Each sample was allowed to clot, then centrifuged, the serum removed and stored in the refrigerator for twenty-four hours. The serum samples then were assayed for their lanatoside C. content by the employment of embryonic duck hearts, as previously described.

Another comparable series of rats (179) was given digitoxin (Sandoz), 1.0 µg per Gm. of body weight, by vein. Blood samples were obtained 5, 20, 30, and 60 minutes; also at 2, 4, 6, 8, 12, 16, and 24 hours after injection. These were treated and assayed exactly as described above.

### Table 1.—The Rate of Disappearance of Lanatoside C. and Digitoxin from Serum of the Rat

<table>
<thead>
<tr>
<th>Time After Inj.</th>
<th>No. Rats</th>
<th>Lanatoside C. (serum) (µg/cc.)</th>
<th>No. Rats</th>
<th>Digitoxin (serum) (µg/cc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average</td>
<td>Range</td>
<td>Average</td>
</tr>
<tr>
<td>1 min.</td>
<td>4</td>
<td>5.2</td>
<td>5.0 to 5.5</td>
<td>10</td>
</tr>
<tr>
<td>3 min.</td>
<td>3</td>
<td>3.7</td>
<td>2.0 to 6.0</td>
<td></td>
</tr>
<tr>
<td>5 min.</td>
<td>8</td>
<td>0.48</td>
<td>0.40 to 7.0</td>
<td>10</td>
</tr>
<tr>
<td>10 min.</td>
<td>11</td>
<td>0.27</td>
<td>0.15 to 0.40</td>
<td>17</td>
</tr>
<tr>
<td>15 min.</td>
<td>14</td>
<td>0.20</td>
<td>0.15 to 0.30</td>
<td>17</td>
</tr>
<tr>
<td>20 min.</td>
<td>13</td>
<td>0.18</td>
<td>0.15 to 0.30</td>
<td>14</td>
</tr>
<tr>
<td>30 min.</td>
<td>15</td>
<td>0.13</td>
<td>0.05 to 0.20</td>
<td>17</td>
</tr>
<tr>
<td>60 min.</td>
<td>5</td>
<td>N.D.*</td>
<td>N.D.</td>
<td>26</td>
</tr>
<tr>
<td>2 hrs.</td>
<td></td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>4 hrs.</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>6 hrs.</td>
<td></td>
<td></td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>8 hrs.</td>
<td></td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>12 hrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 hrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* N. D. = No glycoside detected.
RESULTS

Rate of Disappearance of Lanatoside C. Lanatoside C. was found (see table 1) to disappear very quickly from the serum of the injected rats. Although each cc. of serum contained 5.2 μg one minute after injection, only 0.48 μg could be found five minutes after injection. No lanatoside C. (i.e., less than 0.05 μg per cc. of serum) could be detected in the serum of any of five rats an hour after the intravenous injection of the drug.

Rate of Disappearance of Digitoxin. The intravenous injection of digitoxin into the rats could not be done quickly because of the large amount of alcohol (in which the digitoxin was dissolved) which also had to be injected. The first blood samples, therefore, were obtained approximately five minutes after the beginning of the injection. As table 1 indicates, digitoxin, unlike lanatoside C., disappeared from the blood stream at a relatively slow rate. Thus, its average concentration at the end of five minutes was 2.1 μg per cc. of serum. The concentration then slowly dropped until, at the end of an hour, only 1 μg per cc. remained. Although there was little decrease during the second hour, a progressive diminution occurred after that up to the sixth hour, after which time the concentration of digitoxin remained relatively constant until the eighth hour. After the eighth hour, it progressively decreased so that, whereas small amounts of digitoxin could be detected in the serum of most of the rats sixteen hours after injection, none was found twenty-four hours after injection.

DISCUSSION

In the above experiments, sufficient cardiac glycosides were administered (1 μg per gram of body weight) so that if complete diffusion of the drugs occurred throughout the tissues of the rat, each gram of tissue, including the blood, should contain 1 μg of glycoside. However, within thirty minutes after its intravenous injection, the concentration of lanatoside C. in serum fell to 0.13 μg per cc. Within an hour, moreover, none could be detected. This experimental finding not only indicated that lanatoside C. left the blood stream extraordinarily rapidly, but also that some tissue (or tissues) other than blood was (1) excreting, (2) destroying, or (3) storing the glycoside.

On the other hand, digitoxin did not appear to leave the blood stream at nearly so rapid a rate. The probable adsorption of this drug by the plasma proteins perhaps accounts for its persistence in the blood for over twelve hours. However, its concentration in serum began to fall below 1 μg per cc. one hour after its injection, indicating that it, too, was being excreted, destroyed, or stored by some extravascular tissue(s).

Although no evidence was obtained in this present study concerning the exact cause of disappearance of the two glycosides from blood, it seems quite unlikely that a significant amount of digitoxin was excreted via the kidney because it was found in a previous study that little or no digitoxin was excreted in the urine of rats receiving the amount of glycoside employed in the present study.

CONCLUSIONS

1. The rates of disappearance of both lanatoside C. and digitoxin from the blood of injected rats were studied.

2. Lanatoside C. disappeared from the blood of rats thirty to sixty minutes after the injection of 1 μg. per gram of body weight.

3. Digitoxin at the same dosage disappeared much more slowly from the blood.

ACKNOWLEDGMENTS

The authors wish to express their thanks to Vivian Seay, Nancy Bryant, and Maude Gardner for their aid in the performance of this experiment.

REFERENCES


The Rate of Disappearance of Lanatoside C. and Digitoxin from the Blood of Rats
RENÉ BINE, JR., MEYER FRIEDMAN and CATHERINE BLAND

_Circulation_. 1950;1:1182-1183
doi: 10.1161/01.CIR.1.5.1182
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1950 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/1/5/1182

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/