Hypothermia modifies to a considerable degree the effects of various drugs. Among those investigated in the past have been central nervous system stimulants and depressants, hormones, epinephrine, acetylcholine, insulin, thyroid, ethyl alcohol, Dicumarol, oxygen, carbon dioxide, procaine, and cocaine.1

However, the effect of hypothermia on the action of digitalis has not been extensively investigated. Most of the studies performed have been obtained from cold-blooded animals and in isolated hearts. Experiments on the frog2-7 using various digitalis glycosides, revealed a progressive increase in the mean lethal dose (MLD) of the drug as the temperature was lowered. Studies on isolated rabbit and chick hearts6-8 revealed similar findings. It is also of interest to note that with an increase above normal in the body temperature, a decrease in the toxic dose of digitalis was observed.4-14

Only a few reports are available on the tolerance of the warm-blooded animal to digitalis under hypothermic conditions. Most of these are limited to a relatively few animals or involve a comparison of certain degrees of toxicity. For example, in one study of four cats during hypothermia,10 the dose of digitalis required to produce cardiac arrest was twice that observed in four normothermic animals. In another report,10 the toxicity of ouabain, as determined by the production of extrasystoles, was compared to that of the hypothermic animal (temperature 26 ± 1 C.);

the latter was found to be more resistant to the production of these extrasystoles even with larger doses.

The object of this study was to determine the tolerance of the dog to digitalis during hypothermia as compared to the normothermic animal, using a modification of the method of Hatcher and Brody.17

Methods

Fourteen mongrel dogs, weighing 10 to 25 Kg., were used in these experiments. All the animals were prepared in the following manner: Anesthesia was induced by the intravenous administration of pentobarbital at a dose of 30 mg./kg. Positive pressure breathing was instituted by an apparatus set at 16 c.p.m. (cycles per minute). Femoral vein and artery on one side were exposed and cannulated for drug infusion and arterial blood pressure recording, respectively. The arterial cannula was connected to a Statham strain gauge and two-channel Sanborn direct-writing electrocardiographic recorder. Electrocardiographic and blood pressure recordings were made almost continuously during the experiment.

A single lot of Digoxin powder* was used in all experiments. The powder was dissolved in 70 per cent alcohol to contain 0.5 mg./ml. (USP) and diluted in normal saline according to the animal's weight, so that when infused at a constant rate of 1 ml./min. the lethal dose for the normothermic animal was reached in 90 ± 15 minutes. The drug was infused by the means of a constant flow apparatus at a rate of 1 ml/min.

Hypothermia was accomplished in the following manner: The animal was totally shaved and immersed in a tub filled with ice water, leaving the head and neck out of the bath. The rectal temperature was obtained with a thermistor probe deeply inserted in the rectosigmoid colon and connected to an electric thermocouple apparatus (Yellow Spring Instrument Co.). The temperature was allowed to drop to a level of 2 to 3 C. above the desired level of hypothermia (in most cases between 30 and 28 C.), allowing for further

*Supplied by Burroughs Wellcome Laboratory, Tuckahoe, New York.
Table 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>Weight (Kg.)</th>
<th>Temperature (°C.)</th>
<th>Lethal dose total mg. mg./Kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.3</td>
<td>38</td>
<td>2.295 0.244</td>
</tr>
<tr>
<td>2</td>
<td>10.3</td>
<td>38</td>
<td>2.475 0.240</td>
</tr>
<tr>
<td>3</td>
<td>17.2</td>
<td>39</td>
<td>3.690 0.214</td>
</tr>
<tr>
<td>4</td>
<td>24.0</td>
<td>38</td>
<td>6.020 0.251</td>
</tr>
<tr>
<td>5</td>
<td>10.7</td>
<td>39</td>
<td>2.555 0.246</td>
</tr>
<tr>
<td>6</td>
<td>9.3</td>
<td>38.0</td>
<td>2.220 0.238</td>
</tr>
</tbody>
</table>

Average LD = 0.239 mg./Kg. ± 0.01 S. E.

Table 2

<table>
<thead>
<tr>
<th>Dog</th>
<th>Weight (Kg.)</th>
<th>Temperature (°C.)</th>
<th>Lethal dose total mg. mg./Kg.</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5.500 0.491</td>
</tr>
<tr>
<td>2</td>
<td>20.9</td>
<td>28</td>
<td>8.662 0.415</td>
</tr>
<tr>
<td>3</td>
<td>9.1</td>
<td>28</td>
<td>5.639 0.619</td>
</tr>
<tr>
<td>4</td>
<td>13.1</td>
<td>26</td>
<td>7.565 0.578</td>
</tr>
<tr>
<td>5</td>
<td>11.3</td>
<td>26</td>
<td>5.310 0.467</td>
</tr>
<tr>
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<td>8.7</td>
<td>24</td>
<td>3.625 0.417</td>
</tr>
<tr>
<td>7</td>
<td>8.2</td>
<td>25</td>
<td>3.760 0.458</td>
</tr>
<tr>
<td>8</td>
<td>14.0</td>
<td>24</td>
<td>0.370 0.455</td>
</tr>
</tbody>
</table>

Average LD = 0.489 mg./Kg.

downdrift in temperature which occurred when the animal was removed from the bath. In this manner, the time required to obtain desired temperature level was approximately 20 to 30 minutes.

Two groups of experiments were performed. In group 1 (normothermic animals), six dogs served as a control group for determination of the MLD of Digoxin. The endpoint of the experiments was relatively acute and was characterized by a sudden drop of arterial blood pressure to zero and by the appearance of ventricular fibrillation. In group 2 (hypothermic animals), hypothermia (24 to 28 °C.) was induced in eight dogs, as described above. The Digoxin solution was then infused and electrocardiographic and blood pressure recordings were obtained in a manner similar to that described above.

Results

Control Group

The lethal dose (LD) of Digoxin determined in this control group of six dogs is given in table 1. The length of time of the infusion in all cases fell into the predicted range of 90 ± 15 minutes (75 to 97 minutes). The LD of the drug averaged 0.239 mg./Kg. (S. E. ± 0.01). In all six cases, the endpoint was sharply defined by the onset of ventricular fibrillation and the corresponding sudden drop of the arterial blood pressure to the zero level (fig. 1). Analysis of the electrocardiographic tracings showed the usual patterns associated with the toxic effect of digitalis on the myocardium. These consisted of prolongation of the P-R interval and changes in the S-T and T segments, as well as the appearance of all forms of supraventricular, nodal, and ventricular arrhythmias. The first significant signs of digitalis toxicity (first degree A-V heart block and early ectopic activity) appeared after 40 to 45 per cent of the LD of the drug was administered, while severe toxicity (ventricular tachycardia) was observed after 75 to 85 per cent of the LD was given (fig. 1).

Hypothermic Animals

The results of these eight experiments are summarized in table 2. The temperature of the animals during the infusion period ranged from 28 to 24 °C. This was due to a tendency of the temperature to drift downward by 3 to 4 °C. after cooling was stopped. There was a definite increase in tolerance to Digoxin, as shown by an increase of the LD of the drug compared to the average dose obtained in the normothermic animal. The figures ranged from 0.415 mg. to 0.619 mg./the dose for the normothermic state. With an average lowering of the temperature of 12 Kg., an increase of 74 to 159 per cent over C, the LD increased by an average of 110 per cent. However, at the hypothermic level studied, there was no definite relationship between the degree of hypothermia and the increase of tolerance to the drug.

Spontaneous arrhythmias, which are occasionally observed during hypothermia, were not seen in any of this group. The heart rate slowed from an average of 167 per minute before cooling to 80 per minute at the lower temperature; during the infusion of digitalis the rate tended to be slow even when ectopic rhythms occurred (fig. 2). The P-R interval increased from averages of 0.08 to 0.14 second, and digitalis produced further prolongation to 0.26 second. The QTc interval was also notably prolonged during hypothermia.
Cardiac effects of a constant infusion of Digoxin in the normothermic dog. Electrocardiogram (lead II) and arterial blood pressure recordings are shown, taken at various intervals during the infusion of the drug. (a) Control tracing. (b) Tracing after infusion of 1.35 mg. of Digoxin in 45 minutes; note the prolongation of the P-R interval and the depression of the S-T segment. (c) After a dose of 1.62 mg., infused in 54 minutes, atrial tachycardia with A-V dissociation and ventricular bigeminy are present. The blood pressure has dropped significantly. (d, e, and f) Tracing obtained after infusion of 1.86, 2.16, and 2.19 mg. of Digoxin, in periods of 62, 72, and 73 minutes, respectively. Ventricular tachycardia of varying origin has appeared. (g) Slow speed tracing showing the endpoint of the experiment. The LD of Digoxin is determined at the onset of ventricular fibrillation and a coincident sudden drop of the blood pressure to the zero level.

From a control average figure of 0.34 second, the QTc increased to 0.49 second. During the infusion of digitalis, the QTc either shortened slightly or remained close to the control value. Changes of the QRS, S-T, and T segments also occurred, but these were variable and inconsistent. In this group, the first signs of digitalis toxicity appeared after 45 to 55 per cent of the LD was administered (first degree A-V heart block and initial
Figure 2
Cardiac effects of a constant infusion of Digoxin in the hypothermic dog. Electrocardiogram (lead II) and blood pressure recordings taken at various intervals during the infusion of the drug are shown. (a) Control tracing, temperature 39 C. (b) Tracing during hypothermia temperature 28 C. Note the slowing of the heart rate and prolongation of the P-R interval. (c and d) Tracings after doses of Digoxin of 2.485 and 4.595 mg. infused in periods of 63 and 148 minutes, respectively. Note that further bradycardia and P-R interval prolongation have occurred. It is of interest that the
appearance of ectopic beats); signs of severe toxicity (ventricular tachycardia) appeared after 77 to 85 per cent of the LD was given. It is of interest to note that even though the LD of the drug was increased under hypothermia, the signs of various degrees of toxicity appeared at percentages of the LD similar to those of normothermia.

Discussion

A previous study from this laboratory\(^1\) used this method of standardization of various digitalis glycosides and gave similar results for the lethal dose of Digoxin (0.239 mg./Kg.).

The effect of hypothermia on myocardial activity, particularly as reflected in the electrocardiogram, has been the subject of numerous reports in the literature.\(^{10-24}\) The changes most constantly observed are: (1) a considerable slowing of the heart rate; (2) an increase in conduction parameters (P-R and QRS intervals); and (3) a marked increase in electrical systole (Q-T interval). These changes occurred in all our cases with induction of hypothermia. They are attributed to the direct effect of hypothermia on the metabolic processes within the myocardium,\(^24\) since they occur with direct application of cold to the cardiac muscle. Most striking was the fact that the hypothermic heart, when exposed to toxic doses of digitalis, did not develop ectopic activity until an amount of the drug much over the predicted LD was infused. When ectopic rhythms occurred, the rate, as compared to the normothermic animal (fig. 2), remained relatively slow. On the other hand, the QTc interval was prolonged at the low temperature and only slightly shortened by the infusion of toxic doses of digitalis.

The increase of the LD during hypothermia to a level approximately double that for the normothermic animal is of considerable practical as well as theoretical interest. The mechanism of this effect of hypothermia is undoubtedly complex and involves many factors. In a general way, the tolerance to drugs is increased during hypothermia.\(^1-8, 13\) Some of the underlying mechanisms which may be responsible for the increased lethal dose of digitalis follow: (a) There is a decrease in general metabolism and oxidative enzymatic processes are slowed. (b) There is a decrease in the coronary blood flow and myocardial oxygen consumption.\(^{25}\) (c) There is an inhibition of impulse formation.\(^{26}\) (d) A depression of conduction is present within the heart muscle.\(^{26}\) (e) The close relationship which exists between digitalis and potassium ions is well known; although it is not yet definitely established, it is generally agreed that toxic doses of digitalis lower the myocardial cellular content in potassium.\(^{27}\) Conversely, changes in the myocardial content of potassium influence the action of digitalis. On the other hand, the hypothermic myocardium has been shown to gain potassium, at least under certain conditions of blood pH.\(^{28, 29}\) This apparently opposite effect of digitalis and hypothermia on the potassium concentration in the heart muscle could possibly be an additional factor which might explain the increased tolerance to digitalis in hypothermia. (f) Finally, because of the concomitant hypotensive state, there is probably a decrease in the amount of the digitalis that comes into direct contact with the heart muscle.

The clinical implications of these findings are obvious. Some investigators\(^4, 14\) have warned in the past against the danger of toxicity with the use of the accepted therapeutic doses of digitalis in febrile states. With

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\(^{1}\) The LD of the drug is determined at the onset of ventricular fibrillation and the coincident fall of the blood pressure to the zero level. The LD here is 7.565 mg. or 0.578 mg./Kg. of body weight. This is over twice the predicted LD for the normothermic animal.
the increasing use of hypothermia in recent years, attention should be called to the modification of tolerance to digitalis under these circumstances. When the use of digitalis becomes necessary during hypothermia, one should be aware of the increased tolerance and the probable need of larger-than-usual doses for therapeutic effects. Conversely, in patients who have received digitalis during hypothermia, rewarming might bring about severe toxic reactions to the drug. The above findings also bring up the possibility of using hypothermia in the therapy of severe cases of digitalis toxicity.

Summary

The tolerance to digitalis was studied in eight dogs during hypothermia and compared to that of six normothermic animals. The average lethal dose of Digoxin for the dog under hypothermia was found to be approximately double that of the normothermic dog. Thus, hypothermia significantly increases the tolerance of the drug. The possible explanation for this finding is discussed. It appears that hypothermia, by its direct effect on myocardial metabolism, might counteract the toxic effects of digitalis. Potassium, affected by both hypothermia and digitalis, is also a possible factor. The clinical implications of this finding are discussed.

References


Effect of Hypothermia on the Tolerance of Dogs to Digitalis
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