Effect of Potassium and "Toxic" Doses of Digitalis on the Myocardium

By Charles Fisch, M.D., Edward F. Steinmetz, M.D., Alfred F. Fasola, Ph.D., M.D., and B. L. Martz, M.D.

This study was designed to evaluate further the antagonism between digitalis and potassium. Potassium was given by intravenous infusion to six dogs (1) before digitalization, (2) after injection of "therapeutic" doses of digitoxin, and finally (3) after injection of "toxic" doses of the drug.

Potassium is used in the treatment of cardiac arrhythmias thought to be due to toxic effects of digitalis. In an effort to study the presumed digitalis and potassium "antagonism" the latter was administered to "fully" digitalized patients with atrial fibrillation with or without ventricular ectopic beats. The result was one of depression of both the conduction through the A-V node and of ventricular ectopic beats. The amount of potassium never exceeded 3 mEq./Kg. of body weight given intraperitoneally. The infusion contained 155 mEq./L. of potassium as buffered phosphate salts in distilled water. The solution was injected at a rate of 4.6 ml. or 0.69 mEq. of potassium per minute, the uniformity of administration being assured through the use of a flowmeter. In experiments 1, 4, 5, 9, 10, 13, and 14 (table 1) the infusion was discontinued after a total of 2 mEq. and in experiment 7 after 0.3 mEq./Kg. of potassium was administered. In subsequent trials the injection was continued until A-V block (table 1, exper. 6, 16, 17), supraventricular arrhythmias (table 1, exper. 2, 11) or cardiac standstill (table 1, exper. 3, 8, 12, 15, 18) appeared. The amount of potassium never exceeded 3 mEq./Kg. The electrocardiogram was monitored continuously, using an oscilloscope. All permanent tracings were recorded with direct writing equipment using standard lead II connections.

The present study was undertaken to elucidate further the relation between intravenously administered potassium and digitalis, using dogs intoxicated with digitoxin.

Method

Eighteen experiments were performed on 6 mongrel dogs weighing 8 to 12 Kg. The animals were anesthetized with 30 mg. of sodium pentobarbital per Kg. of body weight given intraperitoneally. The infusion contained 155 mEq./L. of potassium as buffered phosphate salts in distilled water. The solution was injected at a rate of 4.6 ml. or 0.69 mEq. of potassium per minute, the uniformity of administration being assured through the use of a flowmeter. In experiments 1, 4, 5, 9, 10, 13, and 14 (table 1) the infusion was discontinued after a total of 2 mEq. and in experiment 7 after 0.3 mEq./Kg. of potassium was administered. In subsequent trials the injection was continued until A-V block (table 1, exper. 6, 16, 17), supraventricular arrhythmias (table 1, exper. 2, 11) or cardiac standstill (table 1, exper. 3, 8, 12, 15, 18) appeared. The amount of potassium never exceeded 3 mEq./Kg. The electrocardiogram was monitored continuously, using an oscilloscope. All permanent tracings were recorded with direct writing equipment using standard lead II connections.

After a control cardiogram was taken, further records were made whenever any change was observed on the oscilloscope. At the end of the control infusion, digitoxin in doses of 0.2 or 0.3 mg./Kg. was administered intramuscularly and the infusion of potassium was repeated within 48 hours. After approximately three weeks the procedure was repeated; this time however, the last infusion of potassium was repeated within 48 hours. After approximately three weeks the procedure was repeated; this time however, the last infusion of potassium was preceded by intramuscular injection of 0.5 mg. of digitoxin per Kg. Animal 5 died 12 hours after initial infusion of potassium and administration of 6.0 mg. of digitoxin. The cause of death was not ascertained (table 1, exper. 16).

Plasma potassium, using femoral artery or intracardiac blood, was determined during control period, at the end of infusion, and one and two hours after the infusion was discontinued. Urinary excretion of potassium was recorded in six experiments for three hours from start of infusion.

All the data were analyzed with respect of (1) duration of infusion, (2) plasma K levels at the time the injection was discontinued, and (3) electrocardiographic changes. In the latter the time...
Table 1.—Effect of the Infusion on Serum Potassium Level and the Electrocardiogram

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Date of infusion</th>
<th>Date of potassium infusion</th>
<th>Duration of infusion (min.)</th>
<th>Amount of K infused (mEq.)</th>
<th>Control</th>
<th>Early of infusion</th>
<th>P wave</th>
<th>Protracted P</th>
<th>A-V block</th>
<th>Earliest demonstrable change of contour or interval of the EKG (minutes after start of infusion)</th>
<th>Rhythm at end of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8-26-58</td>
<td>28</td>
<td>10.52</td>
<td>12.0*</td>
<td>6.8</td>
<td>21</td>
<td>18</td>
<td>21</td>
<td>18</td>
<td>S-A rhythm, no A-V block</td>
<td>P waves not identifiable, irregular ventricular rhythm, atrial fibrillation</td>
</tr>
<tr>
<td>2</td>
<td>8-27-58</td>
<td>21</td>
<td>14.40</td>
<td>11.8*</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>S-A rhythm, no A-V block</td>
<td>CARDIAC STANDSTILL</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>9-15-58</td>
<td>13</td>
<td>8.97</td>
<td>5.0</td>
<td>5.0</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>2° A-V block</td>
<td>S-A rhythm, no A-V block</td>
</tr>
<tr>
<td>9</td>
<td>7-29-58</td>
<td>30</td>
<td>20.7</td>
<td>4.3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3° A-V block</td>
<td>CARDIAC STANDSTILL</td>
</tr>
<tr>
<td>10</td>
<td>2.2</td>
<td>7-31-58</td>
<td>23</td>
<td>15.87</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>S-A rhythm, no A-V block</td>
<td>A-V nodal rhythm</td>
</tr>
<tr>
<td>11</td>
<td>9-9-58</td>
<td>39</td>
<td>29.91</td>
<td>3.7</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>2° A-V block</td>
<td>S-A rhythm, no A-V block</td>
</tr>
<tr>
<td>12</td>
<td>4.6</td>
<td>9-11-58</td>
<td>13</td>
<td>8.97</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>2° A-V block</td>
<td>CARDIAC STANDSTILL</td>
</tr>
<tr>
<td>15</td>
<td>8-26-58</td>
<td>35</td>
<td>24.15</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>S-A rhythm, no A-V block</td>
<td>S-A rhythm, no A-V block</td>
</tr>
<tr>
<td>16</td>
<td>9-18-58</td>
<td>39</td>
<td>26.94</td>
<td>3.9</td>
<td>3.9</td>
<td>3.9</td>
<td>3.9</td>
<td>3.9</td>
<td>3.9</td>
<td>S-A rhythm with prolonged P-R interval</td>
<td>S-A rhythm, no A-V block</td>
</tr>
</tbody>
</table>

*Experiments 3, 8, 12, 15, 18.
when any alteration in contour or duration of the P, P-R, QRS, ST, or T appeared was noted.

In analyzing the results, a comparison was made between two groups of experiments. Group A included animals which received no digitoxin (table 1, exper. 1, 4, 6, 9, 11, 13, 16, 17) and those that were given either 0.2 mg. (table 1, exper. 5, 10) or 0.3 mg. (table 1, exper. 2, 7, 14) of the drug per Kilogram of body weight before the potassium was infused. Group B consisted of the animals treated with 0.5 mg. of digitoxin per Kg. (table 1, exper. 3, 8, 12, 15, 18). Such a division allowed us to compare the effects of K in the digitoxin "intoxicated" animals with those in animals not intoxicated with the drug.

RESULTS

In group B (table 1, exper. 3, 8, 12, 15, 18) relatively small amounts of potassium caused a rapid rise in plasma level of such magnitude as to result in early cardiac standstill.

Duration of Infusion. The duration of infusion in group A averaged 33.3 minutes (22.7 mEq. of K), and at the end all the animals were alive. Of these 13 infusions, 5 were discontinued because of the appearance of either supraventricular arrhythmia or A-V block (table 1, exper. 2, 6, 11, 16, 17). In the re-
Fig. 2. Experiment 14, belongs to group A. The potassium was given after prior administration of 3.0 mg. of digitoxin. The changes after 35 minutes of infusion (24.1 mEq.) consisted of tenting of T and lowering of P waves. The S-T segment was slightly depressed. In contrast, experiment 15 (group B) performed after administration of 5.0 mg. of digitoxin showed, in rapid succession, spread of the QRS, prolongation of P-R interval with 2° block appearing immediately before ventricular standstill. The latter occurred after only 4 minutes of infusion (2.76 mEq. of K).

remaining 8 the injection was continued, irrespective of presence or absence of EKG changes until the contemplated dose of potassium was infused (table 1, exper. 1, 2, 6, 9, 10, 11, 13, 14). Group B was infused for an average of only 8.8 minutes (6.1 mEq. of K), and at the end of that time the animals were dead as a result of ventricular standstill (fig. 1, exper. 8; fig. 2, exper. 15; fig. 3, exper. 12; fig. 4, exper. 3; fig. 5, exper. 18).

Plasma Potassium. The plasma potassium in group A at the end of infusion varied from 6.6 to 9.3 with an average of 7.8 mEq./L., while that in group B was from 9.4 to 13.4 with an average of 11.6 mEq./L. The determinations in group B were done on intracardiac blood.

Electrocardiographic Changes. Depression of A-V conduction manifested by simple prolongation of P-R interval was observed in 8 of the 13 experiments comprising group A after an average of 28.8 minutes of infusion (table 1, exper. 2, 6, 9, 10, 11, 13, 16, 17). In group B all animals showed prolongation of P-R after an average of 4.0 minutes. Higher degrees of A-V block were seen in 7 of group A and after 31.5 and in all of group B (fig. 1, exper. 1; fig. 2, exper. 15; fig. 3, exper. 12; fig. 4, exper. 3; fig. 5, exper. 18) after an average of 6.6 minutes.

The earliest demonstrable change affecting the QRS was alteration in contour without discernible prolongation of conduction. Prolongations by 0.02 second and that beyond 0.10 second were treated separately. The change in contour was observed in 10 experiments of group A after an average of 19.8 minutes, prolongation by 0.02 second in 6 after an average of 32 minutes, and in one infusion of group A prolongation beyond 0.10 second was
FIG. 3. Experiment 11 (group A) was done in a nondigitalized animal. Peaking of T wave occurred at 3, depression of S-T segment at 15, change in appearance of QRS at 29, A-V blocks at 30 and atrial fibrillation (?) at 39 minutes respectively. The animal survived administration of 20 mg. of K.

Experiment 12 (group B) was performed after prior administration of 4.0 mg. of digitalis. Peaking of T wave and change in contour of QRS was present at 2 minutes, spread of QRS was obvious at 6.5 minutes. Higher degree of A-V block and ventricular systole are seen at 10 and 12 minutes respectively after an injection of 8.2 mEq. of potassium.

recorded (table 1, exper. 10). In group B, change in contour, prolongation by 0.02 second and delay beyond 0.10 second was observed in all infusions after an average of 3.0, 4.6 and 6.5 minutes respectively. In this group electrical alternans of the QRS was a rather frequent finding.

Depression of S-T segment of more than 0.5 mm. was present in all of group A after an average of 23.0 minutes and in four out of five in group B after an average of 3.0 minutes.

Gradual depression of A-V and myocardial conduction was manifest by prolonged P-R interval, A-V blocks and a spread of the QRS.

Detailed observations made during each experiment as to the duration and rate of injection, amount of potassium infused, plasma potassium levels, digitalis administration, and electrocardiographic changes are given in table 1. The electrocardiographic changes are depicted in figures 1 to 5.

DISCUSSION

A possible explanation of the more rapid rise and the high level of plasma potassium in animals intoxicated with digitalis is a blocking effect of the drug on the cell membrane transport of this cation. Alternate explanations would include cumulative effect of the infused potassium, anesthesia, and anoxia. In this study it was observed that when two consecutive infusions were performed without "toxic" doses of digitalis no deleterious effects were detected. It has been shown that extra potassium following acute loading is usually excreted within 1 to 3 hours, and furthermore, Thatcher and his associates found that repeated sublethal injections of potassium increase the animals' tolerance for this cation. In our series the control plasma potassium was the same in groups A and B. Attempt has been made to minimize other factors by using the animal as its own control. Many workers have found that toxic doses of
POTASSIUM AND DIGITALIS

FIG. 4. Experiment 2 (group A) was done 24 hours after 3 mg. of digitoxin was injected intramuscularly. Tearing of T waves was present at 10 minutes, change in contour of QRS, disappearance of P waves and appearance of atrial fibrillation was noted at 21 minutes. The animal survived injection of 14.4 mEq. of K.

Experiment 3 (group B) was performed after administration of 5.0 mg. of digitoxin. Depression of ST segment appeared at 4 minutes, the QRS began to show evidence of spreading, and the P-R became prolonged at 6 minutes. Higher degrees of A-V block appeared at 8 minutes. Atrial activity was difficult to find at 12 minutes. The animal was dead at 12 minutes after administration of 8.2 mEq. of K. Note the alternans of QRS at 10 minutes. This phenomenon was observed frequently during our study.

digoxin cause egress of potassium from the cell and reduce the transfer rate in cardiac and skeletal muscle.11-17 Therefore it would be reasonable to assume that as long as the toxic levels of digitalis block transfer of potassium into the cell the latter, if injected, will reach high levels in the extracellular compartment. Lack of any significant difference between the nondigitalized animals and those infused with potassium after administration of 0.2 or 0.3 mg. of digitoxin per Kg. is in keeping with the findings of many workers that only toxic doses of digitalis cause a significant loss of intracellular potassium.12-14, 18, 19

The observations made during this study correlate to some extent with our earlier findings in "fully" digitalized human beings.6, 7 In each instance the observed change was one of depression of conduction tissue and of the myocardium. So far we have been able to find little if any evidence to support the concept of digitalis and potassium "antagonism" in patients or animals with normal plasma levels of this cation. The evidence presented here on the other hand suggest that potassium given rapidly in the presence of digitalis intoxication and the absence of potassium deficiency may have a deleterious effect.

We feel that further investigation of this problem is needed with special emphasis on (1) state of digitalization, (2) presence or absence of hypokalemia, and (3) speed of administration of potassium.
FIG. 5. Experiment 17 (group A) was performed in a nondigitalized animal. Increase in height of T was noticed at 2 minutes, depression of ST and P with slight change in contour of QRS was present at 14 minutes. P waves disappeared and QRS showed spreading at 31 minutes. At that time the infusion was discontinued. Four minutes later (35 minute strip) a normal sinus rhythm was present. The animal survived administration of 24.0 mEq. of K.

Experiment 18 (group B) was done after injection of 5.0 mg. of digitoxin. Slight change of QRS was obvious at 1 minute, at 4 minutes the ST was depressed, at 6 the P-R prolonged and QRS spread. At 6.5 minutes high degree of A-V block appeared, the QRS became wider and ventricular standstill was noted at 8 minutes after injection of 5.5 mEq. of K. Note the sudden change in direction of QRS (7 minute strip).

SUMMARY

Intravenous potassium was administered 13 times to 6 dogs before digitalization and after administration of "therapeutic" doses of digitoxin. No difference in plasma potassium or electrocardiographic changes was noted between these two sets of experiments, and both are discussed together as group A. The EKG changes consisted of alteration of P and T waves in some, with added A-V blocks and supraventricular arrhythmias in others. There was little or no change of the QRS.

After administration of "toxic" doses of digitoxin intravenous potassium caused a prompt rise in plasma K with depression of conduction through the A-V node and myocardium and resulted in death of the animals (group B).

It is suggested that (1) the effect of potassium in the treatment of arrhythmias accompanying digitalis therapy may be one of nonspecific myocardial depression and (2) that intravenous administration of this cation to organisms intoxicated with digitalis may prove dangerous because of block by digitalis of the intracellular transfer of the infused potassium.

ACKNOWLEDGMENT

We wish to thank Dr. K. G. Kohlstaedt for his continuous encouragement and support.

SUMMARIO IN INTERLINGUA

Kalium intravenousose esseva administrate 13 vices a sex canes ante digitalisation e post le administration de doses "therapeutic" de digitozina. Nullo differentia in le kalium del plasma o in le alterationes electrocardiographic esseva constatate inter le duo mentionate serie de experimentos, e illos es discutite insimul como gruppo A. Le alterationes electrocardiographic esseva consisteva de alterationes del undas P e T in certe casos, con le addition de bloco atrio-ventricular e arrhythmias supraventricular in alteres. Ocurreva pauc o nulle alteration de QRS.
POTASSIUM AND DIGITALIS

Post le administration de doses “toxic” de digitoxina, kalium intravenose causava un prompte aumento del kalium in le plasma con depression del conduction a transverso le nodo atrio-ventricular e le myocardio. Le risultato esseva le morte del animals in iste gruppo (i.e. gruppo B).

Es suggerite (1) che le effecto de kalium in le tractamento de arrhythmias que accompania terapia per digitalis es possibilemente un effecto non-specific de depression myocardial e (2) que le administration intravenose de iste cation a organismos intoxicate per digitalis es possibilemente periculoce a causa del bloco, causate per digitalis, in le transferrimento intracellular del infusionate kalium.

REFERENCES

Effect of Potassium and "Toxic" Doses of Digitalis on the Myocardium

CHARLES FISCH, EDWARD F. STEINMETZ, ALFRED F. FASOLA and B. L. MARTZ

doi: 10.1161/01.RES.7.3.424

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1959 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/7/3/424

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ 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 Research_ is online at:
http://circres.ahajournals.org/subscriptions/