Dibucaine Hydrochloride in the Control of K-Strophanthoside-Induced Ventricular Tachycardia and Other Toxic Manifestations

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Dibucaine hydrochloride in relatively small doses terminated high frequency ventricular tachycardia induced by toxic doses of K-strophanthoside in 9 of 10 dogs. Dibucaine was antidotal to glycoside-induced vagotonia and improved the alertness and apparent general condition of the animals that received it. One death occurred in the 10 strophanthoside tachycardia animals treated with dibucaine, a mortality rate of 10 per cent. Four deaths occurred in seven dogs that received similar doses of strophanthoside but no dibucaine, a mortality rate of 57 per cent.

DIBUCaine HYDROCHLORIDE* has been found in a previous study1 to be an effective suppressor of ventricular tachycardia resulting from myocardial infarction in dogs. This effect was increased and toxic reactions to dibucaine were prevented or minimized by prior administration of phenobarbital. Ventricular tachycardia that results from myocardial infarction is a difficult arrhythmia to control, providing a severe test for antiectopic-rhythm drugs. Results with dibucaine and phenobarbital in those tests suggested that dibucaine might be an effective agent for the suppression of ectopic cardiac rhythms resulting from other causes.

The following experiments were designed to test the effects of dibucaine upon ventricular tachycardia that results from toxic overdosage with digitalis glycosides. It was found that the antidotal effects were not confined to the suppression of ectopic impulses but extended also to certain other aspects of toxic reactions to K-strophanthoside and lanatoside C†. Strophanthoside was chosen as the principal glycoside for use in the study.

TECHNICS

A standard dose of strophanthoside for inducing ventricular tachycardia was established in a preliminary series of experiments. It was found that 0.1 mg. per kilogram sufficed to produce ventricular tachycardia in almost all animals. Smaller doses did not produce the tachycardia. The strophanthoside was administered in a single intravenous dose.

Following these preliminary experiments, 19 dogs were used. Seven were used for tests to record the duration of the strophanthoside-induced ventricular tachycardia when not treated. Ten dogs were used in tests of the ectopic impulse suppressor effect of dibucaine in strophanthoside tachycardia. Two dogs were used to answer specifically the question whether or not dibucaine antagonizes the bradycardia that results from vagotonia induced by cardiac glycosides (strophanthoside was used in one of these animals and lanatoside C in the other).

Morphine, 5 mg. per kilogram, was administered 30 minutes prior to strophanthoside in all dogs except two which received barbiturates. The purpose of the morphine and the barbiturates was the prevention of the severe retching and vomiting which otherwise would be produced by strophanthoside.

In the experiments to test the effectiveness of

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* The dibucaine hydrochloride (Nupercaine hydrochloride) used in these experiments was supplied by Ciba Pharmaceutical Products, Inc. The shortened name dibucaine is used throughout the remainder of this paper.

† The K-strophanthoside (Strophosid) and lanatoside C (Cedilanid) used in this study were supplied by Sandoz Chemical Works, Inc. The names strophanthoside and lanatoside C are used in the remainder of the paper.
The latency of onset of tachycardia after injection varied between 3 and 27 minutes, the average being about 11 minutes. A chart of one of the tachycardias without dibucaine treatment is shown in figure 1.

The durations and maximal frequencies of the strophanthoside ventricular tachycardias in seven dogs that were not treated with dibucaine are shown in table 1. The maximal frequencies in the various experiments ranged from 210 to 260 per minute. Two dogs had tachycardia until death terminated the tests.

Spontaneous termination of the tachycardia occurred in the other five dogs after periods of one and one half hours to five and one quarter hours following injection of the standard tachycardia-inducing dose of strophanthoside. Four deaths occurred in the seven dogs that received tachycardia-inducing doses of strophanthoside but were not treated with dibucaine.

The infusion of dibucaine was begun in each of the 10 dibucaine-treated dogs soon after the tachycardia appeared to be leveling off at a high frequency, 190 to 265. Electrocardiograms reproduced in figure 2 show the ventricular tachycardia (250 per minute) that developed soon after the injection of strophanthoside, and the normal rhythm that was recorded during the first infusion of dibucaine.

### Table 1.—Effects of Strophanthoside without Dibucaine

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Dose stroph. mg./Kg.</th>
<th>Ventricular tachycardia</th>
<th>Duration after inj. stroph.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Max. freq.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>0.1</td>
<td>250</td>
<td>4 hr. 20 min.</td>
<td>Died 48 hours after injection.</td>
</tr>
<tr>
<td>S2</td>
<td>0.1</td>
<td>220</td>
<td>4 hr. 45 min.</td>
<td>Appeared very sick during experiment.</td>
</tr>
<tr>
<td>S3</td>
<td>0.1</td>
<td>210</td>
<td>5 hr. 15 min.</td>
<td>Appeared very sick during experiment.</td>
</tr>
<tr>
<td>S4</td>
<td>0.12*</td>
<td>210</td>
<td>6 hr. 30 min.</td>
<td>Died 4 hr. 55 min. after tachycardia was produced by additional 0.02 mg. per Kg.</td>
</tr>
<tr>
<td>S5</td>
<td>0.1</td>
<td>210</td>
<td>3 hr. 30 min.</td>
<td>Died 4 days after injection.</td>
</tr>
<tr>
<td>S6</td>
<td>0.1</td>
<td>210</td>
<td>Died 55 min.</td>
<td>Very sick, Cheyne-Stokes respiration. Died 55 min. after injection.</td>
</tr>
<tr>
<td>S7</td>
<td>0.1</td>
<td>260</td>
<td>1 hr. 30 min.</td>
<td>Appeared very sick.</td>
</tr>
</tbody>
</table>

Each animal received morphine sulfate, 5 mg. per Kg., to prevent retching and vomiting.

Duration is measured from time of injection to last record that showed ectopic activity.

* Injection of strophanthoside, 0.1 mg. per Kg., did not produce tachycardia in this animal. An additional 0.02 mg. per Kg., was given 1 hour 45 minutes after first injection. Tachycardia followed and persisted to within a few minutes of exitus by cardiac arrest.

dibucaine upon the ventricular tachycardia, the routine procedure was as follows. Morphine, 5 mg. per kilogram, subcutaneously was followed after an interval of 20 to 30 minutes by the intravenous injection of the standard dose of strophanthoside. After the tachycardia was fully established, as demonstrated by series of electrocardiograms, the intravenous infusion of dibucaine was begun. Dibucaine was administered in Locke's solution at a constant rate of 2 mg. per kilogram per hour. The concentration was 2 mg. of strophanthoside per kilogram of animal weight per 100 cc. Infusions were made from a burette via a polyethylene catheter in a saphenous vein.

**RESULTS**

Ventricular tachycardia was produced in 14 of 17 dogs by strophanthoside, 0.1 mg. per kilogram intravenously. In each of the three animals in which this dose failed to produce tachycardia, an additional dose of 0.02 mg. per kilogram precipitated the tachycardia.
DIBUCAINE HYDROCHLORIDE IN VENTRICULAR TACHYCARDIA

Fig. 2. (A) Electrocardiogram showing ventricular tachycardia, 250 per minute, 25 minutes after intravenous injection of strophanthoside, 0.1 mg. per kilogram. (B) Sinus rhythm, 85 per minute, after infusion of dibucaine (Nupercaine), 1.3 mg. per kilogram.

Fig. 3. Chart showing complete experiment from which figure 2 is taken. Squares = heart rate. Circles = ectopic rate.

in an illustrative experiment. The chart from the same experiment (fig. 3) shows the time course of the arrhythmia and treatment in detail. A normal rhythm was restored when the first infusion was about two thirds finished, that is, after administration of about 1.3 mg. per kilogram. The 2 mg. per kilogram infusion was completed and administration stopped. Thirty minutes after the first infusion was finished, ventricular tachycardia returned with a rate of 180 per minute. An additional infusion quickly restored normal rhythm. The infusion was continued until 1 mg. per kilogram had been administered. The rhythm remained normal for two and one half hours after this infusion and then ventricular tachycardia reappeared. Without further treatment the tachycardia subsided spontaneously within the following three hours.

Ventricular tachycardia was suppressed and normal rhythm restored by dibucaine before as much as 2 mg. per kilogram was infused in 9 of the 10 dogs. The other dog appeared very sick following strophanthoside and before dibucaine, and died in cardiac arrest just at the end of infusion of dibucaine, 2 mg. per kilogram in one hour. Administration of this quantity of dibucaine at the rate of infusion employed has been shown to be quite safe in a previous series of 22 dogs. This fatality occurred in one of the two dogs in the treated group which had required an additional dose of strophanthoside (0.02 mg. per kilogram) to induce ventricular tachycardia. The data upon these 10 experiments are summarized in table 2.

Ventricular tachycardia returned after it had been stopped by dibucaine in four of the nine animals, and remained permanently stopped after the first infusion of dibucaine in the other five. An additional small infusion restored normal rhythm permanently or for a period of hours in each of the four animals with recurrence.

Sinus Bradycardia due to Morphine, and to Cardiac Glycoside. The morphine which was used for sedation and antiemetic effect produced a bradycardia which developed before
the injection of strophanthoside. During the ventricular tachycardia that was produced by the strophanthoside, the sinus rate was not observable. After the restoration of sinus rhythm by dibucaine, however, bradycardia again was evident. Sinus bradycardia was observed both before and after the ventricular tachycardia in eight of the nine dogs that received morphine before the administration of strophanthoside. Dibucaine was effective in stopping the ventricular tachycardia, but it evidently did not antagonize the sinus bradycardia. Since bradycardia can be produced by morphine and also by cardiac glycoside, differentiating experiments were planned to determine whether or not dibucaine would antagonize glycoside bradycardia not complicated by morphine.

Bradycardia was produced by cardiac glycosides in two dogs that did not receive morphine. Strophanthoside, 0.08 mg. per kilogram (subthreshold for ventricular tachycardia), was used to produce bradycardia in one of these dogs, and lanatoside C in the same dosage was used to produce bradycardia in the other one. The first of these two dogs received a sedative dose of pentobarbital sodium, 20 mg. per kilogram, instead of morphine for sedation and for prevention of nausea and vomiting. This dose, however, proved to be insufficient to prevent emesis. Following the administration of strophanthoside, the sinus rate showed first an increase and then a decrease. During nausea and vomiting, the sinus rate increased from the control level of 95 to 100 to a maximum of 165. This maximum rate was recorded within 10 minutes after injection of the strophanthoside, and lasted one and one half hours after which vomiting ceased and the sinus rate declined to 60 which may be regarded as a relative bradycardia in this dog.

Dibucaine by venous infusion at a rate of 3
mg. per kilogram per hour increased the heart rate to 103 (and produced vomiting) within 15 minutes. After this there was no further emesis. The dibucaine infusion continued until 3 mg. per kilogram had been given. The heart rate stabilized at about 110 to 115 and remained within this range throughout the two hours of observation after termination of the infusion.

The second dog received pentobarbital sodium, 25 mg. per kilogram, for sedation and antiemetic action. This dose proved to be sufficient to prevent vomiting. Lanatoside C, 0.08 mg. per kilogram, produced a pronounced bradycardia, reducing the heart rate from an average of 85 in control records to a low of 58 within 15 minutes following administration. After the rate had remained at 58 to 60 for 30 minutes, dibucaine infusion began. Within 15 minutes (after infusion of 0.75 mg. per kilogram) the rate had risen to 105. The infusion was continued until 1.5 mg. per kilogram of dibucaine had been given. The heart rate remained between 90 and 130 for about three hours after which the bradycardia returned to a profound degree, varying between 30 and 40 per minute in a series of records. Another infusion of dibucaine, 1.5 mg. per kilogram in 30 minutes, produced an increase in rate to a quite normal frequency of 88. The amount of dibucaine administered was as yet insufficient to maintain permanently a normal sinus rate, therefore a third infusion was begun after an interval of 30 minutes. A normal heart rate again was restored before the end of the infusion of an additional 1.5 mg. per kilogram.

From the foregoing observations on bradycardia, it can be concluded that dibucaine in relatively small quantities antagonizes the bradycardia that results from the administration of digitalis glycosides, but that it does not have a similar effect on bradycardia that results from the action of morphine.

Toxic Reactions and Mortality Rates. Following the administration of the tachycardia-inducing dose of strophanthoside, the dogs appeared very depressed, weak and sick, although morphine prevented signs of nausea. After infusion of dibucaine, 1 to 2 mg. per kilogram, a remarkable improvement in the apparent condition of the animals was observed. More spontaneous movements of tail, eyes and limbs occurred, the eyes seemed clearer and the impression of all observers was that the dogs were more comfortable.

The mortality figures appear to offer more definite evidence that dibucaine antagonizes some toxic effects of glycosides other than ventricular tachycardia. Four deaths occurred in seven dogs that received tachycardia-inducing doses of strophanthoside but no dibucaine. In addition to the two dogs that died during the period of tachycardia (55 minutes and 61 hours after injection) two others died 48 hours and 4 days, respectively, after injection, long after the ventricular tachycardia had ceased spontaneously. Exitus resulted from some other toxic effect or effects of strophanthoside. Mortality rate in the group not treated with dibucaine was 57 per cent. One death occurred in 10 dogs that received tachycardia-inducing doses of strophanthoside and subsequent treatment with dibucaine, a mortality rate of 10 per cent.

Although the mortality percentages undoubtedly would be altered in a larger series, the observations indicate that dibucaine antagonizes a variety of toxic manifestations of the organism to strophanthoside.

Discussion

Dibucaine has proved to be an effective suppressor of high frequency ventricular tachycardia resulting from intoxication with strophanthoside. The dose of dibucaine required over a period of hours has been small, 2 or 3 mg. per kilogram. This is about one third of the dosage required to control severe ventricular tachycardias resulting from myocardial infarction, even with the aid of phenobarbital.1

Phenobarbital was not used in the strophanthoside tachycardia experiments. The morphine that was used to counteract the emetic effect of strophanthoside undoubtedly prevented any emetic reactions that might have resulted from dibucaine administration.

Dibucaine was effective as an antidote to the bradycardia-inducing effect of strophanthoside and of lanatoside C. It also reduced the
mortality rate and improved the condition of
the animals as judged by appearance, attitude
and spontaneous movements. This series of
demonstrated antagonisms to manifestations of
cardiac glycoside toxicity suggests strongly
that dibucaine has a general antitodal effect
upon toxic reactions to cardiac glycosides. A
corollary suggestion is that dibucaine would
benefit patients that have received overdosage
of these substances, whatever the form of the
toxic signs presented.

It is of interest that dibucaine does not
antagonize morphine-induced bradycardia.
Since the vagus nerves are the effector path-
ways in both the morphine and glycoside
bradycardias, it appears to follow that different
nervous system components, afferent to the
vagal nuclei, must act to produce the vago-
tonias that result from morphine and from
cardiac glycosides, and that dibucaine blocks
a component of the glycoside bradycardia
path but no part of the morphine bradycardia
mechanism. These findings may be regarded as
evidence, though inconclusive, against the
hypothesis that the principal toxic effects of
cardiac glycosides in the heart muscle are
secondarily produced by vagotonia.\(^2\) In the
present series of experiments, the appearance
of the animals was improved and mortality
was reduced although vagotonia (from mor-
phine) persisted. It is probable that the prin-
cipal toxic actions as well as the principal
therapeutic actions of digitalis glycosides are
produced by direct effects in cardiac muscle
cells.

The salutary effects of dibucaine following
toxic doses of strophanthoside are in marked
contrast to the effects of procaine amide in
animals that had received toxic doses of oua-
bain. Procaine amide evidently precipitated
ventricular fibrillation and death in a significant
number of animals.\(^3\)

The finding that dibucaine in combination
with phenobarbital is effective in the suppres-
sion of the ventricular tachycardia that results
from myocardial infarction,\(^4\) a difficult kind of
tachycardia to control with the drugs most
commonly used clinically,\(^4, 5\) considered to-
gether with the good control by dibucaine of
tachycardia produced by the glycoside sug-
gests that dibucaine should be considered as an
agent which might be useful in treatment of
ventricular tachycardias from a variety of
causes. It should be borne in mind that pheno-
barbital prevents undesirable reactions to
dibucaine as well as to cocaine and other
members of the cocaine-like local anesthetic
series.\(^6, 7, 8, 9\)

Interest in dibucaine as an agent for use in
the treatment of ectopic rhythms is increased
by reason of its chemical relationship to both
quinidine and procaine. Dibucaine has been
described chemically\(^9\) as 2 butoxy-N-(2-dietylaminoethyl) cinchoninamide hydrochlo-
ride, with the structural formula:

\[
\begin{align*}
\text{N} & \quad \text{O-CH}_2(\text{CH}_3)_2 \text{CH}_3 \\
\text{C-NH-CH}_2 & \quad \text{CH}_3 \text{CH}_2 \text{N(\text{CH}_3 \text{CH}_3)_2 \cdot HCl}
\end{align*}
\]

**Summary**

K-strophanthoside, 0.1 mg. per kilogram,
induced high frequency ventricular tachycardia
in 14 of 17 dogs. In each of the other three ani-
mals an additional dose of 0.02 mg. per kilo-
gram precipitated the tachycardia. Nausea and
vomiting due to strophanthoside were pre-
vented by a prior dose of morphine.

Ten dogs with strophanthoside-induced
ventricular tachycardia were treated by intrav-
avenous infusion of dibucaine in Locke's solu-
tion. In 9 of the 10 dogs, the tachycardia was
converted to sinus rhythm after infusion of
less than 2 mg. per kilogram of dibucaine.
Recurrences of the tachycardia in four of the
nine animals were terminated promptly by
small additional infusions.

Following strophanthoside, the dogs ap-
peared weak and sick. Four deaths occurred
among the seven dogs that did not receive
dibucaine treatment, a mortality rate of 57
per cent. One death occurred in the 10 dogs
that were subsequently treated with dibucaine,
a mortality rate of 10 per cent. Improvement
in apparent condition of the animals was noted
soon after infusion of dibucaine began.

Dibucaine also antagonizes glycoside-in-
duced vagotonia, but does not antagonize morphine-induced vagotonia.

A variety of toxic manifestations of digitalis evidently are counteracted by dibucaine.

**Sumario Español**

Clorhidrato de dibucaine en cantidades relativamente pequeñas terminó taquicardias ventriculares de alta frecuencia inducidas por dosis tóxicas de K-estrofantosido en 9 de 10 perros. Dibucaine fue antídoto para las vagotomías inducidas por glicósido y mejoró la viveza y la condición general de los animales a que se le administró. Una muerte ocurrió en las 10 taquicardias de estrofantosido tratadas con dibucaine: promedio de muerte, 10 por ciento. Cuatro muertes ocurrieron en siete perros que recibieron similares dosis de estrofantosido pero no dibucaine: promedio de muerte, 57 por ciento.

**REFERENCES**


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