The Effects of Diphenylhydantoin Sodium, Glucose and β-Diethylaminoethyl Diphenylpropylacetate Hydrochloride on Cyclopropane-Epinephrine Arrhythmias in the Dog

By C. W. White, Jr., A.M., M.D., Robert Megirian, M.S., and Edward D. Swiss, A.M., Ph.D.

Diphenylhydantoin sodium, glucose, and β-diaethylaminoethyl diphenylpropylacetate hydrochloride were tested for their effects upon the cyclopropane-epinephrine arrhythmias. Diphenylhydantoin in a small dose enhanced the arrhythmias and in a larger dose controlled them when given by vein, but its action following oral administration was uncertain. Glucose increased both the duration and the severity of ventricular ectopic rhythms while β-diaethylaminoethyl diphenylpropylacetate increased the dose of epinephrine which initiated them.

The influence of drugs on cardiac irritability has been the subject of a great deal of experimental work. Investigation has revealed that cardiac arrhythmias induced by the combined action of cyclopropane and epinephrine are influenced by substances of widely different nature such as carbon dioxide,1 simple organic acids,2 diethyl ether3 and adrenergic blocking agents.1, 4

The fact that diphenylhydantoin sodium* has been found to abolish arrhythmias associated with myocardial infarction5 and with overdoses of cardiotonic drugs6 suggested that it might warrant a trial in cyclopropane-epinephrine arrhythmias. The activity of diethylaminoethanol7 and its ester, procaine,1 indicated that beta-diethylaminoethyl diphenylpropylacetate2 might also influence the cyclopropane-epinephrine arrhythmias. In earlier unreported experiments in this laboratory glucose appeared to prolong the activity of ectopic ventricular foci during cyclopropane anesthesia, which recommended it for further study.

Methods

The experiments were carried out on 15 adult mongrel dogs weighing 6 to 12 Kg. Anesthesia was induced with an anesthetic machine using a 50 per cent mixture of cyclopropane in oxygen; a cuffed endotracheal tube was then inserted and attached through a soda-lime cannister to an 80 liter bag containing 30 per cent cyclopropane in oxygen. Twenty, 40, 60, and sometimes 90 minutes after the induction of anesthesia, 10 micrograms (µg) epinephrine hydrochloride made up to a volume of 5 ml. with 0.9 per cent NaCl were carefully given intravenously over a period of 50 seconds. Lead II electrocardiograms were taken before, during and after the administration of this solution; and the times of onset and cessation of continuous ventricular arrhythmias were carefully noted. Records were analyzed to determine precisely the duration of ventricular ectopic rhythms.

Control experiments, in which the test substances were not given, permitted selection of animals which were sensitive to the arrhythmias (short of developing ventricular fibrillation) and indicated the duration of the arrhythmias after each dose of epinephrine.

Diphenylhydantoin sodium (10-20 mg./Kg.) was administered by vein in 5 dogs at the time of induction of anesthesia. The effect of dilantin per os was tested in 6 dogs which had received daily doses of 15 to 40 mg./Kg. for the preceding three to eight days.
days, including the day of the experiment. In the studies on glucose, 500 mg./Kg. were injected by vein immediately before the first dose of epinephrine, and its course of action was followed in the same way as that of diphenylhydantoin. Beta-diethylaminoethyl diphenylpropylacetate hydrochloride was given intravenously to 6 dogs in doses of 0.25, 1.0, 2.0 or 4.0 mg./Kg. The times of administration ranged from 92 minutes before induction of anesthesia to 13 minutes after.

**Results**

Table 1 summarizes the observations of the effects of diphenylhydantoin sodium and glucose upon the cyclopropane-epinephrine arrhythmias. It is apparent that Dilantin increased significantly the duration of the ectopic rhythms at the 10 mg./Kg. dose, while it had the opposite action at 20 mg./Kg. In 7 of 12 observations after the 20 mgm dose, arrhythmias were completely abolished, and their duration was diminished in each of the other 5. Since Dilantin can either increase or decrease the duration of ventricular ectopic activity depending on the amount present, it is not surprising that its effect was not consistent when it was given orally. In three observations of its action following oral administration, the arrhythmias were abolished; in three more they were decreased, and in the remaining 12 there was no change.

Glucose (500 mgm./Kg. by vein) produced a highly significant increase in the duration of arrhythmias in 19 observations. In an additional two observations the injection of epinephrine after glucose produced ventricular fibrillation (as compared to control arrhythmias lasting 30 and 73 seconds). Since ventricular fibrillation cannot be interpreted in terms of duration, these two strongly positive observations could not be used in the statistical analysis.

β-diethylaminoethyl diphenylpropylacetate hydrochloride had no significant effect on the duration of ventricular arrhythmias. It was observed, however, that ventricular arrhythmias consistently began later during the course of the epinephrine injection when this agent had been given than they did in the corresponding controls. Since epinephrine was injected at a uniform rate, the time interval to onset of the arrhythmias may be equated to a dose of epinephrine. Table 2 which is based on this type of data, shows that β-diethylaminoethyl diphenylpropylacetate approximately doubled the dose of epinephrine which

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**Table 1.—Effects of Diphenylhydantoin Sodium and Glucose by Vein on Duration of Cyclopropane-Epinephrine Arrhythmias**

<table>
<thead>
<tr>
<th>Number of Observations</th>
<th>Test Agent and Dose</th>
<th>Time of Observations after Cyclopropane Induction, Minutes</th>
<th>Duration of Ventricular Arrhythmias, Seconds</th>
<th>&quot;p&quot; of Difference between Test and Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dilantin, 10 mg./Kg.</td>
<td>20, 40, 60</td>
<td>111 (±3.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Dilantin, 20 mg./Kg.</td>
<td>20, 40, 60</td>
<td>14 (±5.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Glucose, 500 mg./Kg.</td>
<td>20, 40, 60</td>
<td>84 (±5.3)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

"p" values determined by Student t test.

**Table 2.—Effect of β-Diethylaminoethyl Diphenylpropylacetate Hydrochloride on Dose of Epinephrine Required to Initiate Ventricular Arrhythmias in Dogs under Cyclopropane**

<table>
<thead>
<tr>
<th>Number of Observations</th>
<th>Dose Range mg./Kg.</th>
<th>Time of Observations, Minutes</th>
<th>Dose of Epinephrine to Initiate Ventricular Arrhythmias, μg/Kg.</th>
<th>&quot;p&quot; of Difference between Test and Control Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25-2.0</td>
<td>7-30</td>
<td>5.6 (±0.56)</td>
<td>3.2 (±0.23)</td>
</tr>
<tr>
<td></td>
<td>0.25-4.0</td>
<td>31-70</td>
<td>6.7 (±0.43)</td>
<td>3.3 (±0.16)</td>
</tr>
<tr>
<td></td>
<td>0.25-4.0</td>
<td>71-100</td>
<td>7.5 (±0.63)</td>
<td>4.0 (±0.24)</td>
</tr>
<tr>
<td></td>
<td>1.0-4.0</td>
<td>&gt;100</td>
<td>5.0 (±1.3)</td>
<td>3.8 (±0.43)</td>
</tr>
</tbody>
</table>

"p" values determined by Student t test.
initiated ventricular arrhythmias, and that the duration of this effect was about 100 minutes.

SUMMARY

Three new substances, diphenylhydantoin sodium, glucose and beta-diethylaminoethyl diphenylpropylacetate hydrochloride, have been studied by established techniques for their influence on the cyclopropane-epinephrine arrhythmias.

Diphenylhydantoin sodium, given intravenously, enhanced the arrhythmias at a dose of 10 mg/Kg. and controlled them at a dose of 20 mg/Kg. Its effect was not consistent following oral administration.

Glucose enhanced the duration and the severity of the arrhythmias.

Beta-diethylaminoethyl diphenylpropylacetate hydrochloride diminished the cardiac sensitivity as indicated by an increase in the dose of epinephrine required to initiate the arrhythmias. It had no effect on their duration.

REFERENCES

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