AN EXPERIMENTAL INVESTIGATION ON THE ANTIARRHYTHMIC ACTIVITY OF ANTIEPILEPTIC AGENTS

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Several groups of drugs have been shown to possess antiarrhythmic activity. Some of them e.g. quinidine, procainamide, local anaesthetics, β-receptor blocking agents and diphenylhydantoin etc. have achieved a clinical status as antiarrhythmic drugs. Diphenylhydantoin (dilantin) an anticonvulsant has been successfully employed for the suppression of ventricular arrhythmias due to digitalis over dosage (1) and anaesthesia (2). Atrial arrhythmias on the other hand, did not respond to diphenylhydantoin therapy. Other anticonvulsants like trimethadione (Tridione) and paramethadione (Paradione) have not been studied for the antiarrhythmic activity. Though there is enough clinical evidence of cardiac arrhythmias of central origin viz. arrhythmias during hypothalamic operation (3) electroconvulsive therapy (4) and second stage of anaesthesia, yet in the screening of antiarrhythmic activity most of the workers have neglected the arrhythmias of central nervous system origin. We have recently reported that aconitine induced centrogenic arrhythmia is a good model for screening of antiarrhythmic agents (5). Moreover for the screening of antiarrhythmic activity of CNS active agents, it seems logical that one must include some model of centrogenic arrhythmia as well. In the present investigation diphenylhydantoin, trimethadione and paramethadione have been studied against four types of experimental cardiac arrhythmia viz. (I) aconitine induced centrogenic ventricular arrhythmias (II) aconitine induced auricular arrhythmias (III) hydrocarbon-epinephrine induced ventricular arrhythmias (IV) and coronary-ligation induced ventricular arrhythmias.

METHODS

The experiments were carried out on adult mongrel dogs of either sex. The animals were anaesthetized with pentobarbitone sodium (30 mg/kg i.v.) and maintained on positive pressure artificial respiration. The blood pressure was recorded from one of the carotid artery through mercury manometer on the kymograph paper. The electrocardiogram (EKG lead II) was recorded on Sanborn Polygraph (Model 150). The drugs were administered intravenously through an indwelling polythene cannula in one of the femoral vein.

1. Aconitine induced centrogenic ventricular arrhythmias

Centrogenic cardiac arrhythmia was induced by injecting aconitine (20 μg) into the

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lateral cerebral ventricle of dog (5). At the above mentioned dose, it induced ventricular extrasystoles and tachycardia in all animals. The infusion of the preventing agent was started at the appearance of extrasystoles.

2. Aconitine induced atrial arrhythmias

Atrial fibrillation was induced by the method of Scherf (6). The arrhythmia was produced by injecting 0.05 ml of 0.05 percent freshly prepared solution of aconitine in the region of the head of the sinus node in the angle between superior venacava and right atrial appendix. The titration procedure (1 or 2 mg/kg/min) of Winbury and Hemmer (7) was followed for the injection of the drugs. The end point taken for complete protection was the restoration of 1:1 rhythm with heart rate below 200/min. Before injecting the test drug the arrhythmia was allowed to stabilize at least for 20 minutes in every experiment. In control experiments the arrhythmia lasted for more than four hours.

3. Hydrocarbon-epinephrine induced ventricular arrhythmias

The method of Riker and Wescoe (8) was followed with the modification that all experiments were done in open chest animals to facilitate visual observation. Cardiac arrhythmia was induced in each animal by the intra-tracheal injection of 0.1 ml/kg of petroleum ether (B.P. 40-60°C) followed by intravenous injection of 30 μg/kg of epinephrine. Drug was administered intravenously in a single dose prior to administration of petroleum ether and epinephrine. After the administration of test drug challenging dose of epinephrine was administered at 15, 30, 45 and 60 minutes during petroleum ether inhalation each time. Absence of production of ventricular arrhythmias with the challenging doses of epinephrine during petroleum ether inhalation was taken as protection afforded by the drug. In control experiments the arrhythmias could be induced several times in each case.

4. Coronary ligation induced ventricular arrhythmias

Two stage coronary-ligation was done in dogs by the method of Harris and Kokernot (9). Eighteen to twenty four hours after the ligation the animals exhibited ventricular arrhythmias. The preventing agents were given only when the ectopic ventricular extrasystoles or tachycardia appeared.

The drugs employed in the present study were diphenylhydantoin sodium (Dilantin-Parke Davis), trimethadion (Tridione-Abbott), paramethadione (Paradione-Abbott) and quinidine sulphate (Varick). Solution of diphenylhydantoin sodium and quinidine sulphate were made in propylene glycol and the other two drugs were dissolved in normal saline. In control experiments, the effect of propylene glycol was also studied. The preventing agents were given in the form of slow intravenous infusion at the rate of 1 mg or 2 mg/kg/min till the heart returned to the normal rhythm.

RESULTS

1. Effect of drugs on aconitine induced centrogenic ventricular arrhythmias

Effect of three known antiepileptic agents viz. diphenylhydantoin sodium, trimethadione and paramethadione and a known antiarrhythmic agent quinidine was studied on aconitine (I.C.V.) induced centrogenic cardiac arrhythmias in dogs. The results are summarized in

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TABLE 1. Antagonism of centrogenic cardiac arrhythmia induced by I.C.V. administration of 20 μg aconitine in dogs.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mean protective dose mg/kg i.v. ± S.E.</th>
<th>Duration in min ± S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>14.5 ± 0.5</td>
<td>25 ± 3.2</td>
</tr>
<tr>
<td>Diphenylhydantoin sodium</td>
<td>12.0 ± 0.5</td>
<td>15 ± 2.1</td>
</tr>
<tr>
<td>Trimethadione*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paramethadione*</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Doses up to 50 mg/kg did not protect but reduced the incidence of ventricular extrasystoles.

**CONTROL**

![Control EKG](image1.png)

10 MIN

![Aconitine Effect](image2.png)

30 MIN

![Diphenylhydantoin Effect](image3.png)

40 MIN

![Paradione Effect](image4.png)

**FIG. 1.** Shows the effect of diphenylhydantoin (Dilantin) on the centrogenic cardiac arrhythmia induced by aconitine in dog. Upper panel-Control EKG. Middle-upper panel shows typical cardiac arrhythmias after I.C.V. aconitine. Middle lower panel-12 mg/kg i.v. of diphenylhydantoin had reversed the arrhythmias to normal sinus rhythm. Lower panel-note that arrhythmias have reappeared after about 20 minutes.

**FIG. 2.** Shows the effect of paradione on the centrally induced aconitine arrhythmias in dog. Upper panel-Control EKG. Middle-upper panel shows typical cardiac arrhythmias after 10 minutes of 20 μg I.C.V. aconitine. Middle-lower panel-at arrow paradione 50 mg/kg i.v. was given: see that there is some protection as is evident by lesser number of extra systoles. In the lower panel the arrhythmias have reappeared showing there by a short lived action of the drug.
Table 1. Amongst the drugs studied only quinidine and diphenylhydantoin could antagonize the cardiac irregularities. Diphenylhydantoin was found to be more potent (mean protective dose—12.0 ±0.5 mg/kg i.v.) than quinidine (mean protective dose—14.5 ±0.50 mg/kg i.v.). Fig. 1 shows the records of one typical experiment with diphenylhydantoin. Trimethadione and paramethadione could not completely antagonize the cardiac irregularities even up to 50 mg/kg i.v. doses. However, in the higher doses these agents reduced the incidence of ectopic beats (Fig. 2). The duration of antiarrhythmic effect of quinidine was found to be 25 minutes as compared to 15 minutes of diphenyl hydantoin.

2. Effect of drugs on aconitine induced atrial arrhythmias

Among the antiepileptic drugs tested against aconitine induced atrial fibrillation, only diphenylhydantoin sodium showed antiarrhythmic activity, the other two drugs trimethadione and paramethadione were found to be ineffective. The results of the study are summarized in (Table 2). Diphenylhydantoin sodium in dose of (30 mg/kg, i.v.) completely reversed the atrial fibrillation to normal rhythm and rate (below 200/min). The average duration of effect was 35 minutes.

As regards relative potency, diphenylhydantoin sodium was only half as potent as quinidine in these experiments. However, the duration of action of diphenylhydantoin was more than that of quinidine.

Table 2. Effect of diphenylhydantoin, paramethadione and trimethadione against aconitine induced atrial fibrillation in dogs.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>No. of reversions/ No. of experiments</th>
<th>Average dose producing reversal mg/kg ±S.E.</th>
<th>Duration of effect in min</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>7/8</td>
<td>16.2 ±3.4</td>
<td>20 ±3.2</td>
<td>Reversion to normal rhythm</td>
</tr>
<tr>
<td>Diphenylhydantoin sodium</td>
<td>6/8</td>
<td>30.0 ±2.8</td>
<td>35 ±2.2</td>
<td>»</td>
</tr>
<tr>
<td>Paramethadione</td>
<td>0/4</td>
<td>50.0 ±0.0</td>
<td>—</td>
<td>No reversal</td>
</tr>
<tr>
<td>Trimethadione</td>
<td>0/4</td>
<td>50.0 ±0.0</td>
<td>—</td>
<td>»</td>
</tr>
</tbody>
</table>

3. Preventive action of drugs on the hydrocarbon-epinephrine induced ventricular arrhythmias

The ability of diphenylhydantoin sodium, paramethadione, trimethadione and quinidine to prevent hydrocarbon-epinephrine induced ventricular arrhythmia was studied in 25 dogs of both sexes. Ventricular arrhythmias could be produced every time in all the control experiments when epinephrine was administered during petroleum ether inhalation. The onset of arrhythmia was, at 1 to 2 minutes and it lasted for 3 to 5 minutes each time. It could be repeatedly produced at least five times in control experiments. However, the dogs in whom the effect of drugs were studied, the first challenge with petroleum ether and epinephrine was taken as a control for that experiment. The results of the present study are summarized in (Table 3). Diphenylhydantoin sodium in single dose of 10 mg/kg and quinidine 5 mg/kg showed 90 and 100 percent prevention of ventricular arrhythmias respectively, while paramethadione and trimethadione were ineffective even up to 50 mg/kg doses (Table 3). Typical ventricular arrhythmias induced with epinephrine during petroleum
ether and the effect of paramethadione (Paradione) on the development of arrhythmias are shown in Fig. 3.

**TABLE 3. Prevention of hydrocarbon-epinephrine induced arrhythmias in dogs by drugs.**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose mg/kg</th>
<th>No. of animals</th>
<th>No. of challenges made with petroleum ether and epinephrine</th>
<th>No. of challenges exhibiting ventricular arrhythmia after drug treatment</th>
<th>Percent prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>7 (2)*</td>
<td>22</td>
<td>22</td>
<td>—</td>
</tr>
<tr>
<td>Quinidine</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Diphenylhydantoin sodium</td>
<td>10</td>
<td>5</td>
<td>20</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>Trimethadione sodium</td>
<td>50</td>
<td>4 (1)*</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Paramethadione</td>
<td>50</td>
<td>4 (1)*</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

* Dogs died due to ventricular fibrillation

**Fig. 3.** Shows the effect of paramethadione on hydrocarbon-epinephrine induced arrhythmias in dogs. Upper panel-control (Normal) e.k.g. Middle panel-control arrhythmias induced by epinephrine and petroleum ether (H-I-HC). In the lower panel at arrow paradione 50 mg/kg i.v. was given. At (E+HC) challenging dose of epinephrine and petroleum ether was given. Note that paradione could not prevent the occurrence of the arrhythmias.

**Fig. 4.** Shows effect of diphenylhydantoin (Dilantin) on the coronary-ligation arrhythmias in dogs. Upper panel-control arrhythmias after coronary ligation. Middle panel-at arrow diphenylhydantoin 50 mg/kg given i.v. has shown some protection as the irregularities are diminished. This effect, though partial, could be observed even after 40 minutes of the drug administration (lower panel).

4. **Effect of drugs on coronary-ligation induced ventricular arrhythmias**

In another series of experiments cardiac arrhythmias were induced by two stage coronary-ligation and the effect of three antiepileptic agents and quinidine was studied. Amongst the drugs studied only quinidine could effectively antagonize the cardiac irregularities (mean
protective dose = 12.5 ± 0.50 mg/kg i.v.). None of the antiepileptic agents could completely antagonize the coronary-ligation induced ventricular arrhythmias even up to 50 mg/kg i.v. doses. However, higher doses of these agents could definitely reduce the incidence of the ectopic beats (Fig. 4). The results are summarized in Table 4.

### DISCUSSION

The results of the present investigation clearly show that diphenylhydantoin antagonizes hydrocarbon-epinephrine induced and aconitine induced centrogenic cardiac arrhythmias in 10.0 and 12.0 mg/kg respectively. On the other hand, very high doses of the drug is required to prevent or reduce the aconitine induced auricular and coronary ligation induced ventricular arrhythmias. Mendez and Kabella (12) used diphenylhydantoin with success in the cases of ventricular arrhythmia during anesthesia which is known to be due to catecholamines. However, the drug did not prove beneficial in the cases of atrial flutter and fibrillation. The failure of the drug in clinical atrial arrhythmias seem to be due to the fact that it is not possible to employ such high doses (30 mg/kg i.v.).

Both trimethadione and paramethadione in contrast to diphenylhydantoin were found ineffective against all three types of peripheral arrhythmias (aconitine induced auricular, hydrocarbon-epinephrine and coronary-ligation ventricular arrhythmias). These agents also could not block the aconitine induced centrogenic arrhythmias but reduced the incidence of ectopic beats.

It is obvious from the results that diphenylhydantoin is effective against all types of arrhythmias irrespective of the nature and site of their origin. Such an action can only be due to a nonspecific membrane stabilizing action of the agent. The stabilizing action of diphenylhydantoin against potentiation by repetitive stimuli has been shown on all excitable membranes (10). Moreover, the drug is effective against hyperexcitability of nerve fibres due to low calcium concentration. The above hypothesis is further substantiated by the fact that other antiepileptics viz. trimethadione and paramethadione which appear to be devoid of membrane stabilizing activity as they fail to protect the peripheral nerves against excitatory effects of excessive stimulation or calcium deficit (1), are not effective against aconitine induced auricular, hydrocarbon-epinephrine and coronary-ligation ventricular arrhythmias. The results of our study also point to the absence of membrane stabilizing activity in trimethadione and paramethadione since they were only effective against centrogenic arrhythmias. The observation that trimethadione and paramethadione reduced
the incidence of aconitine induced centrogenic arrhythmia seems logical because these agents are known to depress the transmission at synapses in the central nervous system (11).

**SUMMARY**

Antiarrhythmic activity profile of some antiepileptic agents (diphenylhydantoin, paramethadione and trimethadione) has been investigated in the present work. Emphasis has been specially laid for their effect on aconitine induced arrhythmia of central origin. Diphenylhydantoin (Dilantin) showed protection against central (I.C.V. aconitine induced) and peripheral (aconitine induced auricular, hydrocarbon-epinephrine and coronary-ligation induced) arrhythmias. In contrast to diphenylhydantoin, the other antiepileptics-trimethadione and paramethadione were found ineffective against peripheral arrhythmias. However, they showed some protection against the arrhythmia of central origin. Diphenylhydantoin possibly because of its nonspecific membrane stabilizing nature was effective against all types of arrhythmias irrespective of the nature and site of their origin; while trimethadione and paramethadione were ineffective against all peripheral arrhythmias and showed some protection against arrhythmias of central origin. The effect of the latter two drugs on central arrhythmias may be attributed to their depressant effect at the synaptic transmission in the central nervous system.

**REFERENCES**


10) Toman, J.E.P.: *Pharmac. Rev.* 4, 168 (1952)