ANTIARRHYTHMIC ACTIONS OF BC 105

M. AHMAD AND G. ACHARI
Department of Pharmacology, P.W. Medical College, Patna, Bihar, India

Received for publication July 11, 1968

It was reported earlier (1) that cyproheptadine possesses marked antiarrhythmic action against both atrial and ventricular arrhythmias. Since BC 105 is closely related to cyproheptadine (Periactine) differing only in the substitution of a thiophene nucleus for a benzene nucleus (2), it was taken up for study to see whether this compound also has antiarrhythmic property or not. The present paper deals with the evaluation of antiarrhythmic property of this compound. BC 105 is the malate of 4-(1-methyl-piperidinene-4)-9, 10-dihydro-4H-benzo (1, 2-b) cyclohepta (1, 2-b) thiophen.

METHODS AND MATERIALS

Male and female mongrel dogs weighing from 4.5 to 8 kg were anaesthetized with intravenous pentobarbital sodium (30 mg/kg). Femoral veins were cannulated for administration of drugs. A lead II electrocardiogram was used to monitor the arrhythmia.

Atrial fibrillation:

Atrial fibrillation was produced by a procedure described by Achari and Ahmad (1) and Mokler and Arman (3) which is a modification of method described by Scherf (4). Under positive pressure artificial respiration, right side of the chest was opened by removing 3 and 4 ribs and pericardial cradle was prepared. A cotton pledget fixed at one end of a thin Straw was dipped in 0.05% aconitine solution and allowed to touch the atrium at some distance away from the ventricle. This was held in position with the help of a long artery forceps which was kept in position by a clamp. In those cases where fibrillation did not appear with 0.5% aconitine, a stronger solution (0.075%) was used and fibrillation invariably appeared. Then the drugs under study were infused intravenously by titration method (5) and continued till the end point (1:1 rhythm with the rate below 200/mt) was reached.

Atrial flutter:

Flutter was produced by the injury stimulation procedure of Rosenblueth and Garcia (6). A narrow band of atrial tissue near the intervenous bridge was clearly crushed by haemostat and the atrium was stimulated with square wave, 5-10 V, 25-30 cps and 0.5 to 1 millisecond duration using square wave electronic stimulator. In about 50%
dogs this procedure resulted in an atrial flutter which persisted for more than 30 minutes. When the flutter continued for more than 35 minutes, the drug was injected intravenously by titration method until reversion to normal sinus rhythm occurred.

**Ouabain induced ventricular tachycardia:**

Ventricular tachycardia was induced in anaesthetized dogs by the method described by Mokler and Arman (3) which consisted in administration of ouabain intravenously in the dose of 0.07 mg/kg followed by 0.01 mg/kg at 30 minutes interval till ventricular tachycardia was established. Untreated arrhythmia of this type did not revert to normal sinus rhythm during the period of observation (about 3 hours) in control dogs. Drugs under study were given by titration method till sinus rhythm appeared.

**Petroleum ether-epinephrine induced ventricular arrhythmia:**

In anaesthetized dogs the arrhythmia was produced by the method described by Riker and Wescoe (7). It consisted in intratracheal instillation of 0.2 ml/kg of petroleum ether (melting point 30°-60°) followed by 60 µg/kg of epinephrine intravenously. Ventricular arrhythmia of all types, ranging from multifocal beats to ventricular fibrillation invariably resulted and ultimately all control dogs died. For studying the protecting action, the drug under study was injected 2 hours before the administration of petroleum ether. The drug was considered active if it prevented the appearance of persistent ventricular arrhythmia. The following drugs were used:

BC 105 malate was dissolved in hot water in a concentration of 1 mg/kg and was used after cooling to 37°C. Quinidine sulphate was included to serve as control. Solution of aconitine nitrate, ouabain and quinidine sulphate were freshly prepared in normal saline.

**RESULTS**

**Aconitine induced auricular fibrillation:**

BC 105 was found to be effective in converting this type of arrhythmia to sinus rhythm in all the six dogs used (Table 1). The end point (sinus rhythm with rate below 200/mt) was reached with a total average dose of 2 mg/kg when infused at the rate of 0.02 mg/kg

<table>
<thead>
<tr>
<th>Type of arrhythmia</th>
<th>Compound</th>
<th>Conversion or full protection</th>
<th>Average i.v. converting or full protecting dose mg/kg</th>
<th>Dose range i.v. mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aconitine fibrillation</td>
<td>Quinidine</td>
<td>6/6</td>
<td>26</td>
<td>22 - 28</td>
</tr>
<tr>
<td></td>
<td>BC 105</td>
<td>6/6</td>
<td>2</td>
<td>1.6 - 2.4</td>
</tr>
<tr>
<td>Injury stimulation flutter</td>
<td>Quinidine</td>
<td>3/3</td>
<td>22</td>
<td>18 - 24</td>
</tr>
<tr>
<td></td>
<td>BC 105</td>
<td>4/4</td>
<td>2.2</td>
<td>1.8 - 2.6</td>
</tr>
<tr>
<td>Ouabain vent. tachycardia</td>
<td>Quinidine</td>
<td>3/3</td>
<td>18.8</td>
<td>15.5 - 21</td>
</tr>
<tr>
<td></td>
<td>BC 105</td>
<td>0/3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Petroleum ether epinephrine ventricular arrhythmia</td>
<td>Quinidine</td>
<td>3/3</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>BC 105</td>
<td>1/2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Fig. 1. Illustrates the effect of BC 105 on aconitine induced auricular fibrillation.
(A) Control ECG (B) aconitine induced auricular fibrillation (C) after 0.5 mg/kg of BC 105 (D) note the tendency towards sinus rhythm after 1 mg/kg of BC 105 respectively. (G) the end point (sinus rhythm with rate below 200/min) is reached after 2.1 mg/kg of BC 105 (H) 60 minutes after G sinus rhythm persisting, showing that BC 105 has prolonged action.

FIG. 2. Illustrate the effect of BC 105 in auricular flutter produced by injury stimulation procedure.
(A) Control ECG (B) flutter (C), (D) and (E) after 1, 1.5 and 2 mg/kg of BC 105 respectively (F) 60 minutes after E, note that sinus rhythm is persisting.

per minute (Fig. 1). Thus BC 105 took about 100 minutes to produce its effect. Sinus rhythm once restored persisted during remaining period of observation (more than one hour). Quinidine also with total average dose of 26 mg/kg given at the rate of 1 mg/kg effectively converted auricular fibrillation into sinus rhythm in all the six dogs. Thus on weight basis BC 105 was found to be 13 times more potent than quinidine.

Injury stimulation induced auricular flutter:
BC 105 proved to be effective in this type of arrhythmia. Average total dose required was 2.2 mg/kg when given at the rate of 0.02 mg/kg per minute. It produced reversion in all the four animals used for this test (Fig. 2). Arrhythmia did not reappear during the remaining period of observation. In three control animals quinidine produced reversion to sinus rhythm with a total average dose of 22 mg/kg when infused at the rate of 1 mg/kg per minute. Thus BC 105 has 10 times the relative potency of quinidine on micrograms per milogram basis (Table 1).

Ouabain induced ventricular tachycardia:
BC 105 was not found effective in this arrhythmia as it failed to convert ventricular tachycardia in normal sinus rhythm. But above total dose of 2 mg/kg it markedly de-
FIG. 3. Illustrate the effect of BC 105 on ouabain induced ventricular tachycardia.

(A) Control ECG (B), (C) and (D) after 0.5, 1.0 and 1.5 mg/kg of BC 105 respectively. Note that the ventricular rate is decreased but sinus rhythm not restored (E) after 2 mg/kg of BC 105, there is complete auricular-ventricular dissociation and ventricle is markedly slowed.

creased the ventricular rate and auricular waves were quite independent of ventricular waves (Fig. 3) i.e. there was complete auriculo-ventricular block.

Petroleum ether-epinephrine ventricular arrhythmia:

Three dogs were given 2 mg/kg of BC 105 slowly intravenously 2 hours before instillation of petroleum ether. This drug was given 2 hours before because of the fact that it takes about 2 hours to act. After challenging dose of epinephrine there was protection in only one dog, the other two died of ventricular fibrillation. Quinidine on the other hand protected all the three dogs in which it was given in the dose of 15 mg/kg intravenously 5 minutes before instillation of petroleum ether.

DISCUSSION

BC 105 is a recently synthesized drug which is being developed as an antihistaminic and antiserotonin compound (2). It has not yet been evaluated for its antiarrhythmic property. Therefore, it is of interest to note that BC 105 is 13 times and 10 times more potent than quinidine in auricular fibrillation and flutter respectively. But unlike quinidine it is ineffective in ventricular arrhythmias. Achari and Ahmad (1) reported that average effective dose of cyproheptadine in auricular fibrillation and flutter was 3.15 and 4 mg/kg respectively. Thus it appears that BC 105 is more effective than cyproheptadine in auricular arrhythmia. Failure of BC 105 to have much effect in ventricular arrhythmias might be due to substitution of a thiophene nucleus for a benzene nucleus as in cyproheptadine. Slowing of ventricular rate and complete auricular ventricular dissociation as brought about by BC 105 in ouabain induced ventricular tachycardia shows that BC 105 has significant effect on A.V. node and conducting tissue, the structures which
are poisoned by ouabain earlier than ventricular muscle (8). Failure of BC 105 to convert ouabain induced ventricular tachycardia to normal sinus rhythm may be due to absence of selective action on ectopic foci.

In the past many drugs with antihistaminic properties have been found to possess antiarrhythmic effect (1,9-12) and one of them (Antazoline) has emerged to be a useful antiarrhythmic agent (13). Therefore it is no wonder that BC 105 a powerful antihistaminic and antiserotonin compound, also possesses antiarrhythmic property. But the dose required for its antiarrhythmic effect is much higher than that required for its antihistaminic and antiserotonin effect. This leads us to think that antiarrhythmic property of BC 105 is perhaps mostly due to its direct effect on the atrial tissue.

The anticholinergic and central sedative properties of BC 105 (2) might also contribute to its antiarrhythmic effect since cholinergic factors have been found to have definite role in the auricular arrhythmia (14, 15) and a central sedative and anticonvulsant diphenylhydantoïn has emerged out to be a useful antiarrhythmic drug (16).

Cerletti (2) after extensive toxicological studies of BC 105 reported that this drug has good margin of safety and LD_{50} of this drug in mouse, rat, and rabbit is 43, 17, 19 mg/kg i.v. respectively. LD_{50} of quinidine on the other hand was found to be 56 mg/kg intravenously in albino mice (17). When these results of toxicity studies are analysed with the effective antiarrhythmic doses of the drugs under study it is clear that safety margin with BC 105 is much more than quinidine. Though projection of results from animal experimentation is attended with hazards, on the basis of efficacy, potency and safety of BC 105, it is suggested that this drug shows sufficient promise to warrant further experimental and perhaps clinical trial in selected cases of auricular arrhythmias.

**SUMMARY**

1. Antiarrhythmic property of BC 105, a new antihistaminic and antiserotonin compound, has been studied in dogs using four different types of atrial and ventricular arrhythmias.

2. BC 105 was found to be much more potent than quinidine in both auricular fibrillation and flutter.

3. The significance of these findings and their possible mechanism of action have been discussed.

**REFERENCES**

2) Cerletti, A.: Personal communication (1968)
10) Mekechnie, J.K.: South African M. J. 26, 609 (1952)
15) Burn, J.H.: Br. med. J. 1, 1379 (1960)