REACTION OF ANTIARRHYTHMIC AGENTS WITH AGLYCONES AND ERYTHROPHLEUM ALKALOIDS

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Abstract—The effects of DCI or BW 62–235 on the arrhythmia caused by 3 erythropleum alkaloids, 6 aglycones and 2 glycosides were investigated in the cat anesthetized with sodium secobarbital.

Generally speaking, these agents were ineffective against coumingine or erythropleine arrhythmia, although arrhythmia shortening action was observed in a few cases with cassaine.

These agents were ineffective against gitaloxigenin arrhythmia, however, did show evident antiarrhythmic action against digitoxigenin or periplogenin.

In the cases of arrhythmia produced by hellebrigenin, bufalin or cinobufagin these agents tend to reduce the duration of the arrhythmia.

In arrhythmias elicited by glycosides, duration of thevetin arrhythmia was reduced by DCI and BW 62–235, however, the arrhythmia of scillaren A was not clearly shortened by these agents.

From these results it can be concluded that there is no relationship between the effectiveness of these antiarrhythmic agents and the chemical structures of the arrhythmia inducing drugs, although some question does remain in the case of erythropleum alkaloids concerning intrinsic local anesthetic action. A certain relationship between the effectiveness of these agents and arrhythmic action of these cardiotonics was observed, i.e., the antiarrhythmic agents was effective against the arrhythmia caused by the drugs which have a fleeting arrhythmic action.

Following the discovery of an adrenergic β-receptor blocking effect of dichloroisoproterenol (DCI) (Powell and Slater (1)), antiarrhythmic effects of DCI (Moore and Swain (2, 3), and Gilbert (4)) and β-(2, 5-dimethoxyphenyl)-β-hydroxyisopropylamine hydrochloride (Methoxamine) (Nathanson (5) and Brill et al. (6)) against experimental arrhythmias were reported. Since then, antiarrhythmic action of adrenergic β-receptor blockers (Ghouri and Haley (7)) and the derivatives of sympathetic drugs have been of interest to investigators.

Lucchesi and Hardman (8) reported reversal of ouabain and acetylstrophanthidin arrhythmias by DCI both in the isolated rabbit heart and in the anesthetized dog. Moran et al. (9) observed similar results, however, they stated that DCI did not significantly alter the lethal dose of the glycoside.

The antiarrhythmic effect of Nethalide, isopropylamino-1-(2-naphthyl)-ethanol, another

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\(\beta\)-receptor blocker, against ouabain arrhythmia was reported by Williams and Sekiya (10). It was confirmed by Erlij and Mendez (11) who also stated that the increase in lethal dose and the change in form of death are more likely to occur with digitoxin rather than ouabain. Lucchesi (12) showed that Nethalide possesses the ability to reverse and/or prevent cardiac arrhythmias resulting from toxic doses of ouabain or acetylstrophanthidin both in the isolated rabbit heart and in the dog. Moreover, using the dextro isomer of Nethalide, Lucchesi (13) demonstrated that \(\beta\)-adrenergic receptor inhibition by Nethalide is not the mechanism through which this compound prevents digitalis or hydrocarbon-epinephrine induced arrhythmia, but he suggested \(\beta\)-receptor blockade may be of importance in the prevention of other experimentally induced arrhythmias. He also demonstrated that (+)-Nethalide was not effective in preventing ventricular fibrillation resulting from the combined administration of U-0882 and isoproterenol, unlike the action against digitalis or hydrocarbon-epinephrine arrhythmia.

Somani and Lum (14) reported that a \(\beta\)-adrenergic blocking agent, N-isopropyl-\(p\)-nitrophenylethanolamine (INPEA), antagonized arrhythmias induced by epinephrine but not those by ouabain or coronary artery ligation.

Ellis (15) reported that BW 62-235, \(\alpha\)-methyl-\(\beta\)-hydroxy-\(\beta\)-(2, 5-diethoxyphenyl)-N-isopropyl ethylamine, was effective against arrhythmia caused by several experimental procedures including ouabain and digoxin administration, although it has no \(\beta\)-receptor blocking action. Kikuchi and Chen (16) also reported that arrhythmia caused by rhodexin A was restored to sinus rhythm by BW 62-235 or DCI.

The results suggest that there are some variations in the effectiveness of these antiarrhythmic agents against arrhythmia caused by different procedures.

According to the studies by Bonting (17, 18) and Kahn (19) erythrophleum alkaloids, which differ from cardiac glycosides in chemical structure yet show similar cardiotonic effects, presumably produce effects by the same mechanism as that of cardiac glycosides, i.e., inhibitory action on the Na-K activated ATPase.

In the present paper the effects of these antiarrhythmic agents against arrhythmia caused by erythrophleum alkaloids, cardiac aglycones or glycosides are studied and the relationship between the effectiveness of these antiarrhythmic agents and the chemical structures and arrhythmic action of these cardiotonic drugs are discussed.

**METHODS AND MATERIALS**

Two hundred and twenty-five cats, 1.3 to 2.8 kg, were used. The cat, anesthetized with sodium secobarbital 35 mg/kg i.p. was placed in a supine position. Electrocardiogram, conventional limb lead II, was recorded by means of the Sanborn Visette. In addition, respiration, electrocardiogram, limb lead I and II, were continuously monitored by Physiograph.

Arrhythmia inducing drugs were infused into the femoral vein at the rate of 1 ml/min through a polyethylene catheter until ventricular premature beats or A-V block were observed, then infusion was stopped. With the drugs causing arrhythmia lasting only for
a short period, the infusion was continued until the ventricular tachycardia had been established. Four or more cats were used for each drug.

Antiarrhythmic agents were given i.v. 4 min after the infusion in the former, or immediately after the occurrence of ventricular tachycardia in the latter cases. The injection was repeated every 4 min until sinus rhythm had been restored. When the arrhythmia reappeared after a 4 min interval the antiarrhythmic agent was re-started. The antiarrhythmic agents were usually given in a dose of 2 mg/kg.

Criteria for the effectiveness of antiarrhythmic agents was as follows: 1) Ectopic rhythm was restored to sinus rhythm and the sinus rhythm continued more than 2 hr after the last injection of the antiarrhythmic agents. 2) The ectopic rhythm recovered for 3 to 4 min each time after administration of the antiarrhythmic agents. In these cases the first recovery was regarded as duration of the arrhythmia.

FIG. 1. Chemical structures of cardiotonic substances, erythrophleum alkaloids, classified as group 1.

FIG. 2. Chemical structures of cardiotonic substances, aglycones (cardenolides), classified as group 2.
The antiarrhythmic agents used were DCI (Aldrich Chemicals) and BW 62-235 (Burroughs Wellcome Co.). In some cases Nethalide was also used.

Chemical structures of the drugs used for the induction of ectopic rhythm are shown in Figs. 1-4 and classified into 4 groups.

**RESULTS**

**Group 1. Erythrophleum alkaloids: coumingine, erythrophleine and cassaine**

**Coumingine**: Coumingine hydrochloride was infused in a concentration of 1:100,000 or 1:200,000 until continuous ectopic rhythm had been established. In the control group, in which 7 cats were used, the first ectopic rhythm appeared with the dose of $0.169 \pm 0.014$ mg/kg (geometric mean $\pm$ S.E.) and the infusion was stopped at $0.180 \pm 0.016$ mg/kg. Four out of 7 animals died after 16 to 45 (mean 65) min of the infusion and in 3 cats normal sinus rhythm returned after 52 to 86 min.

When DCI was administered, all 6 cats died 17 to 78 min after the infusion even when there was no significant difference in the total infusion dose of coumingine as compared to that of control.

When treated with BW 62-235 six out of 10 cats died and the ectopic rhythm continued for more than 2 hr in 1 cat and 70 min in another. In the remaining 2 cats the ectopic rhythm was restored to sinus rhythm after 4 and 8 min respectively.

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**Fig. 3.** Chemical structures of cardiotonic substances, aglycones (bufadienolides), classified as group 3.

**Fig. 4.** Chemical structures of cardiotonic substances, glycosides, classified as group 4.
These results indicate that the arrhythmic dose of coumingine is very close to its lethal
dose and DCI is ineffective against the coumingine arrhythmia, however, some antiar-
rhythmic effects were observed with BW 62-235 (Fig. 5).

Erythrophleine: Erythrophleine sulfate was infused in a concentration of 1: 50,000.
In the control in which 4 cats were used, the first ectopic rhythm was observed in the dose
of 0.619 ± 0.072 mg/kg. Continuous ectopic rhythm was obtained with the dose of 0.668 ±
0.079 mg/kg and the infusion was stopped. Three of the cats died 8 to 43 min after cessa-
tion of infusion and in 1 cat the ectopic rhythm continued for more than 2 hr.

When DCI was injected 2 cats died 26 to 32 min after the cessation of the infusion,
and in 1 cat the arrhythmia lasted for more than 2 hr.

Three out of the 4 cats died after treatment with BW 62-235, however, in 1 cat the
arrhythmia was restored to normal sinus rhythm after 9 min.

As mentioned above it appears that DCI and BW 62-235 are ineffective against ery-
throphleine arrhythmia (Fig. 5).

Cassaine: Cassaine hydrochloride was infused in a concentration of 1: 10,000 until
ventricular tachycardia had been established. In the control the first ectopic rhythm was
observed with 0.956 ± 0.158 mg/kg and continuous ventricular tachycardia was produced
with 1.521 ± 0.182 mg/kg. The ectopic rhythm caused by cassaine lasted from 8 to 36
(mean 21) min after the cessation of infusion in 4 cats and 1 cat died after 4 min.

When DCI was given the ectopic rhythm lasted 3 to 12 (mean 7) and 1 cat died
after 13 min.

When the arrhythmia was treated with BW 62-235, the ectopic rhythm lasted 2 to
4 min and 1 cat died after 26 min.

From these results, DCI and BW 62-235 appear to reduce the duration of the arrhyth-
mia (Fig. 5).
Group 2. Aglycones: gitaloxigenin, digitoxigenin and periplogenin

Gitaloxigenin: Gitaloxigenin was infused in a concentration of 1: 100,000 until ventricular tachycardia had been established. In the 7 cats control group the first ectopic rhythm was observed with 0.084±0.012 mg/kg and ventricular tachycardia appeared after 0.111±0.014 mg/kg. Three animals died between 5 to 15 min after the cessation of infusion. In 4 animals the ectopic rhythm was restored to sinus after 18 to 47 min. Mean duration of the ectopic rhythm was 28 min.

In the group to which DCI had been administered 2 out of 6 cats died 8 to 10 min after the infusion stop. Four recovered after 14 to 77 min. Mean duration was 43 min, i.e., the duration of arrhythmia was rather prolonged with DCI.

In the group treated with BW 62–235 one out of 5 cats died and 4 recovered after 15 to 63 (mean 37) min.

When Nethalide was given 2 out of 5 died and 3 cats recovered after 8 to 48 (mean 30) min.

As shown in Fig. 6 there were no significant differences in the arrhythmic dose of gitaloxigenin between the control and the other groups. The duration of the arrhythmia caused by this drug was not shortened but rather prolonged with DCI, BW 62–235 or Nethalide.

Digitoxigenin: Digitoxigenin was infused in a concentration of 1: 25,000 until ventricular tachycardia had been established. The doses of digitoxigenin which caused ectopic rhythm and ventricular tachycardia were 0.118±0.035 and 0.301±0.023 mg/kg respectively. The arrhythmia was restored to the sinus rhythm after 8 to 48 (mean 28) min and 3 out of 9 died, 1 to 16 min after the infusion stop.

When treated with DCI the duration of the arrhythmia was shortened to 1 to 10 (mean 6) min and only 1 out of 9 cats died 16 min after the cessation of infusion.

<table>
<thead>
<tr>
<th>CARDENOLIDE</th>
<th>DOSE (MEAN ± S.E., mg/kg)</th>
<th>ANTI-ARRHYTHMIC DRUGS</th>
<th>DURATION OF ARRHYTHMIA (min)</th>
<th>ARRHYTHMIA IN DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITALOXIGENIN</td>
<td>.111 ± .014</td>
<td>—</td>
<td>30</td>
<td>• • •</td>
</tr>
<tr>
<td></td>
<td>.101 ± .009</td>
<td>DCI</td>
<td>60</td>
<td>• • •</td>
</tr>
<tr>
<td></td>
<td>.094 ± .015</td>
<td>BW62-235</td>
<td>90</td>
<td>• • •</td>
</tr>
<tr>
<td></td>
<td>.116 ± .006</td>
<td>NETHALIDE</td>
<td>120</td>
<td>• • •</td>
</tr>
<tr>
<td>DIGITOXIGENIN</td>
<td>.301 ± .023</td>
<td>—</td>
<td>30</td>
<td>• • •</td>
</tr>
<tr>
<td></td>
<td>.343 ± .043</td>
<td>DCI</td>
<td>60</td>
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<tr>
<td></td>
<td>.311 ± .032</td>
<td>BW62-235</td>
<td>90</td>
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<tr>
<td></td>
<td>.296 ± .023</td>
<td>NETHALIDE</td>
<td>120</td>
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</tr>
<tr>
<td>PERIPLOGENIN</td>
<td>.642 ± .049</td>
<td>—</td>
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<tr>
<td></td>
<td>.528 ± .027</td>
<td>DCI</td>
<td>60</td>
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<td>.547 ± .048</td>
<td>BW62-235</td>
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<tr>
<td></td>
<td>.773 ± .060</td>
<td>NETHALIDE</td>
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</table>

Fig. 6. Effects of DCI, BW 62–235 and Nethalide on the arrhythmia caused by aglycones, cardenolides, belonging to group 2.
After the injection of BW 62-235 the duration of the arrhythmia was also shortened, occurring in 5 to 22 (mean 11) min, however, 3 out of 8 cats died 2 to 22 min after the cessation of infusion.

With Nethalide, shortening of the arrhythmia was clearly observed. The duration was 5 to 22 (mean 9) min and 3 out of 10 cats died after 8 to 20 min.

These results show the arrhythmia caused by digitoxigenin was shortened with DCI, BW 62-235 or Nethalide. The effect was most potent with DCI followed by Nethalide and BW 62-235 (Fig. 6).

Periplogenin: Periplogenin was infused in the concentration of 1:10,000. Ectopic rhythm was observed with a small dose, i.e., 0.177±0.034 mg/kg, however, the infusion was continued until ventricular tachycardia had been established. The infusion dose of periprogenin was 0.642±0.049 mg/kg in the control group and the duration of the arrhythmia was 17 to 39 (mean 28) min. One out of 5 cats died.

When DCI was administered the duration was shortened to 11 to 18 (mean 15) min, however, 1 out of 5 died.

After the treatment with BW 62-235 the duration of the arrhythmia was 3 to 10 (mean 6) min and 1 out of 5 died.

With Nethalide the duration of arrhythmia was also shortened to 5-14 (mean 9) min.

As mentioned above the arrhythmia caused by periplogenin was restored to sinus rhythm with DCI, BW 62-235 or Nethalide. The effect was most potent in the following order; BW 62-235, Nethalide and DCI (Fig. 6).

Group 3. Aglycones (bufadienolides): hellebrigenin, bufalin and cinobufagin

Hellebrigenin: Hellebrigenin acetate was infused in the concentration of 1:200,000 until a continuous ectopic rhythm was established. The geometric mean with which the first ectopic rhythm was observed was 0.044±0.004 mg/kg, and total infusion dose was 0.063±0.004 mg/kg. In the control experiment the ectopic rhythm lasted 32 to 180 (mean 96) min and 2 out of 7 cats died.

When DCI had been administered the duration of the ectopic rhythm was 15 to 180 (mean 74) min and 2 out of 6 cats died.

With BW 62-235 the duration of the arrhythmia was shortened to 9 to 64 (mean 33) min and 1 out of 7 died.

In two animals to which Nethalide had been administered, the duration of the arrhythmia was 45 and 53 (mean 49) min.

As shown above, these drugs were effective against hellebrigenin arrhythmia in the order of BW 62-235 and DCI although the antiarrhythmic effect was not so evident (Fig. 7).

Bufalin: Bufalin was infused in a concentration of 1:100,000 until ventricular tachycardia was observed. In the control experiment the dose which produced the first ectopic rhythm was 0.098±0.011 mg/kg. Total infusion dose was 0.136±0.012 mg/kg. The duration of the arrhythmia was 22 to over 200 min and 2 out of 8 cats died.

With the administration of DCI the duration of the arrhythmia was 9 to more than
142 min and 1 out of 5 died.

When BW 62–235 was administered the duration of the arrhythmia was 9 to 28 (mean 19) min and 2 out of 7 died.

As shown in Fig. 7 BW 62–235 was most effective followed by DCI.

Cinobufagin: Cinobufagin was infused in a concentration of 1: 50,000. With cinobufagin the first ectopic rhythm was observed at the dose of 0.182±0.021 mg/kg in the control group. The infusion was continued until the total dose of 0.267±0.023 mg/kg had been infused. The duration of the arrhythmia was 12 to 60 (mean 30) min and 1 out of 7 cats died.

When DCI was administered the duration of the arrhythmia was 10 to 39 (mean 22) min in 5 animals.

After the administration of BW 62–235 the duration of the arrhythmia was 5 to 57 (mean 17) min in 6 animals.

As stated above, the duration of the arrhythmia caused by cinobufagin was shortened by DCI and BW 62–235. The shortening was much more obvious with BW 62–235 than with DCI (Fig. 7).

Group 4. Glycosides: thevetin and scillaren A

Thevetin: Thevetin was infused in a concentration of 1: 20,000 until ventricular tachycardia appeared. The first ectopic rhythm was observed with 0.647±0.116 mg/kg and total infusion dose was 0.705±0.137 mg/kg. The duration of the ectopic rhythm was 2 to 32 (mean 15) min.

When DCI was administered the duration of the ectopic rhythm was 1 to 9 (mean 3) min in 6 animals.

With BW 62–235 the duration was 2 to 20 (mean 8) min and 2 out of 6 cats died.

As mentioned above DCI was more effective against the ectopic rhythm caused by thevetin than BW 62–235 (Fig. 8).
Scillaren A: Scillaren A was infused in a concentration of 1:100,000 until ventricular tachycardia was observed. In the control, the first ectopic rhythm was observed with 0.126±0.014 mg/kg. Total infusion dose was 0.145±0.010 mg/kg. In 4 animals the ectopic rhythm was restored to the sinus rhythm within 8 to 41 min, however, in 2 animals the ectopic rhythm lasted more than 2 hr. Three out of 9 cats died after 11 to 26 min.

When DCI was administered the ectopic rhythm lasted for 1 to 97 min in 5 animals. In another cat it lasted more than 2 hr while yet another cat died.

When BW 62-235 was given, the ectopic rhythm lasted for 1 to 67 min in 5 animals and another cat died.

As mentioned above DCI and BW 62-235 did not show any clear cut antiarrhythmic effect against scillaren A arrhythmia (Fig. 8).

### DISCUSSION

Among the erythrophleum alkaloids classified as group 1, the arrhythmic dose was smallest with coumingine followed by erythrophleine and cassaine. The results are in accordance with those lethal doses reported by Chen et al. (20, 21) on the etherized cat (Table 1) and by Maling and Krayer (22) on the dog heart-lung preparation. Maling and Krayer also reported that the ratio of minimal dosages leading to irregularities and those which lead to a positive inotropic effect was smallest with coumingine followed by erythrophleine and cassaine. Our experiment demonstrated that the arrhythmic and the lethal doses were closer with coumingine as many cats died even when the infusion was stopped in the early stages of the arrhythmia. Generally speaking, DCI and BW 62-235 were ineffective against arrhythmia caused by two erythrophleum alkaloids, coumingine and erythrophleine, although in some cases, when treated with BW 62-235, a shortening of the duration of the arrhythmia was observed. The effect of cassaine was sharply different from these two erythrophleum alkaloids showing fleeting arrhythmic action and the duration of the arrhythmia was reduced by DCI or BW 62-235, although not so evident.

It is said that erythrophleum alkaloids have local anesthetic action because of their
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Table 1. Geometric mean of the lethal doses of cardiotonic substances.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Geometric mean ± S.E. (mg/kg)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumaryline HCl</td>
<td>0.1277 ± 0.0059</td>
<td>21</td>
</tr>
<tr>
<td>Erythropleine sulfate</td>
<td>0.3640 ± 0.0228</td>
<td>21</td>
</tr>
<tr>
<td>Cassaine HCl</td>
<td>1.111 ± 0.102</td>
<td>21</td>
</tr>
<tr>
<td>Gitaloxigenin</td>
<td>0.0975 ± 0.0037</td>
<td>26</td>
</tr>
<tr>
<td>Digitoxigenin</td>
<td>0.4591 ± 0.0363</td>
<td>21</td>
</tr>
<tr>
<td>Periplogenin</td>
<td>0.7193 ± 0.0813</td>
<td>21</td>
</tr>
<tr>
<td>Hellebrigenin</td>
<td>0.0642 ± 0.0029</td>
<td>27</td>
</tr>
<tr>
<td>Bufalin</td>
<td>0.1370 ± 0.0102</td>
<td>28</td>
</tr>
<tr>
<td>Cinobufagin</td>
<td>0.2016 ± 0.0181</td>
<td>28</td>
</tr>
<tr>
<td>Thevetin</td>
<td>0.8890 ± 0.0316</td>
<td>21</td>
</tr>
<tr>
<td>Scillaren A</td>
<td>0.1460 ± 0.0101</td>
<td>21</td>
</tr>
</tbody>
</table>

chemical structure, esters of dimethylaminoethanol. Relationship between the local anesthetic action and the antiarrhythmic effect of many agents has been demonstrated by Dawes (23). It has been generally accepted that antiarrhythmic effect of some adrenergic β-receptor blocking agents is based on the local anesthetic action shared by the β-blockers (24). It is probable that the intrinsic local anesthetic effect shared by the erythropleine alkaloid may influence the arrhythmia inducing action per se. The relatively great number of deaths and ineffectiveness of the antiarrhythmic drugs in the group 1 may be explained by the above stated reason. Cassaine, however, which belongs to the group 1, showed only a fleeting arrhythmic action and the arrhythmia caused by cassaine was suppressed by antiarrhythmic drugs.

In group 2, aglycones which have a 5 membered unsaturated lactone ring at C 17, gitaloxigenin caused ectopic rhythm with smallest doses followed by digitoxigenin and periplogenin. These observations coincide with the results of Chen (25) and Henderson et al. (26) on the cardiotonic activities of the same drugs. The arrhythmic doses of gitaloxigenin were very close to the lethal dose. With digitoxigenin and periplogenin, however, the arrhythmic doses were smaller than the lethal doses of these drugs. Against gitaloxigenin arrhythmia neither DCI, BW 62–235 nor Nethalide showed any antiarrhythmic action. Duration of digitoxigenin and periplogenin arrhythmia were clearly shortened by DCI, BW 62–235 or Nethalide. Against digitoxigenin arrhythmia DCI was most active while BW 62–235 was most effective against periplogenin arrhythmia.

Among the group 3 aglycones, which have a 6 membered unsaturated lactone ring at C 17 and classified as bufadienolides, hellebrigenin showed the strongest arrhythmic action followed by bufalin and cinobufagin. The arrhythmic doses of these 3 bufadienolides were close to those lethal doses reported by Chen et al. (27, 28). DCI and BW 62–235 caused shortening of the arrhythmia produced by bufadienolides, however, the effects were not evident.

In group 4, thevetin, a glycoside with a 5 membered unsaturated lactone ring at C
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17, caused arrhythmia with larger doses than scillaren A which has a 6 membered unsaturated lactone ring at the same position. These results are in accordance with the lethal doses of these drugs (28). The arrhythmic doses of these drugs were smaller than the lethal doses reported by Chen (28). Effects of DCI and BW 62–235 against scillaren A arrhythmia were questionable, however, shortening of the duration of the thevetin arrhythmia was observed after the treatment with DCI and BW 62–235. These differences in reactions against antiarrhythmic agents can be produced by the variation of the duration of the arrhythmia.

As stated above, in the cases of the arrhythmia caused by erythrophleum alkaloids, where chemical structures are completely different from those of aglycones, DCI and BW 62–235 were relatively ineffective except for cases of cassaine arrhythmia. The effects of DCI and BW 62–235 differed according to the drug against arrhythmia caused by aglycones, regardless of whether they have a 5 membered or 6 membered unsaturated lactone ring in their chemical structures. There were also some differences in the activities of these antiarrhythmic agents against arrhythmia caused by glycosides.

From the point of view of the reaction of arrhythmia caused by these cardiotonic substances to antiarrhythmic agents it appears that there are no differences in the mechanisms by which these drugs produce the ectopic rhythm. However, there are definite quantitative differences in their effects, i.e., these antiarrhythmic agents were ineffective against the arrhythmia elicited by the drugs which have potent and long lasting arrhythmic action, however, against the arrhythmia caused by drugs which have fleeting arrhythmic activities these agents showed a distinctive antiarrhythmic effect.

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