Effect of Quinidine and Pronethalol on Acetylstrophanthidin-Induced Ventricular Arrhythmia in Cats Treated with Reserpine

By Barrie Levitt, M.D., and Jay Roberts, Ph.D.

ABSTRACT

With pronethalol, quinidine, and reserpine it was necessary to increase the dose of acetylstrophanthidin which produced arrhythmia in combination with vagal stimulation. However, in reserpine-treated animals, quinidine and pronethalol were ineffective. The capability of large doses of acetylstrophanthidin to produce ventricular arrhythmia was not diminished by quinidine, pronethalol, or reserpine. While pronethalol decreased the S-A nodal rate in normal animals, it failed to produce an effect on rate after reserpine pre-treatment. Since after catecholamine depletion by reserpine, pronethalol and quinidine did not affect acetylstrophanthidin-induced ventricular arrhythmia, it is suggested that the antidigitalis effect of these agents is related to their actions to diminish adrenergic nervous activity.

ADDITIONAL KEY WORDS

digitalis toxicity antiarrhythmic agents
adrenergic innervation beta receptor blockade
antiadrenergic agents

A relationship between adrenergic nervous activity and digitalis-induced ventricular arrhythmia has been suggested in previous reports.\(^1,2\) Roberts et al.\(^1\) demonstrated that ventricular arrhythmias produced by small doses of acetylstrophanthidin could be prevented by treatment with reserpine, whereas those produced by large doses were not affected. Erlij and Mendez\(^2\) reported that reserpine as well as sympathectomy and adrenalectomy caused an increase in the dose of digitoxin necessary to produce death. Pronethalol, which blocks the effects of catecholamines on the heart,\(^3,4\) has also been reported to block the arrhythmia induced by digitalis materials.\(^5-7\) However, since none of the studies with pronethalol were performed in hearts depleted of catecholamines, it was not clear whether its effect on the "digitalis arrhythmia" was related to blockade of adrenergic activity. If the action of pronethalol was dependent on its antiadrenergic properties, it should have a diminished antidigitalis effect in reserpine-treated animals.

Quinidine has also been reported to block arrhythmias induced by small doses of acetylstrophanthidin.\(^8\) Moreover, quinidine is known to antagonize the cardiac effects of exogenous catecholamines\(^9-11\) and therefore it is possible that the antidigitalis properties of quinidine are related, at least in part, to blockade of adrenergic activity.

This investigation was undertaken to explore the influence of quinidine and pronethalol on the capability of acetylstrophanthidin to produce ventricular arrhythmia in normal and reserpine-treated cats. The results of this study indicate that neither pronethalol nor quinidine exert an antidigitalis action in hearts treated with reserpine.
Methods

Experiments were performed on cats anesthetized with Dial-urethane (Ciba), 0.5 ml to 0.6 ml per kg, given intraperitoneally. Changes in cardiac rhythm were recorded on Lead II of the ECG (Cambridge Simpliscribe). Mean arterial pressure was recorded by cannulating the carotid artery and monitoring the blood pressure on a mercury manometer. An indwelling endotracheal tube was used in all animals to maintain a patent airway.

Body temperature was measured by means of a laboratory rectal thermometer. Since reserpine has been reported\(^{12}\) to lower body temperature, special efforts were made to keep the laboratory and animal rooms warm (23 to 25°C). Under these conditions, body temperature in 7 reserpine-treated animals anesthetized with Dial-urethane was 37.6 ± 0.39°C, while in 12 anesthetized untreated animals, it was 37.4 ± 0.31°C.

Arrhythmia induced by the combined action of acetylstrophanthidin and vagal stimulation

A modification of the "vagus amine test"\(^{10}\) was used to study the arrhythmia induced by small doses of acetylstrophanthidin.\(^*\) The method is based on the fact that the inherent automaticity of the atrioventricular (A-V) node and the ventricle is normally masked by the higher automaticity of the sino-atrial (S-A) node, and becomes manifest only when either A-V block is present or the S-A node is slowed in one way or another to a point below the potential rate of the lower "centers," giving rise to so-called nodal or ventricular "escape." In animals whose S-A nodal rate differs in each animal, S-A nodal rates during vagal stimulation. After quinidine, before and after quinidine, similar S-A nodal rates were determined in normal animals and those treated with reserpine. Reserpine (5 mg per kg) was administered intraperitoneally 20 to 36 hours with reserpine. Reserpine (5 mg per kg) was administered intraperitoneally 20 to 36 hours before the experiment. Pronethalol was administered intravenously at a rate of 2 mg per ml per min. Doses of 2.5, 5, and 10 mg per kg were given in this way. Atrial arrhythmias produced by these doses of acetylstrophanthidin developed only during vagal stimulation, and that the critical S-A nodal rate was generally not influenced by acetylstrophanthidin in the doses used.

The effect of pronethalol on the dose of acetylstrophanthidin required to produce arrhythmia in combination with critical S-A nodal rate was determined in normal animals and those treated with reserpine. Reserpine (5 mg per kg) was administered intraperitoneally 20 to 36 hours before the experiment. Pronethalol was administered intravenously at a rate of 2 mg per ml per min. Doses of 2.5, 5, and 10 mg per kg were given in this way. Atrial arrhythmias produced by these doses of acetylstrophanthidin developed only during vagal stimulation, and that the critical S-A nodal rate was generally not influenced by acetylstrophanthidin in the doses used.

Since quinidine in large doses (15 mg per kg) produced vagal blockade, it was not possible to achieve critical S-A nodal rate following the administration of this dose of quinidine. Therefore, the experiments could not be performed using the critical S-A nodal rate. Accordingly, the method was modified to establish and to maintain, before and after quinidine, similar S-A nodal rates during vagal stimulation. After quinidine, the slowest S-A nodal rate that could be produced by vagal stimulation was used to de-

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*Acetylstrophanthidin was kindly supplied by Eli Lilly and Company.
†Pronethalol was kindly supplied by Dr. Sahagian-Edwards, Ayerst Laboratories.
terminate the threshold dose of acetylstrophanthidin. This S-A nodal rate was also used 4 to 5 hours later to determine the "control" acetylstrophanthidin threshold dose. Thus, in 7 cats, the S-A nodal rate during control determinations was on the average $112 \pm 6.9$ beats per min compared to $135 \pm 12.7$ beats per min following quinidine ($P > 0.1$). In 5 reserpinetreated animals, the S-A nodal rate was $74 \pm 8.7$ beats per min during control determination as compared with $71 \pm 9.1$ beats per min following quinidine ($P > 0.1$).

Quinidine (5 mg per kg) did not produce significant vagal blockade and therefore it was possible to determine the dose of acetylstrophanthidin needed to produce arrhythmia in combination with critical S-A nodal rate. The control threshold dose of acetylstrophanthidin was determined 4 hours after the administration of this dose of quinidine. Quinidine sulfate (5 mg per ml) was given at a rate of 5 mg per min; doses of 5 and 15 mg per kg of quinidine were administered in this way. Experiments were begun 10 min after quinidine administration.

ARRHYTHMIA INDUCED BY ACETYLASTROPHANTHIDIN WITHOUT ELECTRICALLY INDUCED VAGAL STIMULATION

In separate groups of animals, acetylstrophanthidin was given intravenously until ventricular tachycardia of at least 5 min duration was produced. It should be emphasized that these arrhythmias occurred without electrical vagal stimulation. A loading dose of acetylstrophanthidin 50 \mu g per kg was given, followed at 5 min intervals by 20 \mu g per kg doses for 5 doses. Thereafter, if necessary, 30 \mu g per kg was given every 5 min until ventricular tachycardia developed. The arrhythmia was induced in 37 animals with bilaterally sectioned vagi. The dose schedule was arranged so that arrhythmia could be produced within 30 min of the initial administration of acetylstrophanthidin.

On occasion, before the appearance of sustained ventricular tachycardia, intermittent ventricular extrasystoles (also bigemini or trigemini) were noted. These rarely lasted more than a minute. In contrast to the sustained ventricular tachycardia, these arrhythmias could be terminated by vagal stimulation. These arrhythmias have been attributed to a reentry process by Vassalle et al.\(^1\) In any case, such arrhythmias were not used as an end point in this study.

The effect of pronethalol on the dose of acetylstrophanthidin necessary to produce arrhythmia was determined both in reserpine-treated and normal animals; the effect of quinidine, however, was determined only in untreated animals. Quinidine, pronethalol, and reserpine were administered in the same manner as described above. The threshold dose of acetylstrophanthidin was determined 10 min later. The standard error is indicated after the mean value, and the statistical significance for group comparisons (Tables 1 and 2) and for paired comparisons (Tables 3 and 4, and heart rates) was determined by using the Student 't' test.

Results

EFFECT OF RESERPINE, PRONETHALOL, AND QUINIDINE ON ARRHYTHMIA INDUCED BY THE COMBINED ACTION OF ACETYLASTROPHANTHIDIN AND VAGAL STIMULATION

After pronethalol or quinidine, a larger dose of acetylstrophanthidin was needed to produce ventricular arrhythmia in combination with vagal stimulation. The data are summarized in Table 1. In animals not treated with reserpine, the control dose of acetylstrophanthidin required to produce arrhythmia closely agrees with the dose previously reported from this laboratory.\(^1\) In that study, $27 \pm 3 \mu g$ per kg was necessary to produce arrhythmia, while in the present study in three separate control groups 33, 45, and 29 \mu g per kg were required ($P > 0.1$). After pronethalol, the dose of acetylstrophanthidin required to produce arrhythmia was increased from $33 \mu g$ per kg to $85 \mu g$ per kg ($P < 0.01$). This protective effect was evident even after doses of $2.5 \mu g$ per kg (not shown in table). Since doses larger than $5 \mu g$ per kg resulted in considerable toxicity (10 mg per kg caused death in all 5 animals), their effect on the acetylstrophanthidin-induced ventricular arrhythmia was not explored.

After quinidine, the threshold for acetylstrophanthidin-induced ventricular arrhythmia was raised in all the animals. Thus, whereas $92 \mu g$ per kg of acetylstrophanthidin was required to induce arrhythmia after 5 mg per kg of quinidine, only $45 \mu g$ per kg was needed in the controls ($P < 0.05$). After 15 mg per kg of quinidine, $88 \mu g$ per kg of acetylstrophanthidin was required as compared with $29 \mu g$ per kg in the controls ($P < 0.01$). Although the control thresholds in the quinidine series were determined against a background of critical S-A nodal rate in one case and higher rates in the other (see Methods), the average threshold doses were not significantly different. (Table 1; $P > 0.1$). This
Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Threshold Dose of Acetylstrophanthidin (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
</tr>
<tr>
<td>Control</td>
<td>33 ± 4.7 (9)†</td>
</tr>
<tr>
<td>Pronethalol</td>
<td>85 ± 12.5 (6)‡</td>
</tr>
<tr>
<td>(5 mg per kg)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>45 ± 11.5 (6)‡</td>
</tr>
<tr>
<td>Quinidine</td>
<td>92 ± 18 (6)‡</td>
</tr>
<tr>
<td>(5 mg per kg)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>29 ± 4.6 (6)‡</td>
</tr>
<tr>
<td>Quinidine</td>
<td>68 ± 8.2 (7)‡</td>
</tr>
<tr>
<td>(15 mg per kg)</td>
<td></td>
</tr>
</tbody>
</table>

*Threshold dose determined 20 to 36 hours after reserpine (5 mg per kg) administration.
†Numbers in parentheses represent number of experiments.
‡Significantly different from the respective control series (P < .05).
§Three animals died prior to control determination.
¶One animal died prior to control determination.
‖Two animals died prior to control determination.

is probably due to the fact that the dose regimen employed results in some overestimation of the "threshold" dose required to produce arrhythmia so that moderate differences in S-A nodal rate induced by vagal stimulation are not reflected in threshold changes.

It is conceivable that the increase in the dose of acetylstrophanthidin needed to produce arrhythmia after 15 mg per kg of quinidine may have resulted from the action of quinidine to depress intrinsic ventricular automaticity. Ordinarily, depression of intrinsic ventricular automaticity by drugs is not a factor since the S-A nodal rate is lowered by vagal stimulation to the same level, namely, to a rate just above that at which the ventricle escapes. However, vagal blockage by quinidine (15 mg per kg) prevented lowering of S-A nodal rate to the critical level. In this circumstance, against a background of lower intrinsic ventricular automaticity, more acetylstrophanthidin might have been required to raise the automaticity of the ventricle to usurp sinus dominance than if critical S-A nodal rate, and protection equivalent to that hand, 5 mg per kg of quinidine did not prevent the attainment of the critical S-A nodal rate, and protection equivalent to that of 15 mg per kg was observed. It appears, therefore, that the action of quinidine to depress intrinsic ventricular automaticity per se was not a factor in the quinidine depression of acetylstrophanthidin-induced ventricular arrhythmia.

In our previous study, it was found that with reserpine treatment it was necessary to increase the dose of acetylstrophanthidin required to produce arrhythmia. In the present study, arrhythmia occurred in the reserpine-treated animals after 64 μg per kg, while in untreated animals, it required 33 μg per kg, (P < .01).

Most striking was the finding that the administration of pronethalol or quinidine to reserpine-treated animals did not affect the reactivity of the ventricle to acetylstrophanthidin. Thus, the same dose of pronethalol which more than doubled the acetylstrophanthidin threshold dose in untreated animals did not alter the threshold dose in the reserpine-treated group (64 μg per kg as compared to 78 μg per kg; P > .2). Quinidine was also ineffective after reserpine (Table 1).

**EFFECT OF RESERPINE, PRONETHALOL, AND QUINIDINE ON VENTRICULAR ARYTHMIA PRODUCED BY ACETYLSTROPHANTHIDIN WITHOUT ELECTRICALLY INDUCED VAGAL STIMULATION**

The capability of acetylstrophanthidin to induce arrhythmia was studied in a group of animals with bilaterally crushed vagi; vagal
stimulation was not performed in these experiments. In this series, the prior administration of reserpine had no effect on the dose of acetylstrophanthidin required to produce ventricular tachycardia (Table 2). Similarly, pronethalol and quinidine failed to alter the ventricular response to acetylstrophanthidin. Furthermore, the administration of pronethalol to animals treated with reserpine did not change the acetylstrophanthidin threshold dose.

**OTHER EFFECTS OF RESERPINE, QUINIDINE, AND PRONETHALOL**

**S-A Nodal Rate**

In all cases, S-A nodal rate was measured 10 min after the administration of quinidine or pronethalol. Quinidine in doses of 5 mg and 15 mg per kg did not change S-A nodal rate; however, in pronethalol-treated (5 mg per kg) animals, a substantial fall in S-A nodal rate was noted. After pronethalol, S-A nodal rate fell from an average of 230 ± 13.1 beats per min to an average of 159 ± 12.2 beats per min (P < .01). In reserpine-treated animals, no change in S-A nodal rate was noted after the administration of either pronethalol or quinidine. Thus, the S-A nodal rate in reserpine-treated animals was on the average 175 ± 7.8 beats per min before pronethalol, while after the drug, it was 167 ± 8.5 beats per min (P > .05). Failure of pronethalol to slow the S-A nodal rate after reserpine is consistent with the finding by Donald et al. that pronethalol did not affect the heart rate in animals with chronic cardiac denervation.

**Critical S-A Nodal Rate**

As was previously noted, reserpine treatment greatly diminished the capability of the ventricle to escape from S-A nodal dominance during vagal stimulation. In the present study, in 20 reserpine-treated cats, it was possible to slow the S-A nodal rate to an average of 44.1 ± 8.9 beats per min before the ventricle escaped, while in 19 untreated cats, S-A nodal rate could be slowed only to an average of 85.2 ± 11.8 beats per min (P < .01).

Following the administration of pronethalol, it was also possible to slow the S-A nodal rate to much lower levels before ventricular arrhythmia developed (Table 3). In reserpine-treated animals, however, pronethalol did not influence the critical S-A nodal rate.

Quinidine in doses of 15 mg per kg diminished the ability of the vagus to slow the S-A nodal rate. Thus, the critical S-A nodal rate determined just prior to the administration of quinidine was on the average, 91 ± 14.4 beats per min while 10 min after quinidine, the S-A nodal rate could be slowed on the average only to 135 ± 12.7 beats per min (P < .05). The vagal blocking action of quinidine was also evident in reserpine-treated animals. Thus, while critical S-A nodal rate just prior

### Table 2

Effect of Quinidine and Pronethalol on Acetylstrophanthidin-Induced Ventricular Tachycardia in Cats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose of Acetylstrophanthidin Necessary to Produce Ventricular Tachycardia* (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
</tr>
<tr>
<td>Control</td>
<td>97 ± 8.8 (6)‡</td>
</tr>
<tr>
<td>Pronethalol (5 mg per kg)</td>
<td>78 ± 8.9 (6)§</td>
</tr>
<tr>
<td>Quinidine (5 mg per kg)</td>
<td>87 ± 9.8 (6)§</td>
</tr>
<tr>
<td>Quinidine (15 mg per kg)</td>
<td>103 ± 12.5 (6)§</td>
</tr>
</tbody>
</table>

*Vagi crushed bilaterally.
†Reserpine (5 mg per kg) was administered 20 to 36 hours prior to the experiment.
‡Number in parentheses indicates number of experiments.
§Not significantly different from the control (P > .1).
to quinidine administration was 33 ± 10.0 beats per min, after quinidine, the S-A nodal rate could be slowed on the average only to 71 ± 9.1 beats per min (P > .05).

Quinidine in doses of 5 mg per kg did not significantly affect the capacity of the vagus to slow the S-A nodal rate, in either normal or reserpine-treated animals (Table 3).

**Blood Pressure**

The administration of pronethalol in doses of 5 mg per kg and quinidine in both 5 and 15 mg per kg doses, resulted in appreciable lowering of blood pressure (Table 4). In reserpine-treated animals, although the blood pressure was lowered by quinidine and pronethalol (Table 4), only after pronethalol did the decrease in blood pressure prove statistically significant. Although this decrease in blood pressure is smaller than in animals not given reserpine, it confirms the observation that pronethalol vasodepression is still present after chronic sympathectomy.15

**Discussion**

Several reports indicate that pronethalol diminishes the capability of digitalis materials to induce ventricular arrhythmia.8,6,7 Most pertinent is the observation that in anesthetized dogs, pronethalol increased tolerance to the cardiotoxic effects of acetylstrophanthidin.8 The present investigation demonstrated that in the cat, pronethalol, like reserpine, protected against the arrhythmias induced by small doses of acetylstrophanthidin in combination with vagal stimulation but was not effective against arrhythmia induced by large doses. While it has been reported that reserpine and pronethalol also influence the effects of large doses of digitalis materials, it should be emphasized that in these investigations ouabain and digitoxin were used as the digitalis preparations.2,17 Levitt and Roberts18 have recently demonstrated significant differences in the degree to which arrhythmias induced by different digitalis glycosides are blocked by prior administration of reserpine. These observations may explain, at least in part, the apparent differences in the effect of antiarrhythmic drugs on the arrhythm-
TABLE 4

Effect of Pronethalol and Quinidine on Mean Carotid Blood Pressure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Blood pressure</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated animals</td>
<td>Reserpine-treated animals*</td>
</tr>
<tr>
<td></td>
<td>Control (mean ± SE)</td>
<td>10 min after drug (mean ± SE)</td>
</tr>
<tr>
<td>Quinidine (5 mg per kg)</td>
<td>179 ± 5.3 (6)</td>
<td>140 ± 9.8 (6)</td>
</tr>
<tr>
<td>Quinidine (15 mg per kg)</td>
<td>177 ± 9.8 (7)</td>
<td>96 ± 9.5 (7)</td>
</tr>
<tr>
<td>Pronethalol (5 mg per kg)</td>
<td>178 ± 7.2 (6)</td>
<td>79 ± 15.1 (6)</td>
</tr>
</tbody>
</table>

*Reserpine (5 mg per kg) was given intraperitoneally 20 to 36 hours prior to each experiment.
†Determined just prior to drug administration.
‡Numbers in parentheses indicate the number of animals in each group.

mias induced by large doses of various digitalis preparations.

There have been several attempts to explore the influence of quinidine upon digitalis-induced cardiac arrhythmias. While negative findings have been reported by Rodensky et al., other investigators have been able to demonstrate blockade. The results of the present investigation showed that quinidine was effective only against arrhythmias induced by small doses of acetylstrophanthidin in combination with vagal stimulation. This may explain why it was possible for Lucchesi and Shivak to overcome quinidine blockade when they employed sufficiently high doses of acetylstrophanthidin. The data obtained in the present investigation showed that the protection by quinidine was limited to that part of the acetylstrophanthidin-induced ventricular arrhythmia which was also affected by pronethalol and reserpine. After reserpine treatment, the antidigitalis effects of quinidine could no longer be demonstrated.

There are several possible explanations for the finding that quinidine and pronethalol blocked the same component of the acetylstrophanthidin-induced ventricular arrhythmia as reserpine; e.g., direct myocardial depression, "beta"-adrenergic blockade, or adrenergic neuronal depression.

It is well known that quinidine and local anesthetics produce direct myocardial depression, and it has been proposed that pronethalol and reserpine also act in this manner. Sekiya and Vaughan Williams demonstrated that pronethalol produced many "quinidine-like" effects on the transmembrane action potential of cardiac muscle and suggested that this action paralleled their local anesthetic effect. However, more recently, Morales-Aguilera and Vaughan Williams were not able to correlate the local anesthetic potency of pronethalol and its congener propranolol with their myocardial depressant effects. Moreover, unlike quinidine and pronethalol, reserpine treatment does not affect the transmembrane action potential of isolated rabbit atrium. In addition, reserpine, dichloroisoproterenol (DCI) and pronethalol do not abolish arrhythmias induced by coronary ligation in dogs, whereas quinidine and local anesthetics are effective. Finally, the depressant action of reserpine, quinidine, and pronethalol did not extend to the arrhythmias induced by large doses of acetylstrophanthidin. Even when used together, quinidine and reserpine or pronethalol and reserpine failed to depress ventricular reactivity to large doses of acetylstrophanthidin. In view of these considerations, it is doubtful that direct myocardial depression explains the antidigitalis action of reserpine, pronethalol, and quinidine.

Since the effects of reserpine on acetyl-
strophanthidin-induced ventricular arrhythmia may result from depletion of catecholamines from storage sites, it is possible that the action of pronethalol and quinidine also results from some form of reduction in adrenergic influences on the heart. Quinidine and pronethalol have been shown to antagonize the cardiac effects of exogenous isoproterenol and epinephrine. It is possible that these agents act by blocking the effect of the adrenergic transmitter released by the digitalis preparation on the adrenergic receptors of the heart. However, Lucchesi has shown that “beta” blockade may be produced by pronethalol at dose levels which are not effective against acetylstrophanthidin-induced ventricular arrhythmia. Moreover, he has recently demonstrated potent antidigitals with the dextrorotatory isomer of pronethalol although this isomer is only 1/40 as active as the racemic mixture in blocking the cardiac effects of exogenous catecholamines. Somani and Lum found that while both n-isopropyl p-nitro phenylethylamine (INPEA) and pronethalol blocked the cardiac effects of exogenous catecholamines, only pronethalol affected ouabain-induced ventricular arrhythmia. In this regard, it has also been found that p-methyl isoproterenol (PMI) which blocks the cardiac effects of exogenous catecholamines, is ineffective against the arrhythmia caused by small doses of acetylstrophanthidin. Therefore, the ability of drugs to block exogenous catecholamines does not correlate with their blockade of digitalis-induced arrhythmia.

Pronethalol and quinidine may antagonize the digitalis-induced arrhythmia by acting on the adrenergic nervous system through another mechanism. It has been demonstrated that 2-(2, 6 dimethylphenoxy) propyl trimethyl ammonium chloride (βTM10), an agent which reportedly blocks release of the transmitter from the adrenergic nerve terminals, prevented the increase in ventricular rate induced by acetylstrophanthidin in dogs with surgically induced heart block. However, ganglionic blockade by hexamethonium did not affect the increase in ventricular rate. These observations suggest that the action of acetylstrophanthidin to influence adrenergic activity is not the result of drug-induced cardiovascular reflex or the manifestation of a central action of the drug to increase adrenergic nervous activity; rather, they imply an action of acetylstrophanthidin directly on the adrenergic postganglionic nerve fiber in the heart. Therefore, it is conceivable that the effects of agents like pronethalol and quinidine on the digitalis-induced ventricular arrhythmia may be mediated, at least in part, through an effect on the adrenergic postganglionic fiber. A nerve terminal action for pronethalol at the neuromyal junction has recently been demonstrated. The dissimilarities in the action of pronethalol, INPEA and PMI might result from differences in the capacity of these agents to depress the activity of the postganglionic fibers. The dextrorotatory isomer of pronethalol which does not exert potent “beta”-adrenergic blocking action, may also antagonize digitalis-induced arrhythmia by an action to diminish digitalis-induced adrenergic postganglionic activity.

Since it was demonstrated in these experiments that quinidine and pronethalol did not antagonize the acetylstrophanthidin-induced ventricular arrhythmia in hearts pretreated with reserpine, it would be most informative to study other cardiac effects of quinidine and pronethalol in hearts depleted of catecholamines pharmacologically or surgically. This procedure for evaluating the role of adrenergic activity in drug action was used by Innes and Krayer in studying the action of veratrum alkaloids. Veratramine, which was previously thought to act by antagonism of epinephrine, continued to exert its effect in catecholamine-depleted hearts. Thus, it would be most important to see whether pronethalol continues to exert its cardiac depressant effects in reserpine-treated animals.

References


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