Use of Potassium Canrenoate to Suppress Ouabain-Induced Ventricular Arrhythmias in Dogs

By Billy K. Yeh, Pei-Kun Sung, and Asis K. Soha

ABSTRACT

Potassium canrenoate, a steroidal compound and a specific antagonist of aldosterone, had (1) a potent protective effect against ouabain-induced ventricular tachycardia in intact closed-chest dogs and (2) a potent antiarrhythmic effect in abolishing ventricular bigeminy and ventricular tachycardia due to ouabain intoxication in dogs. Conversion of ouabain-induced arrhythmias was usually associated with an improvement in atrioventricular conduction, but no significant alterations in blood pressure or myocardial contractility occurred. Equivalent doses of potassium chloride failed to delay the occurrence of or to abolish the ouabain-induced ventricular tachycardia. Therefore, the antiarrhythmic activity of potassium canrenoate does not seem to be related to the potassium ion in the molecule. Since the compound combines both antiarrhythmic and diuretic activity, potassium canrenoate may be a valuable clinical agent for patients on digitalis therapy.

KEY WORDS

potassium chloride ventricular bigeminy atrioventricular conduction ventricular tachycardia myocardial contractility

Potassium canrenoate or Soldactone (potassium 3-[3-oxo-17β-hydroxy-4, 6-androstadien-17α-yl]propanoate) is a newly synthesized steroidal compound which specifically inhibits the effects of aldosterone on the renal tubules (personal communication from G. D. Searle & Company). Like spironolactone, it induces diuresis and natriuresis in animals with and without secondary aldosteronism. In contrast to spironolactone, potassium canrenoate has a high water solubility and can be given parenterally. The diuretic and natriuretic potency of potassium canrenoate is comparable to that of the thiazides. At a daily dose of 200–900 mg, clinically beneficial responses have been observed in postoperative patients (1) and in patients with refractory cardiac edema (2). We have discovered that potassium canrenoate, in addition to being a diuretic agent, also has potent antiarrhythmic activity in digitalis toxicity; moreover, this activity is unrelated to the potassium ion in the molecule. The molecular structure of potassium canrenoate is shown in Figure 1.

Methods

Adult mongrel dogs weighing 14–20 kg were anesthetized with sodium pentobarbital (30 mg/kg, iv) and maintained with controlled respiration. Arterial blood pressure was recorded through a catheter inserted into a femoral artery and connected to a Statham P23DB transducer. Multiple surface electrocardiograph leads were monitored. Two peripheral veins were cannulated. Recordings from the area of the sinoatrial (SA) node were obtained with an electrode catheter in intact closed-chest dogs and with plunge wires in open-chest dogs. His bundle electrograms were recorded in each experiment by an electrode-catheter technique (3). The atrium was paced at increasing rates until second degree atrioventricular (AV) nodal block developed; pacing was used before and during ouabain infusion and after conversion from ouabain-induced arrhythmias so...
that AV conduction could be studied at controlled rates. In addition, a strain-gauge arch was sutured on the right ventricular wall for monitoring segmental isometric tension (4) in all open-chest dogs. A total of 52 dogs was used in the present study.

The 28 closed-chest dogs consisted of four groups. All 28 dogs received the same regimen of ouabain: a priming dose of 7.5 μg/kg followed by a continuous intravenous infusion of 2 μg/kg min⁻¹. The dogs also received simultaneous infusions of saline, potassium canrenoate, or potassium chloride (0.02 mEq/min, iv). All infusions in any given group were stopped when the end point was reached. Table 1 summarizes the protocol for the closed-chest dogs.

The 24 open-chest dogs were subdivided into three groups. Groups 1’ and 2’ consisted of ten dogs each, and these dogs received the same ouabain regimen as did the closed-chest dogs. In addition, dogs in group 1’ received a simultaneous infusion of normal saline, and those in group 2’ received a simultaneous infusion of potassium canrenoate (0.02 mEq/min, iv). Group 3’ consisted of four dogs; these dogs received no ouabain but were given bolus injections of potassium chloride (0.5 mEq, iv) and potassium canrenoate (0.5 mEq, iv). The interval between the two injections was 15–20 minutes. Changes in myocardial contractility induced by the injections were evaluated.

One minute after the occurrence of ventricular tachycardia, a bolus injection (0.5 mEq, iv) of potassium chloride or potassium canrenoate was given in alternate dogs in all groups. The four closed-chest dogs with ouabain-induced ventricular bigeminy also received an injection of potassium canrenoate (0.25 mEq, iv).

Both potassium chloride and potassium canrenoate were dissolved in normal saline solution, and the volume of each injection was 4 ml. All dogs were observed for 2–4 hours after the beginning of infusions.

Results

Protection against Ouabain-Induced Ventricular Tachycardia by Simultaneous Infusion of Potassium Canrenoate.—Ventricular tachycardia developed 34 minutes after the beginning of the ouabain infusion in the control groups for both the closed- and the open-chest dogs (groups 1 and 1’). Potassium canrenoate, infused simultaneously with ouabain, significantly delayed the time of onset of ventricular tachycardia in the closed-chest dogs (47 minutes, P < 0.02) but not in the open-chest dogs. Equivalent doses of potassium chloride failed to delay the occurrence of ventricular tachycardia (Table 2).

Conversion of Ouabain-induced Ventricular Bigeminy and Ventricular Tachycardia by Potassium Canrenoate.—A bolus injection of potassium canrenoate in a dose of 0.25 mEq successfully converted ventricular bigeminy in all four dogs (group 4) in whom bigeminal rhythm developed as a result of ouabain infusion. In all four experiments, conversion took place within 20 seconds after potassium canrenoate was administered. Figure 2 shows a representative example of such a conversion. No recurrence of the arrhythmia was noticed after conversion in any of the four dogs for the duration of the experiment.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Infusions</th>
<th>End point of infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>Ouabain + normal saline</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>Ouabain + potassium canrenoate</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Ouabain + potassium chloride</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Ouabain + normal saline</td>
<td>Ventricular bigeminy</td>
</tr>
</tbody>
</table>

N = number of dogs tested.
TABLE 2
Effects of Simultaneous Infusions of Potassium Canrenoate and Potassium Chloride on the Development of Ouabain-Induced Ventricular Tachycardia in Dogs

<table>
<thead>
<tr>
<th>Group</th>
<th>Infusion</th>
<th>Time for VT to appear (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Closed-Chest Dogs</td>
<td></td>
</tr>
<tr>
<td>1 (8)</td>
<td>Ouabain + normal saline</td>
<td>34 ± 1</td>
</tr>
<tr>
<td>2 (8)</td>
<td>Ouabain + potassium canrenoate</td>
<td>47 ± 3</td>
</tr>
<tr>
<td>3 (8)</td>
<td>Ouabain + potassium chloride</td>
<td>34 ± 2</td>
</tr>
<tr>
<td></td>
<td>Open-Chest Dogs</td>
<td></td>
</tr>
<tr>
<td>1' (10)</td>
<td>Ouabain + normal saline</td>
<td>34 ± 1</td>
</tr>
<tr>
<td>2' (10)</td>
<td>Ouabain + potassium canrenoate</td>
<td>36 ± 2</td>
</tr>
</tbody>
</table>

Each group received the same ouabain regimen: a priming dose of 7.5 μg/kg followed by a continuous intravenous infusion of 2 μg/kg min⁻¹. Normal saline, potassium canrenoate, or potassium chloride were infused at a rate of 0.02 mEq/min simultaneously with ouabain. Values shown are means ± SE. Note that simultaneous infusion of ouabain and potassium canrenoate significantly delayed the occurrence of ouabain-induced ventricular tachycardia (VT) in intact closed-chest dogs (P < 0.02) but not thoracotomized open-chest dogs. Number of dogs in each group is given in parentheses.

A bolus injection of potassium canrenoate (0.5 mEq or 200 mg) successfully abolished ouabain-induced ventricular tachycardia in 13 of the 22 experiments, the conversion rate being 59%. The conversion rate with potassium canrenoate was comparable in the closed- and the open-chest dogs (7/12 vs. 6/10) and was essentially the same in ouabain-induced ventricular tachycardia in all groups, i.e., those receiving normal saline, potassium canrenoate, or potassium chloride infusion simultaneously with ouabain infusion (Table 3). All conversions took place within 1 minute after intravenous injection of potassium canrenoate. The sinus rates increased, decreased, or remained unchanged during the conversions. Normal sinus rhythm was maintained in all dogs with successful conversion for as long as the dogs were observed (2-4 hours after the beginning of infusions). Equivalent doses of potassium chloride under these same circumstances failed to convert ventricular tachycardia in any of the 22 experiments in which it was used (Table 3). Figures 3 and 4 demonstrate the effects of equimolar doses of potassium chloride and potassium canrenoate.

![Figure 2](image-url)
TABLE 3

Comparison of the Effects of Potassium Canrenoate and Potassium Chloride on Ouabain-Induced Ventricular Arrhythmias in Dogs

<table>
<thead>
<tr>
<th></th>
<th>Potassium canrenoate</th>
<th>Potassium chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventricular Bigeminy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>4/4  (100%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ventricular Tachycardia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closed-chest dogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>2/4  (50%)</td>
<td>0/4  (0%)</td>
</tr>
<tr>
<td>Group 2</td>
<td>3/4  (75%)</td>
<td>0/4  (0%)</td>
</tr>
<tr>
<td>Group 3</td>
<td>2/4  (50%)</td>
<td>0/4  (0%)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>7/12 (58%)</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>Open-chest dogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1'</td>
<td>3/5  (60%)</td>
<td>0/5  (0%)</td>
</tr>
<tr>
<td>Group 2'</td>
<td>3/5  (60%)</td>
<td>0/5  (0%)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>6/10 (60%)</td>
<td>0/10 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>13/22 (59%)</td>
<td>0/22 (0%)</td>
</tr>
</tbody>
</table>

Values are the ratios of dogs showing conversion to total number of dogs tested. Groups 1, 2, 3, and 4 were closed-chest dogs, and groups 1' and 2' were open-chest dogs. Each dog received a priming dose of 7.5 µg/kg of ouabain followed by a continuous intravenous infusion of 2 µg/kg min⁻¹, until the development of ventricular bigeminy (group 4) or ventricular tachycardia (groups 1, 2, 3, 1', and 2'). In addition to ouabain, groups 1, 1', and 4 received simultaneous infusions of normal saline and groups 2 and 2' received simultaneous infusions of potassium canrenoate, 0.02 mEq/min; group 3 received a simultaneous infusion of potassium chloride, also 0.02 mEq/min. Treatments were given 1 minute after the occurrence of the arrhythmias: 0.25 mEq of potassium canrenoate, or potassium chloride in a bolus injection for dogs with ventricular tachycardia.

Abolition of ouabain-induced ventricular tachycardia by rapid injections of potassium canrenoate was associated with shortening of the atrium-His bundle interval in 8 of the 13 conversions (0.1 > P > 0.05). Figure 5 shows the shortening of the P-R interval and the improvement in AV nodal transmission associated with conversion of ventricular tachycardia in one experiment. No depression of intra-atrial, AV nodal, or intraventricular conduction by potassium canrenoate was noted in any experiment.
experiment, the rate effect on myocardial contractility was eliminated.

Table 4 summarizes the results. Injections of 0.5 mEq of potassium chloride and potassium canrenoate had no effect on myocardial contractility in control dogs that were not given ouabain. Ouabain caused an average increase of 60% in the segmental isometric tension of ventricular myocardium before ventricular tachycardia developed in six dogs ($P < 0.001$). Conversion induced by potassium canrenoate caused a slight, statistically insignificant decrease in the inotropic effect of ouabain. A mean increase of about 50% in

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**FIGURE 3**

Effects of a bolus injection of 0.5 mEq of potassium chloride on ventricular tachycardia induced by ouabain in a dog. In addition to ouabain, this dog received a simultaneous infusion of normal saline, and ventricular tachycardia developed 35 minutes after the beginning of the ouabain infusion. None of the 22 dogs treated with potassium chloride was converted to sinus rhythm. Note the markedly depressed SA electrograms. The interval between time lines is 1 second. Abbreviations are the same as in Figure 2.

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**FIGURE 4**

Conversion of ouabain-induced ventricular tachycardia (VT) by potassium canrenoate. This dog received simultaneous infusions of ouabain and potassium canrenoate (group 2), and ventricular tachycardia developed 45 minutes after the beginning of the infusions. At this stage of ouabain toxicity, sinoatrial standstill occurred. Note that the ventricular tachycardia was converted to sinus rhythm within 25 seconds after a bolus injection of 0.5 mEq of potassium canrenoate and that the rate of tachycardia decreased from 200 to 190/min before the conversion took place. Also, return of the SA electrogram is apparent after potassium canrenoate treatment. The interval between time lines is 1 second. Abbreviations are the same as in Figure 2.
isometric tension induced by ouabain persisted more than 1 hour after conversion ($P < 0.01$).

**Discussion**

This study indicates that potassium canrenoate significantly delays the occurrence of ouabain-induced ventricular tachycardia in intact closed-chest dogs but not in open-chest dogs. This difference in the protective efficacy of potassium canrenoate against ouabain toxicity is not clearly understood at present. One possible explanation is that the open-chest dogs respond to the trauma of major surgery by secreting a large amount of aldosterone. This acute secondary hyperaldosteronism induced by open-chest surgery might inhibit the manifestation of the protective effect of slow intravenous infusion of the aldosterone antagonist, potassium canrenoate. On the other hand, it seems paradoxical that the rate of conversion of ouabain-induced ventricular tachycardia is essentially the same in open- and closed-chest dogs. This finding might be explained if the peak concentration of potassium canrenoate reached after the bolus injection of the drug is the major determinant of the success or failure of conversion. Even though a greater antiarrhythmic activity of a bolus injection of potassium canrenoate (0.5 mEq) was expected in closed-chest dogs than in open-chest dogs, a comparable antiarrhythmic efficacy might
result, as in the present study, if somehow the peak levels of potassium canrenoate achieved immediately following injection are above the antiarrhythmic threshold in a similar percent of closed- and open-chest dogs.

The mechanism of conversion of ouabain-induced ventricular arrhythmias by potassium canrenoate is not well understood at present. The conversion of both ventricular bigeminy and ventricular tachycardia takes place without any consistent change in sinus rate: the sinus rate increased, decreased, or remained unchanged. Thus, the conversions of ouabain-induced arrhythmias probably do not result from the suppression of ventricular foci by increased supraventricular impulses.

Our data show that potassium canrenoate effectively abolishes ventricular bigeminy and ventricular tachycardia due to ouabain. Lamarche and Royer (5) have recently reported that potassium canrenoate suppresses arrhythmias induced by formiloxine (a derivative of digoxin) in isolated rabbit atria. This antiarrhythmic activity of potassium canrenoate probably is not due to the presence of potassium in the molecule, because equimolar doses of potassium chloride fail to delay the occurrence of ventricular tachycardia or to abolish ventricular tachycardia due to ouabain toxicity. Although previous studies have demonstrated that potassium chloride temporarily abolishes ventricular arrhythmias due to cardiac glycosides (6, 7), the present study indicates that potassium chloride (0.5 mEq) injection is ineffective. This difference is probably due to the larger dose used by previous investigators—10–80 times that used in this study.

The conversion of ouabain-induced arrhythmias by potassium canrenoate always occurred within 1 minute. Thus, the protective effect of potassium canrenoate in ouabain toxicity is mediated through a mechanism unrelated to the relatively nonspecific protective or "catatonic" effect of steroids (8, 9), which is mediated through the induction of hepatic microsomal enzymes and requires several days to develop (10).

Significantly, the conversion of the toxic electrophysiological effects of ouabain took place without affecting the inotropic response to the glycoside. Furthermore, in contrast to quinidine (11, 12), procaine amide (11, 13), and propranolol (14–16), potassium canrenoate conversion is usually associated with an improvement rather than a depression in cardiac conduction. In no instance did we observe any depressant effect of potassium canrenoate on intra-atrial, AV nodal, or intraventricular conduction. These findings are consistent with data obtained from microelectrode studies (17) and with our observations that the canrenoate molecule does not affect the arrhythmias induced by catecholamines or acute coronary artery ligations (18) or the inotropic response of cat papillary muscles to a cardiac glycoside. Thus, the canrenoate molecule might be a specific antagonist to the electrophysiological effects of cardiac glycosides on cardiac cell membranes.

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References

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