Inability of Potassium Canrenoate to Convert Experimentally Induced Ouabain Arrhythmias in the Canine Heart

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ABSTRACT

The antiarrhythmic effects of potassium canrenoate were examined in 20 closed-chest, pentobarbital-anesthetized dogs with ouabain-induced ventricular tachycardia. In a group of 8 dogs, a mean dose of ouabain of 64.4 ± 3.7 μg/kg induced sustained ventricular tachycardia. Subsequent administration of potassium canrenoate (30 mg/kg, iv) caused ventricular fibrillation in 1 dog and sinus tachycardia in 3 dogs. Stimulation of the distal end of the cut right vagus in the latter 3 dogs slowed the sinus rhythm enough to permit the ventricular focus to become the dominant pacemaker. In the other 4 dogs, potassium canrenoate did not alter the ouabain-induced ventricular tachycardia. In a second group of 12 dogs, ventricular tachycardia was also induced by administering a toxic dose of ouabain (65.5 ± 2.9 μg/kg, iv). After ouabain intoxication, atrial overdrive suppression of the ventricular rhythm was initiated by electrically pacing the right atrium at a mean frequency of 184.5 ± 7.9 beats/min. Subsequent administration of potassium canrenoate (30 mg/kg, iv) to these dogs restored sinus rhythm in 4 of the dogs; however, stimulation of the distal end of the cut right vagus caused a reappearance of the ventricular ectopic focus. After potassium canrenoate administration, the minimum atrial pacing rate required to capture the ventricular rhythm was 160.9 ± 9.4 beats/min. This rate represents a significant reduction (P < 0.005) in the rate of the ouabain-induced ventricular ectopic focus, but in no instance was the focus directly suppressed by potassium canrenoate. Propranolol, in contrast to potassium canrenoate, restored normal sinus rhythm in all 20 ouabain-intoxicated dogs and suppressed the ouabain-induced ectopic pacemaker during the period of vagally induced sinoatrial arrest. The results of this study show that potassium canrenoate fails to exert an antiarrhythmic effect against digitalis-induced arrhythmias and that any apparent restoration of sinus rhythm in response to potassium canrenoate is due to overdrive suppression of the ouabain-induced ventricular ectopic pacemaker.

KEY WORDS: overdrive suppression, ventricular tachycardia, atrial pacing, sinus tachycardia, vagal stimulation, digitalis.

Potassium canrenoate (Soldactone or potassium 3-[3-oxo-17-β-hydroxy-4,6, androstadien-17-α-yl][propanoate]), a diuretic which specifically antagonizes aldosterone, reportedly can prevent or terminate experimentally-induced digitalis arrhythmias (1-4). Yeh and Lazarra (3) showed that 5 × 10^-5M potassium canrenoate restored resting membrane potential, action potential overshoot, rate of rise of the action potential (dV/dt), and membrane excitability in canine Purkinje fibers poisoned with ouabain. Yeh and Sung (1) found that potassium canrenoate (0.5 mEq, iv) abolished ouabain-induced ventricular tachycardia in 6 of 11 dogs; all conversions took place within 1 minute after the intravenous administration of the drug. These authors described the response to potassium canrenoate as an "all or none phenomenon" and the conversion as "permanent."

These all or none responses to potassium canrenoate could have resulted from either a slowing of the dominant ouabain-induced ectopic pacemaker site or an enhancement of the pacemaker activity of the sinoatrial node without an actual suppression of the ouabain-induced automaticity. Therefore, the so-called all or none effect might be related to the occurrence of overdrive suppression following the administration of potassium canrenoate. The data of Yeh and Sung (1) and of Yeh et al. (2) do show that potassium canrenoate decreases the rate of the ouabain-induced ventricular ectopic focus, but the conversion to normal sinus rhythm occurs at a rate which exceeds that of the ventricular pacemaker. Thus, the sinoatrial node becomes the dominant pacemaker.

The present study explored the antiarrhythmic properties of potassium canrenoate, especially its ability to antagonize ouabain-induced arrhythmias. The results indicate that potassium...
canrenoate does not possess a specific antiarrhythmic effect against digitalis-induced cardiac arrhythmias and that any apparent conversion is due to the enhancement of sinus or junctional pacemaker activity leading to overdrive suppression of the digitalis-induced ectopic pacemaker.

Methods

Twenty male mongrel dogs (7.8–13.4 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv). Arterial blood pressure was recorded by a Statham 23DB transducer connected to a catheter inserted into a femoral artery. All drugs were administered into the cannulated left external jugular vein. The right vagus was sectioned, and its distal end was stimulated with 1.0-msec square pulses (40 Hz, 8–10 v) delivered from a Grass SD-5 stimulator. The lead II electrocardiogram was monitored continuously on an oscilloscope and recorded along with the arterial blood pressure.

In 12 of the 20 dogs, a bipolar pacemaker electrode (USCI-NBIIH) was placed in the right atrium via the right external jugular vein. An AEL 104A stimulator and isolation unit were used to pace the heart via the atrial electrode. When the heart was not being paced, the atrial bipolar electrode was used to monitor and record the atrial electrogram. All recordings were made on a Grass model 7 polygraph.

Ventricular tachycardia was induced in each dog by intravenously administering an initial dose of ouabain of 40 μg/kg at a rate of 80 μg/min. Thirty minutes later, a second dose of ouabain (20 μg/kg) was administered, and then additional doses (10 μg/kg) were given every 15 minutes until ventricular tachycardia developed (5). Once the arrhythmia had been established, it was permitted to continue for 20 minutes before potassium canrenoate was administered. The distal end of the cut right vagus in each of these three dogs slowed the supraventricular activity. The atrial pacing rate required to achieve ventricular capture or atrial overdrive suppression of the ventricular rhythm was determined in 12 dogs by gradually increasing the frequency of atrial stimulation. This determination was made during the control period before the administration of ouabain, after the ouabain-induced tachycardia had developed, and, finally, after the administration of potassium canrenoate.

The criteria used to determine antiarrhythmic activity were (1) reversion to normal sinus rhythm for a period of at least 30 minutes, and (2) failure of right vagal stimulation to expose automatic ectopic ventricular activity during the period of vagally induced sinoatrial slowing or arrest.

Results

EFFECTS OF POTASSIUM CANRENOATE ON OUABAIN-INDUCED VENTRICULAR TACHYCARDIA

A total of eight dogs received a mean dose of ouabain of 64.4 ± 3.7 μg/kg; this treatment resulted in sustained ventricular tachycardia. Stimulation of the distal end of the cut right vagus during the phase of ventricular tachycardia failed to alter the ouabain-induced ventricular automaticity. The arrhythmia was allowed to continue uninterrupted for at least 20 minutes to ensure against a spontaneous return to normal sinus rhythm. Then, each ouabain-intoxicated dog was given a dose of potassium canrenoate (30 mg/kg, iv). One of the eight dogs developed ventricular fibrillation 4 minutes after the administration of potassium canrenoate and died. In four of the dogs, potassium canrenoate did not reverse the ouabain-induced ventricular tachycardia. However in three of the dogs, the administration of potassium canrenoate caused the development of sinus tachycardia. Stimulation of the distal end of the cut right vagus in each of these three dogs slowed the supraventricular rhythm enough to permit the ventricular focus to again become the dominant pacemaker. Therefore, the apparent restoration of a sinus mechanism by potassium canrenoate in three of the eight dogs was due to atrial overdrive suppression of the ouabain-induced ventricular ectopic pacemaker. The seven dogs remaining in this group were given propranolol (2.3 ± 0.14 mg/kg, iv) until normal sinus rhythm was restored and maintained for at least 30 minutes. Next, the right vagus was stimulated for 10 seconds; sinoatrial arrest and ventricular standstill occurred in each ouabain-intoxicated dog, thus demonstrating propranolol’s ability to suppress the ouabain-induced ventricular ectopic focus. The subsequent administration of insulin (80 U, iv) restored the ouabain-induced arrhythmia, indicating that ouabain was still present in amounts sufficient to produce cardio toxic effects.
To answer this question, we determined the minimum atrial pacing rate needed to capture the ventricular rhythm before and after the administration of potassium canrenoate to the ouabain-intoxicated dog. The administration of a mean dose of ouabain of 65.5 ± 2.9 μg/kg resulted in ventricular tachycardia in all 12 dogs. The rate of the ouabain-induced ventricular tachycardia (185.0 ± 10.3 beats/min) was increased significantly (P < 0.005) over the control spontaneous sinoatrial rate (142.5 ± 4.9 beats/min). The atrial pacing rate needed to achieve ventricular capture by overdrive suppression (184.5 ± 7.9 beats/min) did not differ significantly (P > 0.05) from the rate of the ouabain-induced ventricular rhythm. This observation demonstrates that atrial overdrive suppression can occur in the presence of toxic amounts of ouabain and that the atrioventricular node can conduct at a rate sufficient to permit ventricular capture. The administration of potassium canrenoate (30 mg/kg, iv) to each of the 12 ouabain-intoxicated dogs led to a significant reduction in the atrial pacing rate required to achieve ventricular capture (160.9 ± 9.4, P < 0.005). These data suggest that potassium canrenoate caused a reduction in the discharge rate of the ouabain-induced ventricular ectopic focus. The atrial pacing rate required to achieve ventricular capture after the administration of potassium canrenoate did not differ significantly from the control spontaneous sinoatrial rate.

**Failure of potassium canrenoate to suppress the ouabain-induced ventricular ectopic focus in the canine heart.** A–D show the right atrial electrogram (not recorded in C), the lead II electrocardiogram (EKG), and the femoral artery blood pressure. A: Control record illustrating the effectiveness of right vagal stimulation in producing sinoatrial arrest and the absence of a ventricular ectopic pacemaker. During the period of vagal stimulation, a single escape beat from the sinoatrial node was the only evidence of automaticity. B: Record obtained after the dog had received a toxic dose of ouabain. In this particular experiment, the ventricular ectopic pacemaker discharged at a rate less than the original sinoatrial rate. Stimulation of the right vagus did not influence the ouabain-induced ectopic focus. C: Record showing the effectiveness of right atrial pacing (2.6 Hz) in suppressing the ouabain-induced ventricular ectopic pacemaker. Decreasing the atrial pacing rate to 2.5 Hz resulted in a loss of overdrive suppression. D: Record obtained after administration of potassium canrenoate (30 mg/kg, iv). There was an immediate restoration of sinus rhythm which could be converted to ventricular rhythm during vagally induced slowing of the supraventricular pacemaker. Potassium canrenoate was unable to suppress the ouabain-induced ectopic focus.
(P > 0.05). In this group of ouabain-intoxicated dogs, the intravenous administration of potassium canrenoate restored sinus rhythm in 4 of the dogs. In 2 of these 4 dogs, the duration of sinus rhythm was less than 15 minutes, whereas in the other 2 dogs it exceeded 120 minutes. As noted previously, however, stimulation of the distal end of the cut right vagus resulted in a suppression of the supraventricular pacemaker and a reappearance of the ventricular ectopic rhythm in the 4 dogs which had developed an apparent sinus rhythm after administration of potassium canrenoate. Thus, potassium canrenoate depressed the rate of the ventricular ectopic focus enough to permit a supraventricular mechanism to become the dominant pacemaker and suppress the ventricular pacemaker (overdrive suppression). Figure 1 is a representative example of an experiment in which potassium canrenoate restored sinus rhythm in a ouabain-intoxicated dog. It is important to note that atrial overdrive suppression of the ventricular focus can be accomplished by either increasing the atrial rate through electrical pacing or decreasing the rate of the ventricular ectopic focus through the administration of potassium canrenoate. The latter was possible in 4 of the 12 dogs in this group. In the remaining 8 dogs, the ouabain-induced ventricular tachycardia was not reversed. Thus, the effect of potassium canrenoate on the rate of ventricular ectopic discharge was variable—an increase occurred in 1 dog, no change occurred in 1 dog, and a decrease occurred in 10 dogs. The overall effect of potas-

**FIGURE 2**

Inability of potassium canrenoate to suppress the ouabain-induced ventricular tachycardia in the dog. Each section shows the arterial blood pressure and the lead II electrocardiogram (EKG). Top Center: Control tracing illustrating the ability of right vagal stimulation to suppress the supraventricular pacemaker. Middle Left: Effects of a toxic dose of ouabain. The ouabain-induced ventricular tachycardia was not influenced by stimulation of the right vagus. Middle Right: The administration of potassium canrenoate (30 mg/kg, iv) led to a decrease in the rate of the ventricular ectopic focus but it did not restore sinus rhythm. As before, vagal stimulation was without effect on the ventricular ectopic focus. Bottom Left: Administration of propranolol restored normal sinus rhythm and suppressed the ventricular ectopic focus as evidenced by the ability of vagal stimulation to produce cardiac arrest. Bottom Right: Subsequent administration of insulin through its ability to decrease serum potassium led to a return of the ouabain-induced ectopic focus and provided evidence for the continued presence of ouabain in a concentration sufficient to produce cardiotoxicity.
Sodium canrenoate was to depress, but not to suppress, the ouabain-induced ventricular pacemaker.

The importance of ruling out overdrive suppression as a possible mechanism for the restoration of sinus rhythm is illustrated further in Figure 2. Although potassium canrenoate produced a decrease in the ventricular ectopic rate, the dose was not sufficient to permit overdrive suppression by the sinoatrial pacemaker. Propranolol (2.0 ± 0.6 mg/kg), on the other hand, restored normal sinus rhythm by directly suppressing the ventricular focus as evidenced by the fact that vagal stimulation failed to elicit ventricular activity and led to cardiac arrest. Subsequently, the administration of insulin (80 U, iv) restored the spontaneous ventricular rhythm, demonstrating the continued presence of the cardiotoxic concentrations of ouabain. These results were found in each of the 12 dogs tested.

Discussion

Previous studies (1–4) have suggested that potassium canrenoate is an antagonist to the cardiotoxic actions of ouabain. Supposedly, the drug induces conversion to sinus rhythm in an all or none manner in ouabain-intoxicated dogs. In the present study, 7 of 20 dogs poisoned with ouabain converted to a sinus rhythm after the administration of potassium canrenoate. However, in every instance in which an apparent conversion had occurred, stimulation of the distal end of the cut right vagus slowed the supraventricular pacemaker enough to allow the ouabain-induced ectopic focus to again become the dominant pacemaker. It is apparent, therefore, that potassium canrenoate’s all or none effect is due to its ability to produce overdrive suppression of the ventricular ectopic focus.

Reference to Figure 4 in the publication by Yeh et al. (2) may provide an answer to the discrepancy between their results and those obtained in the present study. Note that the rate of the ventricular ectopic focus decreases from 200 to 190 beats/min soon after the administration of potassium canrenoate. The sinus rhythm (sinus tachycardia) which follows the decrease in ventricular rate is at a rate of 200 beats/min, a rate which exceeds that of the ventricular ectopic focus and thus becomes the dominant rhythm. The ability of atrial overdrive to suppress the ventricular ectopic focus in the presence of a toxic dose of ouabain was demonstrated in the present study. Furthermore, potassium canrenoate, as shown by this study as well as by those of Yeh and Sung (1) and Yeh et al. (2), decreases the rate of ectopic discharge and increases the occurrence of atrial overdrive. When the rate of ventricular ectopic discharge is decreased below that of the existing sinoatrial rate, an apparent sinus rhythm will occur in response to potassium canrenoate. Vagal stimulation can unmask this event and thus establish whether or not potassium canrenoate specifically antagonizes the digitalis-induced arrhythmia (1, 2). The present study demonstrated that potassium canrenoate does not have the ability to suppress digitalis-induced automaticity in the intact canine heart and that the all or none effect reported by previous investigators (1, 2) is probably related to a masking of the ventricular ectopic focus by a supraventricular pacemaker with a faster discharge rate.

Although ouabain decreases the rate of atrioventricular transmission, it is apparent from the data presented that overdrive suppression from a supraventricular site can occur in the presence of cardiotoxic doses of ouabain. It is possible that the administration of potassium canrenoate introduces enough potassium ions to reduce the rate of the ouabain-induced ventricular ectopic focus. The reduction in the ectopic rate after administration of potassium canrenoate might then be sufficient to permit overdrive suppression from a supraventricular site. It is evident from these data that potassium canrenoate (or the potassium ions alone) is unable to suppress completely the ouabain-induced ventricular pacemaker. On the other hand, propranolol, as well as other antiarrhythmic agents can reverse digitalis-induced arrhythmias to the point of complete suppression (6, 7) by a direct effect on the ectopic pacemaker. The present observations, although at variance with those of previous workers (1, 4), are in agreement with those recently reported by Baskin et al. (8). The latter group has reported that potassium canrenoate fails to modify ouabain-induced arrhythmias in Langendorff-perfused guinea pig hearts except at very high concentrations; this effect has been attributed to the increased potassium ion concentration. Furthermore, potassium canrenoate fails to prevent or alter the inhibitory action of the cardiac glycosides on sodium-potassium—activated adenosinetriphosphatase. Likewise,
recent studies in isolated rabbit hearts have failed to show a specific antiarrhythmic effect of potassium canrenoate against acetylstrophanthidin-induced arrhythmias (9).

References
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