Suppression of Ouabain-induced Ventricular Rhythms with Aprindine HCl

A Comparison with Other Antiarrhythmic Agents

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SUMMARY Three groups of dogs were given ouabain (mean 60 μg/kg) until an accelerated ventricular escape (AVE) and repetitive ventricular response (RVR) followed cessation of pacing. In a group of six control dogs, the AVE and RVR were found to occur at stable escape intervals for periods of at least three hours. A second group of dogs received various antiarrhythmic agents in an attempt to suppress the AVE and RVR. Quinidine, diphenhydantoin, lidocaine, procainaamide, and propranolol, were successful in only 0 to 33% of trials. Potassium canrenoate, 12 mg/kg was unsuccessful in three dogs. Verapamil, by bolus, suppressed RVR in 41% and AVE in 21% of trials. KCl, infused until AVE and RVR were suppressed, was successful when the mean serum potassium rose from 3.8 mEq/L to 7.2 mEq/L. Aprindine, 2.86 mg/kg, suppressed AVE and RVR in 14 of 14 dogs. In the third group of dogs, verapamil was infused continuously and suppressed RVR and AVE at a mean cumulative dose of 2.93 mg/kg. Calcium chloride reversed aprindine and verapamil-induced suppression of RVR and AVE. This study demonstrates that RVR and AVE resist suppression by available antiarrhythmic agents in clinically-used doses. Only aprindine was 100% successful at doses used in man. The ionic pathogenesis of RVR and AVE is unknown, but some data suggest the slow current may play an important role.

STUDIES BY Castellanos,1 Lown,2, 9 Wittenberg,4 and Zipes5 with their respective associates, demonstrated that following digitalis administration, ventricular escape beats could be elicited in the intact dog heart. Of interest was the fact that these escape beats exhibited overdrive acceleration, rather than overdrive suppression, and occurred at very consistent intervals. Observations from microelectrode studies performed by Ferrier et al.3 and Rosen et al.5 established a possible cellular basis for these escape beats, and Ferrier and Moe9 suggested that they may be dependent on transmembrane calcium fluxes involving the slow current.

Because the intervals of these escape beats remain quite fixed to the preceding complex, when heart rate and number of cycles are held constant, the ventricular escape beats in the intact dog heart are quite amenable to testing the effects of various antiarrhythmic agents. In so doing, Whiting and Lown9 found that propranolol failed to suppress these ventricular escape beats. We considered that verapamil, a slow-channel blocker,10 might be more effective than propranolol if the slow current plays an important role in the pathogenesis of these escape beats. The purpose of this study was to compare the efficacy of verapamil with other antiarrhythmic agents in suppressing these ventricular escapes. In addition, we evaluated the effects of a new antiarrhythmic agent, aprindine hydrochloride (AC-1802), a very potent local anesthetic agent11, 12 with electrophysiologic properties that resemble lidocaine in many ways,13 but with possible slow-current blocking capabilities.14

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Methods and Materials

Adult healthy mongrel dogs were anesthetized with sodium secobarbital, 30 mg/kg (repeated in doses of 2-5 mg/kg as needed to maintain anesthesia), and ventilated with a Harvard respirator. A heating blanket was used to maintain normal body temperature. Following cannulation of the external jugular vein and the common carotid artery, the heart was exposed via a midline sternotomy and was suspended in a pericardial sling. Arterial blood pressure was continuously monitored with a Statham strain gauge transducer (Model 23 BD) and 5% dextrose in normal saline was infused into the venous line (except during drug infusions) at a rate of approximately 200 ml/hr. The sinus node was crushed to achieve a slower spontaneous heart rate.

All recording and stimulating was performed using bipolar electrodes, having an interelectrode distance of 1-2 mm. These electrodes were made from stainless steel needles (0.3 mm diameter) which were bent in the shape of a J and insulated except for the curved portion and tip, which was hooked into the epicardium.

Recording electrodes were placed in the sinus node area, the right and left atrial appendages, and the midanterior right and left ventricles on either side of the septum. A standard lead II was also recorded. Tracings were displayed on a switched-beam oscilloscope (DR8 Electronics for Medicine) using filter settings between 40 Hz and 500 Hz and were recorded on photographic paper at speeds of 100 mm/sec. Measurements were made from the tracings on the photographic paper.

Stimulating electrodes were placed close to the sinus node area and the midanterior right ventricle, near the right ventricular recording electrode. Stimuli were delivered through an isolation transformer (Digipulser, model 830, Isopulser, model 850, W. P. Instruments, Inc.) simultaneously to the right atrium and right ventricle at 1½ to 2 times the diastolic threshold as rectangular pulses of 2 msec duration. The stimuli were delivered in a continuous train of 12 pulses at
basic cycle lengths of 300 and 350 msec. Following the last stimulus of the basic train, two events were studied. First, a premature stimulus was delivered 250-275 msec after the last basic pulse simultaneously to the right atrium and ventricle and pacing was discontinued for approximately 2 seconds to allow emergence of spontaneous activity, if any (fig. 1A, C). Second, pacing was abruptly terminated following the last stimulus of the basic train without delivering the premature stimulus and pacing was resumed approximately 2 seconds later (fig. 1B, D).

Prior to ouabain administration, a supraventricular escape beat (atrial or junctional) occurred after the last paced beat, at cycle lengths usually exceeding 750-1000 msec (fig. 1A, B). These escape beats demonstrated overdrive suppression, i.e., a faster basic pacing rate was followed by a longer escape interval. Following ouabain administration, a ventricular escape beat resulted 385-600 msec after the last paced beat and exhibited overdrive acceleration, i.e., a faster basic pacing rate was followed by a shorter escape interval. For purposes of the present discussion, the ventricular escape beat which followed premature ventricular stimulation was called a repetitive ventricular response (RVR) (fig. 1C) while the ventricular escape beat which followed abrupt cessation of pacing was called an accelerated ventricular escape (AVE) (fig. 1D). The term, escape, is used arbitrarily in this context and does not connote mechanism (i.e., automaticity or re-entry). Accelerated atrial escapes occurred, and also demonstrated overdrive acceleration, but generally at cycle lengths too long to conduct to the ventricle prior to the ventricular escape. When atrial escapes preceded ventricular escapes, conduction to the ventricle (with aberration) was ruled out by demonstrating the independent nature of the ventricular escape beats with a change in the programmed atrial stimulation.

Ouabain was administered intravenously, in an initial dose of 25 μg/kg with subsequent doses of 10-15 μg/kg at 30 minute intervals until stable ventricular escapes followed premature stimulation and cessation of pacing. The rhythms were continuously observed and recorded every five minutes on photographic paper. Escape intervals were measured to the electrogram of the earliest escaping ventricle.

In some studies, plunge wire recordings of His bundle activity confirmed that the escaping beats were of ventricular origin. Most often, the altered QRS contour and prolonged duration at cycle lengths which were known to permit normal ventricular conduction provided sufficient evidence of ventricular origin.

Group 1. Ouabain Controls

Three groups of dogs were studied. The first group of six dogs was studied to establish the stability and duration of the RVR and AVE. In these dogs, once a stable RVR and AVE were elicited with ouabain, no further drugs were given, and the duration of stable escape intervals was determined.

Group 2. Multiple Drug Comparison

The second group was studied to evaluate the efficacy of various antiarrhythmic agents in suppressing the RVR and AVE. This group consisted of 53 dogs given various antiarrhythmic agents following the onset of stable, ouabain-induced ventricular escape beats. Drugs were given as single injections intravenously over 30-90 seconds and repeated at

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![Figure 1](https://circ.ahajournals.org/doi/fig/10.1161/01.CIR.53.2.316)

**Figure 1** Ouabain-induced repetitive ventricular response (RVR) and accelerated ventricular escape (AVE). Panels A and B, control; panels C and D, after ouabain administration; panel C, RVR; panel D, AVE. Stimuli delivered to right atrium and ventricle simultaneously. Basic cycle length, 300 msec; premature stimulus interval, 250 msec. Last three stimuli for each period of pacing are depicted. In the control state, a supraventricular escape beat initiated by discharge in or near the His bundle followed cessation of pacing (H-V interval, 35 msec). After ouabain administration, a ventricular escape followed termination of pacing, (H activation begins after onset of ventricular activation). RA, right atrial electrogram; RV, right ventricular electrogram; LV, left ventricular electrogram; HBE, His bundle electrogram; II, scalar lead II; S, stimulus. Time lines 100 mm/sec; paper speed 100 mm/sec. Escape intervals in msec.
the same or higher concentration after 30 minutes of observation if the drug failed to suppress the RVR or AVE. Average single dose per trial was: quinidine 4 mg/kg; diphenylhydantoin 12 mg/kg; lidocaine 3 mg/kg; procainamide 10 mg/kg; propranolol 0.4 mg/kg; potassium canrenoate 12 mg/kg; and verapamil 0.56 mg/kg. There were the following exceptions: 1) KCl was infused at 1/2 mEq/min until suppression of the RVR and AVE resulted; 2) one dog received doses of diphenylhydantoin every 5 minutes to a total cumulative dose of 14.3 mg/kg; 3) apripine was given (recommended clinically) in eight divided doses (0.357 mg/kg/dose) every 2 minutes to a total amount of 2.86 mg/kg. If a successful suppression (see below) of either AVE or RVR occurred, the duration of the suppression was observed, or calcium chloride (100 mg/min) or isoproterenol (0.2 μg/kg/min) was infused in an attempt to reverse the suppression. Further studies to again suppress the RVR or AVE, after its return, were not performed, except for KCl infusions.

Group 3. Verapamil Infusion

The third group of dogs (N = 16) was studied to determine the amount of verapamil that was required to suppress the RVR and AVE and to test whether calcium administration could overcome the suppressive effects of verapamil. In these dogs, verapamil (10-30 μg/kg/min) was infused, following initiation of stable RVR and AVE, until suppression occurred. Seven of these dogs were observed for 30 minutes to document the duration of verapamil-induced suppression; in nine dogs, calcium chloride (100 mg/min) was infused 15 minutes after discontinuing the verapamil to observe its effect on the lengthened ventricular escape intervals.

Definition of “Successful Suppression”

A “successful suppression” of ouabain-induced ventricular escapes (both RVR and AVE) by a particular drug was defined as a 50% or greater prolongation of the ventricular escape interval. The constancy of the ventricular escape intervals in the control dogs established that this degree of prolongation would be extremely significant (P < 0.0005). Measurements of escape intervals were made at 5 minute intervals for a minimum of 15 minutes following drug administration. The longest consistent prolongation of escape intervals between 5 and 15 minutes for a specific basic cycle length and premature interval was calculated as the percent prolongation of the control value for that trial. Once AVE or RVR was suppressed, a dog was not used for further trials to test other antiarrhythmic agents. When isoproterenol or calcium was infused in a dog which had the AVE and RVR successfully suppressed, a “% return” of the escape interval was calculated by the following formula:

\[
\text{% Return} = \frac{\text{suppressed escape interval} - \text{escape interval after calcium or isoproterenol}}{\text{suppressed escape interval} - \text{initial escape interval after ouabain}} \times 100
\]

Results

Group 1: Ouabain Controls

Ouabain (mean total dose, 60 μg/kg, range 45-80 μg/kg) was infused into six dogs until stable AVE and RVR were obtained; the dogs were then observed without administration of any further drugs. After three hours, the ventricular escape intervals had lengthened by a mean of 15% for the RVR, and 26% for the AVE (table 1). Therefore, significant prolongation of these escape intervals following drug administration and within 1-2 hours of the initial development of stable ventricular escapes was felt to be due to the effects of the drug studied and not dissipation of the effects of ouabain.

Group 2: Multiple Drug Group (table 2)

a. Quinidine successfully suppressed the RVR in 3/13 trials and AVE in 3/12 trials. The average cumulative dose at suppression for RVR was 11.3 mg/kg and for AVE, 10 mg/kg.
b. Diphenylhydantoin suppressed both the RVR and the AVE in 2/9 trials (22%). The cumulative dose at suppression was 40 mg/kg over 90 min in one dog and 40 mg/kg over 120 min in the other. The single dog which received doses every 5 minutes to a total amount of 14.3 mg/kg had a 30% prolongation of the AVE and suppression of the RVR.
c. Lidocaine was successful in 1/10 trials (10%) for both RVR and AVE. The success occurred with a cumulative dose of 6 mg/kg over 30 minutes. One dog received a 2 mg/kg bolus followed by a constant infusion of 70 μg/kg/min of lidocaine with no significant suppression of the escapes.
d. Propranolol suppressed both RVR and AVE in 4/12 trials. The average cumulative dose at suppression of the RVR was 20 mg/kg and for the AVE, 21.3 mg/kg.
e. Propranolol suppressed RVR in 1/5 trials, with a first dose of 0.3 mg/kg. It was unsuccessful for AVE.
f. Potassium canrenoate (12 mg/kg) uniformly failed to prolong the RVR or AVE escape intervals in three dogs.
g. Verapamil suppressed the RVR in 5/12 trials and AVE in 3/14 trials. The average cumulative dose given to the 3 dogs with AVE successfully suppressed was 1.3 mg/kg given over 60 min. The RVR suppressed at an average dose of 1.1 mg/kg within 30-60 minutes.
h. KCl was infused at a rate 1/2 mEq/min until successful suppression of AVE and RVR (average = 0.8 mEq/kg over 28-50 min). By experimental design, KCl was successful in each dog (5/5). However, the serum potassium rose from 3.5-4.4 mEq/L (average 3.8 mEq/L) at the time AVE and RVR controls were established, to 6.6-8.5 mEq/L (average 7.2 mEq/L) at the moment of suppression.
i. Aprindine (2.86 mg/kg) successfully suppressed the AVE and RVR in all dogs (14/14, 100%) (fig. 2). Suppression usually occurred between the fourth and sixth doses of the suggested eight divided doses (all eight doses were given.

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>RVR Escape intervals (msec)</th>
<th>AVE Escape intervals (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control 3 hr</td>
<td>Control 3 hr</td>
</tr>
<tr>
<td>1</td>
<td>420</td>
<td>510</td>
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<tr>
<td>2</td>
<td>460</td>
<td>480</td>
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<tr>
<td>3</td>
<td>435</td>
<td>520</td>
</tr>
<tr>
<td>4</td>
<td>410</td>
<td>450</td>
</tr>
<tr>
<td>5</td>
<td>440</td>
<td>510</td>
</tr>
<tr>
<td>6</td>
<td>460</td>
<td>560</td>
</tr>
</tbody>
</table>

Table 1. Prolongation of Ouabain-induced Escape Intervals at 3 Hours: Group 1
Table 2. Multiple Drug Comparison: Group 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>RVR</th>
<th>AVE</th>
<th>No. dogs</th>
<th>No. trials suppressed/total</th>
<th>Average single dose per trial</th>
<th>Average cumulative dose at suppression</th>
<th>Maximal cumulative dose in dogs which failed to suppress</th>
<th>Time to suppression (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>RVR</td>
<td>5</td>
<td>3/13</td>
<td>4 mg/kg</td>
<td>11.3 mg/kg</td>
<td>8 mg/kg</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVE</td>
<td>5</td>
<td>3/12</td>
<td>4 mg/kg</td>
<td>10 mg/kg</td>
<td>8 mg/kg</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Diphenhydantoin</td>
<td>RVR</td>
<td>5</td>
<td>2/9</td>
<td>12 mg/kg</td>
<td>40 mg/kg</td>
<td>20 mg/kg</td>
<td>90-120</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVE</td>
<td>5</td>
<td>2/9</td>
<td>12 mg/kg</td>
<td>40 mg/kg</td>
<td>20 mg/kg</td>
<td>90-120</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>RVR</td>
<td>7</td>
<td>1/10</td>
<td>3 mg/kg</td>
<td>6 mg/kg</td>
<td>3.8 mg/kg</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVE</td>
<td>7</td>
<td>1/10</td>
<td>3 mg/kg</td>
<td>6 mg/kg</td>
<td>3.3 mg/kg</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>RVR</td>
<td>5</td>
<td>4/12</td>
<td>10 mg/kg</td>
<td>21.3 mg/kg</td>
<td>30 mg/kg</td>
<td>30-60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVE</td>
<td>5</td>
<td>4/12</td>
<td>10 mg/kg</td>
<td>21.3 mg/kg</td>
<td>30 mg/kg</td>
<td>30-60</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>RVR</td>
<td>3</td>
<td>1/5</td>
<td>0.4 mg/kg</td>
<td>0.3 mg/kg</td>
<td>0.9 mg/kg</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVE</td>
<td>3</td>
<td>0/5</td>
<td>0.4 mg/kg</td>
<td>—</td>
<td>0.8 mg/kg</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Potassium canrenonate</td>
<td>RVR</td>
<td>3</td>
<td>0/3</td>
<td>12 mg/kg</td>
<td>—</td>
<td>12 mg/kg</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVE</td>
<td>3</td>
<td>0/3</td>
<td>12 mg/kg</td>
<td>—</td>
<td>12 mg/kg</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>RVR</td>
<td>6</td>
<td>5/12</td>
<td>0.56 mg/kg</td>
<td>1.1 mg/kg</td>
<td>1.3 mg/kg</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVE</td>
<td>6</td>
<td>3/14</td>
<td>0.56 mg/kg</td>
<td>1.3 mg/kg</td>
<td>1.3 mg/kg</td>
<td>30-60</td>
<td></td>
</tr>
<tr>
<td>KCl</td>
<td>RVR</td>
<td>5</td>
<td>5/5*</td>
<td>13.6 mEq*</td>
<td>0.8 mEq/kg</td>
<td>—</td>
<td>16-50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVE</td>
<td>5</td>
<td>5/5*</td>
<td>13.6 mEq*</td>
<td>0.8 mEq/kg</td>
<td>—</td>
<td>16-50</td>
<td></td>
</tr>
<tr>
<td>Aprindine</td>
<td>RVR</td>
<td>14</td>
<td>14/14</td>
<td>2.86 mg/kg†</td>
<td>2.86 mg/kg†</td>
<td>—</td>
<td>8-12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVE</td>
<td>14</td>
<td>14/14</td>
<td>2.86 mg/kg†</td>
<td>2.86 mg/kg†</td>
<td>—</td>
<td>8-12</td>
<td></td>
</tr>
</tbody>
</table>

*15 mEq/min until suppression.
†In eight divided doses.

However, and lasted at least 30 minutes in 5/6 dogs observed (table 3). One dog had return of AVE and RVR after 23 minutes. Calcium chloride administration (100 mg/min infused for 3-5 minutes) 15 minutes following the last dose of aprindine, produced an 87% return of the escape interval for AVE and 92% return for RVR (mean value) in seven of eight dogs (P < 0.0012) (table 4). In the eighth dog, calcium chloride failed to restore the accelerated escapes at 15 minutes. However, thirty minutes following the aprindine dose, while AVE and RVR were still successfully suppressed, a second infusion of calcium chloride caused a 95% and 97% return of AVE and RVR, respectively. Isoproterenol infused at 0.2 μg/kg/min for 4 minutes resulted in an 80% return of the escape interval for RVR in two dogs and 89% return for AVE in three dogs (mean value).

Figure 2. Suppression of ouabain-induced RVR and AVE with aprindine and return of RVR and AVE following calcium administration. Conventions as in figure 1. After aprindine administration (panels A and B), a supraventricular escape beat initiated by discharge in or near the bundle of His followed cessation of pacing (H-V interval prolonged to 40 msec following aprindine). Thus, an RVR or AVE escape interval would exceed the supraventricular escape interval. After calcium administration (panels C and D), a ventricular escape beat followed termination of pacing (H-V interval shortened to 5 msec in panel C and 20 msec in panel D, indicating ventricular initiation of a probable fusion beat). Interrupted line indicates earliest recorded onset of ventricular activation.
TABLE 3. Suppression of RVR and AVE after Aprindine

<table>
<thead>
<tr>
<th>RVR</th>
<th>30 min after aprindine</th>
<th>AVE</th>
<th>30 min after aprindine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>480</td>
<td>950</td>
<td>540</td>
</tr>
<tr>
<td></td>
<td>480</td>
<td>&gt;1630</td>
<td>475</td>
</tr>
<tr>
<td></td>
<td>480</td>
<td>790</td>
<td>550</td>
</tr>
<tr>
<td></td>
<td>470</td>
<td>790</td>
<td>510</td>
</tr>
<tr>
<td></td>
<td>490</td>
<td>&gt;1390</td>
<td>530</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>450*</td>
<td>440</td>
</tr>
</tbody>
</table>

*Significantly suppressed until 23 min, but not at 30 min.

Group 3: Verapamil Infusions

After initiating stable ventricular escapes with ouabain, verapamil (10–30 μg/kg/min) was continuously infused intravenously in 16 dogs (range of total dose 1.1–3.75 mg/kg, mean 2.93 mg/kg) until suppression of RVR and AVE. The duration of infusions was well below three hours (range 35–125 minutes, mean 81.8 minutes). By experimental design, in all cases the verapamil infusion was continued until it suppressed the AVE and RVR. Seven of the 16 animals were observed for 30 minutes to document the duration of suppression by verapamil. In one dog the RVR returned after 23 minutes and in another dog the AVE returned at 25 minutes. All other dogs continued to demonstrate successful suppression at 30 minutes after infusion (table 5).

In the remaining nine animals, 15 minutes after completion of the verapamil infusion, while the RVR and AVE were still suppressed, calcium chloride (100 mg/min) was infused intravenously. Within 8–15 minutes (mean 9.7 min) of calcium infusion, AVE had returned to 93% (mean) of control and RVR to 94% (mean) of control in the nine dogs ($P < 0.0004$) (table 6).

Discussion

We chose to study the efficacy of various antiarrhythmic agents in suppressing RVR and AVE for two reasons. First, it has been suggested that the slow current may represent the ionic basis for these rhythms and we wished to compare the effectiveness of verapamil, a slow-current blocker, with other antiarrhythmic agents. Second, we felt that the consistent ventricular escape intervals established a very stable model to study the effects of various drugs on digitalis-induced arrhythmias. The phenomenon of ouabain-induced AVE and RVR occurs at an early stage of digitalis toxicity, before overt ventricular extrasystoles or ventricular tachycardia becomes manifest and therefore analysis of the complex, chaotic ventricular arrhythmias accompanying larger doses of ouabain is avoided. Lown and Cannon induced the RVR after giving 50–60% of the dose needed to precipitate ventricular fibrillation in dogs and showed, as did we, that the escape intervals are very stable, for at least three hours. We have been able to induce the RVR and AVE after as little as 25% of the lethal dose of ouabain.

Results from this study demonstrate the remarkable resistance of the AVE and RVR to suppression by the common antiarrhythmic agents, even with doses clearly in the supraclinical or toxic range. A greater incidence of suppression might have been achieved in dogs which failed to suppress had we used cumulative doses of quinidine, diphenylhydantoin and lidocaine equal to the doses used in dogs which did suppress. Regardless, the doses for both groups were still quite excessive. Microelectrode studies in Purkinje fibers exposed to ouabain or acetylcholinethad* suggest that the cellular basis for these rhythms is the transient depolarization (low amplitude potential), which could be suppressed in vitro by manganese and verapamil. However, our in vivo findings show verapamil was only slightly more effective than the other drugs tested, and did not suppress the RVR and AVE in a large number of dogs except when given in high doses by continuous infusion.

These ventricular escape rhythms are clearly unusual for at least two reasons: first, the escapes represent an early stage of digitalis intoxication, yet they resist suppression with large doses of agents that effectively suppress the spontaneous ventricular ectopy manifest with even greater degrees of digitalis excess. Second, the RVR and AVE exhibit overdrive acceleration. This phenomenon of overdrive acceleration could be used to overcome drug-induced suppression of the RVR and AVE by pacing the heart at a faster basic cycle length.

It is possible that these unusual features may be manifestations caused by the slow current. In this regard, we have recently demonstrated that ventricular arrhythmias produced with barium and strontium, cations which are able to replace calcium in vitro as slow-current carrying ions, also exhibit overdrive acceleration. This observation plus the almost complete return of RVR and AVE to control values following calcium or isoproterenol administration provide indirect data suggesting a slow-channel pathogenesis.

TABLE 4. Effect of CaCl₂ Infusion on Aprindine Suppression of RVR and AVE

<table>
<thead>
<tr>
<th>Control</th>
<th>15 min after aprindine</th>
<th>RVR</th>
<th>Percent return</th>
<th>AVE</th>
<th>Percent return</th>
</tr>
</thead>
<tbody>
<tr>
<td>430</td>
<td>750</td>
<td>450</td>
<td>93</td>
<td>Control</td>
<td>405</td>
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<td>480</td>
<td>&gt;1665</td>
<td>523</td>
<td>96</td>
<td>600</td>
<td>&gt;1230</td>
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<td>480</td>
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<td>&gt;760</td>
<td>550</td>
<td>83</td>
<td>430</td>
<td>&gt;760</td>
</tr>
<tr>
<td>400</td>
<td>&gt;1030</td>
<td>480</td>
<td>87</td>
<td>440</td>
<td>&gt;940</td>
</tr>
<tr>
<td>490</td>
<td>&gt;880</td>
<td>530</td>
<td>90</td>
<td>530</td>
<td>&gt;980</td>
</tr>
<tr>
<td>430</td>
<td>&gt;2200</td>
<td>480*</td>
<td>97</td>
<td>480</td>
<td>&gt;2200</td>
</tr>
</tbody>
</table>

*supranormal capture.
*P < 0.0012 as compared to group of animals in table 3.
**Required second 5 min infusion of CaCl₂.
The reason for the ineffectiveness of verapamil in clinically-used doses (0.14 mg/kg), and the singular success of aprindine after only one-half to two-thirds the usual clinical dose (on a mg/kg basis) to suppress the RVR and AVE, particularly if these rhythms are due to the operation of the slow channel, is unknown. Some data indicate that aprindine also blocks the slow channel,14 while other studies suggest it is solely a fast-channel blocker.15 Perhaps aprindine is capable of blocking both the fast and slow channels, an action which may be required to suppress the RVR and AVE. Although this may be true, combinations of verapamil and lidocaine (to inhibit the rapid current) were ineffective in several trials in the present study.

It has been suggested that the sinus and A-V nodes are dependent on slow-channel mechanisms; these cells appear quite sensitive to the effects of verapamil and other slow-channel blockers.16-20 When verapamil was given by continuous intravenous infusion in the present study, the amount required to suppress the RVR and AVE was approximately ten times the amount necessary to slow spontaneous sinus node discharge rate or prolong A-V nodal conduction time and refractory period in the intact dog (Zipes, unpublished observations). Thus if the sinus and A-V nodes represent the “gold standard” against which to compare the response of a slow current to the blocking effects of verapamil, the RVR and AVE were an order of magnitude more resistant. Such comparisons are not entirely valid because, even if the sinus node and the ouabain-induced escapes are both dependent on slow current properties, fundamental differences exist between them.28 For example, the sinus node exhibits overdrive suppression26 while the RVR and AVE exhibit overdrive acceleration. Also, calcium administration reverses the suppressive effect of verapamil on the RVR and AVE, but does not reverse the suppressive effect of slow-channel blockers on the sinus and A-V nodes in the whole dog.29 It is possible that these digitalis-induced arrhythmias and sinus and A-V nodal cells are not both slow-current dependent; or perhaps more than one calcium-dependent slow channel exists, with different electrophysiologic properties.

Further speculation as to the reason for the total success of aprindine would be premature until additional studies have been accomplished both in vivo and in vitro to elucidate better its electrophysiologic properties and mechanism of action. Preliminary data27 indicate that aprindine slows spontaneous sinus node automaticity and prolongs conduction time and refractory period in atrial and ventricular muscle, and in the A-V node. Depression of ventricular conduction may cause ventricular fibrillation in dogs with acute myocardial infarction at rapid pacing rates.28

In the present study, following administration of the eighth dose of aprindine, transient marked QRS widening often was noted. Intraventricular conduction time (IVCT), measured from the right to left ventricular epicardial recording electrodes during right ventricular pacing, was prolonged by 81% in 10 dogs immediately following aprindine (range 33-125%), and by 27% in 5 dogs (range 11-40%) thirty minutes following aprindine administration, although in each case the ventricular escapes were still significantly suppressed. However, successful suppression of RVR and AVE usually occurred between the fourth and sixth doses, which preceded the marked QRS prolongation.

Potassium chloride has long been known to be of value in treating arrhythmias due to digitalis intoxication.29 Because of problems in deciding what a “usual clinical dose” would be, KCl was infused at ½ mEq/min until suppression of the ventricular escapes occurred. At this time, serum potassium was clearly in the toxic range. The suppressive effects of potassium probably cannot be considered very discriminatory in terms of mechanism of suppression at such high levels and may simply point out the difficulty in suppressing the RVR and AVE. However, current concepts regarding the kinetics of the slow current18 suggest that it should be more resistant to the depolarizing effects of hyperkalemia. When equilibration of the serum potassium was allowed to take place over approximately 15-30

---

**Table 5. Suppression of RVR and AVE Following Verapamil Infusions: Group 3**

<table>
<thead>
<tr>
<th>RVR</th>
<th>Control 30 min after infusion</th>
<th>AVE 30 min after infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>380</td>
<td>1060</td>
<td>370</td>
</tr>
<tr>
<td>280</td>
<td>&gt; 920</td>
<td>&gt; 840</td>
</tr>
<tr>
<td>440</td>
<td>470*</td>
<td>370</td>
</tr>
<tr>
<td>540</td>
<td>&gt; 1900</td>
<td>&gt; 770**</td>
</tr>
<tr>
<td>480</td>
<td>&gt; 1140</td>
<td>&gt; 1310</td>
</tr>
<tr>
<td>420</td>
<td>&gt; 1910</td>
<td>&gt; 2140</td>
</tr>
<tr>
<td>370</td>
<td>990</td>
<td>610</td>
</tr>
</tbody>
</table>

> = supraventricular capture.
* = suppressed (> 1010) until 23 min.
** = suppressed (> 1900) until 23 min.

---

**Table 6. Effect of CaCl₂ Infusion on Verapamil Suppression of RVR and AVE**

<table>
<thead>
<tr>
<th>Control</th>
<th>Verapamil</th>
<th>CaCl₂</th>
<th>Percent return</th>
</tr>
</thead>
<tbody>
<tr>
<td>440</td>
<td>1530</td>
<td>560</td>
<td>89</td>
</tr>
<tr>
<td>540</td>
<td>&gt; 1290</td>
<td>600</td>
<td>100</td>
</tr>
<tr>
<td>490</td>
<td>&gt; 2100</td>
<td>600</td>
<td>93</td>
</tr>
<tr>
<td>490</td>
<td>&gt; 1350</td>
<td>600</td>
<td>93</td>
</tr>
<tr>
<td>490</td>
<td>&gt; 2130</td>
<td>600</td>
<td>93</td>
</tr>
<tr>
<td>490</td>
<td>&gt; 1910</td>
<td>600</td>
<td>93</td>
</tr>
<tr>
<td>490</td>
<td>&gt; 1210</td>
<td>570</td>
<td>99</td>
</tr>
<tr>
<td>370</td>
<td>&gt; 1060</td>
<td>470</td>
<td>100</td>
</tr>
</tbody>
</table>

> = supraventricular capture.

*P < 0.0004 as compared to group of dogs presented in table 5.
minutes, the AVE and RVR returned, at which time
the mean serum potassium was 5.8 mEq/L (range 4.6-8.9 mEq/L).

Potassium canrenoate was tried because of reports indicating
that it effectively suppressed digitalis-induced arrhythmias.30 It did not affect the RVR or AVE.

The mechanism responsible for the RVR and AVE (re-
entry or automaticity) cannot be deduced from the present
study. The similarity of the ectopic activity with that noted
in isolated Purkinje6,7 or atrial44 preparations suggests that
automaticity may be the cause. It is likely that both
the RVR and AVE are due to the same mechanism, differing
only by effects produced by a shorter last cycle. Why RVR
and AVE did not respond to all drugs in an exactly parallel
fashion or why the RVR, which also had the effects of the
shorter final cycle, was not more resistant is not entirely
clear. Naturally, it is difficult to rule out re-entry following
premature stimulation, and because of this, we elected to
study also the AVE which would seem more likely to be
caused by automatic discharge. Transient depolarizations,
presumably due to automaticity, exhibit fixed coupling,
and therefore the presence of fixed coupling, even following
premature stimulation, does not a priori mean re-entry.8

The relation, if any, of these observations to clinically oc-
curring ventricular arrhythmias caused by digitalis is
presently unknown. Perhaps these rhythms are ordinarily
suppressed by the dominant sinus rhythm, unless a sudden
slowing of the cardiac rhythm occurs. This study does
suggest, however, that aprindine has a uniquely different
antiarrhythmic action since it was the only antiarrhythmic
agent tested that successfully suppressed the ouabain-
induced AVE and RVR in clinically used doses. Aprindine
holds potential promise as a new antiarrhythmic agent.9
To date, we have found it useful in several patients with
ventricular tachycardia and ventricular fibrillation which were
resistant to lidocaine, quinidine and procainamide.33

In summary, we conclude that: 1) although the RVR
and AVE represent an early stage of digitalis intoxication, they
resist suppression with large doses of agents that effectively
suppress the spontaneous ventricular ectopy manifest with
even greater degrees of digitalis excess; 2) aprindine was the
most successful agent in clinically-used doses capable of sup-
pressing the RVR and AVE; 3) the ionic pathogenesis of the
RVR and AVE is presently uncertain, although some data
suggest the slow current may play a role; the return after
suppression of the RVR and AVE with calcium infusion is
consistent with a slow current concept, but the resistance to
suppression with verapamil is not; 4) aprindine holds
promise as a new antiarrhythmic agent.

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