Flunarizine Allows Differentiation Between Mechanisms of Arrhythmias in the Intact Heart

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Jet D.M. Leunissen, and Hein J.J. Wellens, MD

The calcium antagonist flunarizine suppresses pathologic accumulation of calcium intracellularly without affecting the fast sodium or the slow calcium channel. To establish its value in differentiating between mechanisms of arrhythmias in the canine heart, the effect of flunarizine was investigated on ventricular tachycardia (VT) induced by ouabain intoxication or occurring 16–24 hours after occlusion of the left anterior descending coronary artery. Four groups of dogs were studied. Group 1 consisted of 13 animals with VT induced by ouabain intoxication (triggered-activity group). Group 2 included nine dogs in whom VT developed 16–24 hours after occlusion of the left anterior descending coronary artery (abnormal automaticity group). Group 3 included six dogs with normally conducted sinus beats, whereas group 4 consisted of six animals having a ventricular escape rhythm. With the exception of group 3, all dogs had surgically induced complete atrioventricular block. All animals were studied while conscious and without premedication. In groups 1 and 2, 2–3 mg/kg flunarizine was given intravenously after VT had persisted for at least 20 minutes. In groups 3 and 4, 2 mg/kg flunarizine was given after the rhythm was registered for 20 minutes. The cycle lengths of the different rhythms were compared before and after flunarizine. In group 1, flunarizine increased the cycle length of the VT from 300±30 to 410±50 msec ($p$≤0.001). Termination of VT was seen in 11 out of 13 animals. In group 2, flunarizine resulted in a nonsignificant shortening of the RR interval from 450±60 to 440±60 msec. Persistent termination was observed in only one of nine dogs. A significant acceleration in rate was seen in groups 3 and 4. In conclusion, flunarizine slows and terminates ventricular arrhythmias resulting from triggered activity but accelerates rhythms based on normal and abnormal automaticity. These findings suggest that flunarizine can be used to differentiate between mechanisms of arrhythmias. (Circulation 1990;81:343–349)

Two decades ago, clinically occurring cardiac arrhythmias were thought to result from either automaticity, reentry, or a combination of these mechanisms. In vitro, other mechanisms have been described, like triggered activity induced by early and delayed afterdepolarizations (DADs) and abnormal automaticity. While reentry has been proven to be responsible for a number of human supraventricular and ventricular arrhythmias, the clinical relevance of the other mechanisms is not known. Because the arrhythmogenic mechanisms have been demonstrated to occur under different pathophysiologic circumstances (for review see Reference 5), it seems conceivable that clinical arrhythmias may be caused by mechanisms other than reentry.

To differentiate between arrhythmogenic mechanisms, several methods have been studied, including programmed electrical stimulation, monophasic action potentials, and drugs specifically suppressing one mechanism. The latter approach is especially intriguing because drugs have advantages for identifying mechanisms of arrhythmias on theoretical and practical grounds. Drugs can easily be administered either intravenously or orally, can terminate the tachycardia, and may give information about the pathophysiology of the arrhythmia. Until now only a few drugs having such a specific action have been developed. An example is doxorubicin, which specifically suppresses ouabain-induced triggered activity. Due to its toxicity, doxorubicin cannot be used clinically for this purpose. In general, different drugs must be used sequentially for determining the mechanism involved. A good example is the...
combination of lidocaine and ethmozin for differentiating between abnormal automaticity and triggered activity.10–12

Our interest was directed to flunarizine because of its interesting electropharmacologic profile. Flunarizine, a calcium antagonist, is clinically used for the prophylaxis of migraine and epilepsy,13 and it does not possess unfavorable side effects. In myocardial tissue, flunarizine does not inhibit the sodium or the calcium channel.14 However, this drug has been shown to markedly delay the onset of ouabain-induced ventricular tachycardia (VT) in anesthetized guinea pigs.15 These arrhythmias are most likely based on triggered activity resulting from DADs9,16–19 occurring in the presence of intracellular calcium overload.20 The above observations suggest that flunarizine does not affect rhythms based on normal automaticity (sinus node or ventricular escape rhythms) or tachycardias due to abnormal automaticity. The latter condition originates from a reduced diastolic membrane potential and, depending on the level of depolarization, is partly dependent on the sodium and/or calcium channel.21

It was the purpose of this study to establish the value of flunarizine in differentiating between two mechanisms of ventricular arrhythmias in the canine heart: 1) ouabain-induced VTs that are thought to be based on DADs and 2) arrhythmias occurring spontaneously 16–24 hours after occlusion of the left anterior descending coronary artery (LAD). The latter tachycardias are most likely caused by abnormal automaticity,12,22,23 although triggered activity resulting from DADs has also been described as the underlying mechanism.24 In addition, the effect of flunarizine on two types of normal automaticity was investigated: 1) sinus rhythm and 2) ventricular escape rhythm in complete atioventricular block. It was hypothesized that flunarizine would affect ouabain-induced tachycardias but not 16–24-hour infarct arrhythmias or the two forms of normal automaticity. When appropriate, flunarizine could become a clinical tool to differentiate between arrhythmogenic mechanisms.

Methods

Preparation of Study Dogs

The experiments were performed in mongrel dogs of either sex weighing 20–35 kg. All animals were studied in the conscious state and without premedication. With the exception of the dogs in normally conducted sinus rhythm, all animals had surgically induced complete atioventricular block. Through a right thoracotomy, block was produced by injection of 37% formalin.25 During the same procedure, one electrode was sutured on the basal part of the right ventricle and another one on the apex of the left ventricle. The electrodes were exteriorized through the skin of the dorsal surface of the neck. Postoperative care followed the guidelines of the American Physiological Society.

The animals were not studied during the 2 weeks after the operation because spontaneous episodes of VT are known to occur after creation of atioventricular block.26,27 For the nine dogs undergoing a second thoracotomy, which consisted of the two-stage Harris protocol,28 the time period between operations was at least 4 weeks. We slightly adjusted this procedure by ligating the second diagonal of the LAD in two stages. This was done to reduce infarct size in dogs that had already undergone a first thoracotomy to induce atioventricular block. During the operation lidocaine was administered to prevent lethal arrhythmias. This drug was given as a 3 mg/kg bolus injection followed by a continuous infusion (100 μg/kg/min) throughout the procedure. Lidocaine administration was stopped 1 hour after the first occlusion.

Experiments

Six external electrocardiographic and one epicardial leads were simultaneously registered. Pacing in the ouabain-treated animals and in the dogs with LAD occlusion was performed by use of a programmable stimulator with a synchronizing circuit. Unipolar stimuli were given with a stimulus strength of twice the diastolic threshold. A computerized QRS complex–detecting system was used, and values of RR intervals were continuously displayed on a monitor screen. This display allowed instantaneous evaluation of the heart rate in the four protocols.29

Overdrive pacing during the tachycardia was performed to confirm the underlying arrhythmogenic mechanism. On reducing the interstimulus interval, we expected shortening of the first postpacing interval for the triggered arrhythmias,19,30 but no change of this interval was expected for the tachycardias resulting from abnormal automaticity.12,21 In 13 dogs, VT was induced by ventricular pacing after ouabain administration. First, ouabain was given (mean, 48±6 μg/kg; range, 40–55 μg/kg) over a 2-minute period. The amount of this dosage is inversely related to the body weight (unpublished observation). Eight minutes later, corresponding infusions of 0.072–0.099 μg/kg/min ouabain were begun.31 These infusions continued throughout the whole experiment. The pacing protocol began 15 minutes after the start of the administration of ouabain and consisted of trains of 10 and 50 stimuli with interstimulus intervals of 800, 600, 400, and 200 msec. Each set of eight stimulation trains was completed in 15 minutes and randomly repeated until sustained tachycardia occurred.

After its initiation, the arrhythmia had to persist for 10–15 minutes before overdrive pacing was started. This protocol consisted of stimulation for 15, 60, and 120 seconds with an interstimulus interval between 300 and 200 msec. Thereafter, flunarizine was administered according to the dose regimen below. In cases in which flunarizine terminated ouabain-induced VT, the pacing train previously able to initiate the arrhythmia was repeated until sustained tachycardia occurred again.

The spontaneous VTs occurring 16–24 hours after myocardial infarction were registered for 20 minutes.
Then overdrive pacing during 15, 60, and 120 seconds was performed with interstimulus intervals of 400, 300, and 200 msec. After this stimulation protocol, flunarizine was given.

In dogs studied during sinus rhythm and idioventricular rhythm, the ECGs were recorded for 20 minutes before flunarizine was given.

Flunarizine (dissolved in cyclodextrin) was administered intravenously (2 mg/kg) over a 2-minute period. In four ouabain-treated animals and in one dog included in the adjusted Harris protocol, this dosage was increased by 1 mg/kg given in 1 minute for a total of 3 mg/kg flunarizine.

Measurements

Not only was flunarizine studied to determine its effectiveness in termination of arrhythmia, but its effect on rhythmic rate before and after administration was also investigated. For this purpose the cycle length was determined every minute as the average of 10 consecutive intervals beginning at least 5 minutes before flunarizine administration and ending 25 minutes thereafter. If tachycardia was terminated, the mean of the last 10 intervals before termination was used. In cases in which the arrhythmia did not terminate, the longest or shortest mean RR interval was used for comparison.

Statistical Analysis

Student’s paired t test was used to compare the cycle lengths before and after flunarizine administration. Analysis of variance was applied to determine significance of the first postpacing interval in relation to the different interstimulus intervals used. All data are presented as mean±SD.

Results

Ouabain-Induced Arrhythmias

In the 13 animals investigated, ouabain intoxication combined with pacing induced sustained VTs 78±50 minutes after the start of ouabain administration. Overdrive stimulation of these sustained VTs resulted in a significant shortening of the first postpacing interval (p<0.001) on decreasing the interstimulus interval from 300 to 200 msec (Table 1).

Flunarizine increased the cycle length of the tachycardia from 300±30 to 410±50 msec (p<0.001) in all dogs (Table 2). Termination of the VT was related to the rate of the arrhythmia. A VT having an RR interval above 305 msec (mean, 330±20 msec; seven animals) was always terminated by 2 mg/kg flunarizine (Figure 1). An additional dosage of 1 mg/kg flunarizine also resulted in termination of the faster tachycardias (mean, 280±15 msec) in the four experiments in which this was tested.

Flunarizine terminated the arrhythmia after 5.5±4.1 minutes. After termination, the tachycardias were not reinducible by pacing for 27±18 minutes.

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**Table 1. The Effect of Overdrive Pacing on the First Postpacing Interval**

<table>
<thead>
<tr>
<th></th>
<th>Vs-Vs (msec)</th>
<th>Vs-V (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouabain-induced VT</td>
<td>300</td>
<td>380±25</td>
</tr>
<tr>
<td></td>
<td>275</td>
<td>395±25</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>360±40</td>
</tr>
<tr>
<td></td>
<td>225</td>
<td>340±20</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>310±20</td>
</tr>
<tr>
<td>Infarct-induced VT</td>
<td>400</td>
<td>580±40</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>560±120</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>590±270†</td>
</tr>
</tbody>
</table>

Values are mean±SD.

Vs-Vs, interstimulus interval; Vs-V, first postpacing interval; ouabain-induced VT, ouabain-induced ventricular tachycardia; infarct-induced VT, spontaneous tachycardia occurring 16–24 hours after left anterior descending coronary artery occlusion.

*Significant shortening after decrease of Vs-Vs from 300 to 200 msec (p<0.001).
†No significant shortening after decrease of Vs-Vs from 400 to 200 msec.

Arrhythmias Occurring 16–24 Hours After Myocardial Infarction

In the nine animals studied, spontaneous VT was observed approximately 1 day after occlusion of the second diagonal of the LAD. Decreasing the interstimulus interval did not result in any change in the

**Table 2. The Effect of Flunarizine on the Cycle Length of the Tachycardia**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Ouabain-induced VT</th>
<th>Infarct-induced VT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VT&lt;sub&gt;pre&lt;/sub&gt; (msec)</td>
<td>VT&lt;sub&gt;F&lt;/sub&gt; (msec)</td>
</tr>
<tr>
<td>1</td>
<td>335</td>
<td>370†</td>
</tr>
<tr>
<td>2</td>
<td>305</td>
<td>365</td>
</tr>
<tr>
<td>3</td>
<td>285</td>
<td>500</td>
</tr>
<tr>
<td>4</td>
<td>305</td>
<td>335*</td>
</tr>
<tr>
<td>5</td>
<td>305</td>
<td>390*</td>
</tr>
<tr>
<td>6</td>
<td>320</td>
<td>435*</td>
</tr>
<tr>
<td>7</td>
<td>315</td>
<td>390*</td>
</tr>
<tr>
<td>8</td>
<td>290</td>
<td>430†</td>
</tr>
<tr>
<td>9</td>
<td>345</td>
<td>500*</td>
</tr>
<tr>
<td>10</td>
<td>265</td>
<td>380*†</td>
</tr>
<tr>
<td>11</td>
<td>270</td>
<td>420*†</td>
</tr>
<tr>
<td>12</td>
<td>360</td>
<td>410*</td>
</tr>
<tr>
<td>13</td>
<td>260</td>
<td>350†</td>
</tr>
</tbody>
</table>

Mean: 300 410 450 440

SD: 30 50 60

p<0.001

Ouabain-induced VT, ouabain-induced ventricular tachycardia (VT); infarct-induced VT, spontaneous VT occurring 16–24 hours after left anterior descending coronary artery occlusion; VT<sub>pre</sub>, cycle length of VT before flunarizine; VT<sub>F</sub>, cycle length of VT after 2 mg/kg flunarizine; NS, not significant.

†Persistent termination.
‡Administration of 1 additional mg/kg flunarizine for a total of 3 mg/kg.
first postpacing interval (Table 1). Pacing of the longest duration (120 seconds) and the fastest inter-stimulus interval (200 msec) frequently resulted in termination of the arrhythmia. However, reinitiation always occurred after a few spontaneous beats.

Flunarizine (2 mg/kg) decreased the cycle length of the tachycardia from 450±60 to 440±60 msec, which is not statistically different (Table 2). An example is presented in Figure 2. Acceleration reached its peak after 2.3±1.2 minutes. Then a slow return to the basal rate was observed, which was reached after 7.0±6.4 minutes. Persistent termination was only observed once.

**Rhythms Based on Normal Automaticity**

Flunarizine decreased the cycle length significantly ($p \leq 0.01$) in all six animals in sinus rhythm (from 550±120 to 370±50 msec) and in all six dogs having an idioventricular escape rhythm (from 1,400±410 to 1,070±250 msec). In both groups, the shortest RR interval was reached after 3.1±1.2 minutes and was followed by a slow return to the
basal rate taking 13.5±3.2 minutes. No suppression of either rhythm was observed.

Discussion
In this study, we have demonstrated that the effect of the calcium antagonist flunarizine is different in ouabain-induced VTs as compared with ventricular arrhythmias occurring 16–24 hours after myocardial infarction. Administration of flunarizine resulted in an increase in cycle length followed by termination of the ouabain-induced VTs. In contrast, an acceleration in rate was frequently observed in the ventricular arrhythmias occurring 16–24 hours after LAD occlusion. Also, flunarizine increased the rate of rhythms resulting from normal automaticity: sinus node activity and an idioventricular escape rhythm. These results are consistent with our expectations, which were based on the following considerations.

Triggered Activity Resulting From Delayed Afterdepolarizations
Flunarizine has been shown to protect the myocardial cell against calcium overload that was induced by exposure to a depolarizing concentration of potas-
sium\textsuperscript{14} or veratrine administration\textsuperscript{32} in cardiac myocytes. Also, flunarizine markedly delayed the onset of ouabain-induced arrhythmias in anesthetized guinea pigs.\textsuperscript{15} In these studies, flunarizine was far more effective than the selective calcium blockers, like verapamil and nifedipine. Previous studies\textsuperscript{9,16–19,33} have shown that ouabain-induced arrhythmias are most likely based on triggered activity resulting from DADS. They occur in the setting of an increased intracellular calcium concentration.\textsuperscript{20} When the sarcoplasmic reticulum becomes overloaded with calcium, it releases this electrolyte in an oscillatory fashion.\textsuperscript{34} This increases monovalent cation conductance and induces a transient inward current, which is thought to be responsible for DADS.

The results of programmed electrical stimulation were in agreement with previous studies,\textsuperscript{12,16–19,33} which supported the hypothesis that DADS are responsible for the arrhythmias. Overdrive pacing resulted in a specific behavior (Table 1) of the first postpacing interval that was found to have a concordant relation to the interstimulus interval.\textsuperscript{12,18}

At present it is not clear how flunarizine effects triggered activity resulting from DADS. Hypothetically, flunarizine may act in a number of ways: 1) by preventing or reducing the calcium overload, 2) through inhibition of the oscillatory release from the sarcoplasmic reticulum, and/or 3) by blocking the transient inward current.

\textbf{Rhythms Based on Normal and Abnormal Automaticity}

As shown by Borgers et al,\textsuperscript{14} in myocardial cells flunarizine has no effect on 1) phases 0 and 2 of the action potential, 2) the inotropic state, even in high concentrations, or 3) the enhanced contractility elicited by increasing concentrations of calcium in electrically stimulated cells. However, Tytgat et al\textsuperscript{35} recently demonstrated that flunarizine in high doses blocks both types of calcium channels: T-type and L-type calcium channels. This is in contrast to verapamil or nifedipine, which only affect the L-type calcium channel.\textsuperscript{36} The described effect of flunarizine on the T-type calcium channel is of interest because it was suggested that this channel is involved in sinus node automaticity\textsuperscript{37} and may contribute to abnormal automaticity.\textsuperscript{36}

In this study, we did not find a suppressing effect of flunarizine on normal automaticity. Instead, acceleration was seen. Also, our observation that the P waves persisted and the idioventricular rhythm rapidly returned after termination of the ouabain-induced arrhythmias supports these findings (Figure 1).

Arrhythmias occurring 16–24 hours after acute myocardial infarction are most likely based on abnormal automaticity.\textsuperscript{12,22–24} They arise from a (partly) depolarized diastolic membrane potential.\textsuperscript{21} Depending on the level of depolarization, the sodium channel, the calcium channel, or both are activated during these arrhythmias. The greater influence of the sodium channel, the more pronounced the suppression of these rhythms after stimulation. The sodium potassium pump, which is likely to be responsible for overdrive suppression,\textsuperscript{21} is sodium dependent and will not be activated when only calcium fluxes are involved. Our finding that no overdrive suppression could be induced in the infarct-induced arrhythmias (Table 1) indicates that these arrhythmias arise from an intermediate or low resting membrane potential. Long stimulation trains (120 seconds) and short interstimulus intervals (200 msec) resulted in termination of these arrhythmias; these findings suggest activation by the sodium channel and point to the intermediate resting potential as the mechanism for these tachycardias. The fact that flunarizine does not terminate these tachycardias makes it an effective diagnostic tool that is capable of differentiating between arrhythmogenic mechanisms.

Flunarizine is specific for arrhythmias occurring in the setting of calcium overload, like triggered activity induced by DADS. In contrast, verapamil and nifedipine suppress both arrhythmogenic mechanisms.\textsuperscript{11,15,27,38,39}

Acceleration of the rhythms based on normal and abnormal automaticity seen after flunarizine administration is probably caused by a sympathetic reflex as a result of the vasodilatation of the peripheral vessels often seen in calcium blockers with an action on vascular smooth muscle. In the infarct-induced arrhythmias, this increase in rate was less pronounced. This may be due to the already high sympathetic activity after the recent myocardial infarction.

\textbf{Clinical Implications}

The ability to differentiate between arrhythmogenic mechanisms is important because it improves our insight into the pathophysiology underlying the arrhythmia. This understanding may open new ways for a more rational treatment. Although we have a wide variety of antiarrhythmic drugs, their use in the clinical setting is frequently empirical. As with antibiotic therapy, there is a clear advantage in selecting specific antiarrhythmic drugs for specific mechanisms. To develop these drugs, better understanding of the pathophysiologic mechanisms of the different arrhythmias is required.

We think that flunarizine is an example of a clinically available drug that is able to differentiate between arrhythmogenic mechanisms. General application of this drug in human arrhythmias has to be awaited to assess its proper value in clinical cardiology.

\textbf{Acknowledgments}

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\textbf{References}


Key Words • ouabain • arrhythmias • ventricular tachycardia
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