Amiloride

Antiarrhythmic and Electrophysiologic Actions in Patients With Inducible Sustained Ventricular Tachycardia

Henry J. Duff, MD, L. Brent Mitchell, MD, Katherine M. Kavanagh, MD,
Dante E. Manyari, MD, Anne M. Gillis, MD, and D. George Wyse, MD, PhD

This study assessed the antiarrhythmic activity of amiloride in 35 patients with inducible sustained ventricular tachycardia. Patients had failed to respond to 3.6±1.0 antiarrhythmic drugs. Ventricular tachycardia was reproducibly induced by programmed electrical stimulation in all patients at the baseline study. Amiloride was given at 10 and 20 mg/day p.o. on a twice-daily schedule that achieved serum concentrations of 21±17 and 36±18 ng/ml, respectively. The mean left ventricular ejection fraction was unchanged from 36±14% at baseline to 37±17% during amiloride treatment. Amiloride significantly increased serum potassium from 4.6±0.4 to 5.1±0.4 mM. Four patients failed amiloride therapy with spontaneous nonsustained ventricular tachycardia. The remaining 31 patients were assessed by repeat programmed stimulation. Six patients had complete antiarrhythmic response, and an additional six patients had less than 15 beats of ventricular tachycardia induced. Therefore, amiloride was an efficacious antiarrhythmic treatment in 12 of 35 (34%) patients. Amiloride concentrations were significantly higher (52±20 ng/ml) in patients that responded than in patients that did not respond (30±15 ng/ml). The only electrophysiologic measurement that changed significantly was the ventricular functional refractory period (from 269±24 to 283±25 mSec, p<0.05). Amiloride also suppressed frequent, spontaneous ventricular premature beats in eight of 15 patients (53%). No somatic side effects occurred. Two of the five patients discharged on amiloride therapy developed asymptomatic nonsustained ventricular tachycardia, and this prompted a change in antiarrhythmic therapy. Both died suddenly of arrhythmia during substitute empiric antiarrhythmic drug therapy. The other three patients have been followed for a mean of 18±7 months and have not had a recurrence of ventricular tachycardia. In conclusion, amiloride has antiarrhythmic activity in humans and has a low incidence of adverse effects. (Circulation 1989;79:1257–1263)

Amiloride is chemically classified as a guanidinium. The guanidinium group is a chemical moiety common to a number of drugs with known antifibrillatory and antiarrhythmic properties such as bethanidine and meobentine. In vitro studies in Purkinje fibers show that amiloride prolongs action potential duration without alteration in the maximum rate of rise of phase 0. These electrophysiologic characteristics of amiloride are shared by a number of highly effective antiarrhythmic agents such as bretylium. Indeed, previous studies in our laboratory show antiarrhythmic activity of amiloride in dogs with inducible sustained ventricular arrhythmias 10 days after myocardial infarction. Accordingly, the present study was designed to assess electrophysiologic effects and antiarrhythmic efficacy of amiloride in patients with inducible sustained ventricular tachyarrhythmias.

Methods

Patients

Patients undergoing serial catheter electrophysiologic studies for assessment of sustained monomorphic ventricular tachycardia were candidates for this study. Patients were only included when their arrhythmias were reproducibly inducible and when therapy with at least two other antiarrhythmic medications had been ineffective. None of the patients had previously received amiodarone. All patients gave written, informed consent, and the study protocol was approved by the Conjoint Ethics
Committee of the Foothills Hospital and the University of Calgary Faculty of Medicine.

Protocol

Dietary sodium intake was maintained at 2 g/day throughout this study. After all electrophysiologically active medications had been discontinued for at least 5 half-lives, baseline indexes were obtained by measuring body weight, urinary electrolytes, and serum electrolytes and by performing radionuclide ventricular angioscopy and an electrophysiologic study. The initial dosage of amiloride was 10 mg/day. Three days later, the dosage was increased to 20 mg/day. These total amounts were given in two equal daily dosages. Repeat measurements of body weight, urinary electrolytes, and serum electrolytes and repeat electrophysiologic studies were performed only at both dosages at steady state (at least 3 days on each dosage). Radionuclide ventricular angioscopy was repeated only at the highest dosage.

Assessment of Electrophysiologic Effects

Electrophysiologic testing was performed with standard pacing and extrastimulus techniques. Surface electrocardiographic leads I, AVR, and V5 were recorded simultaneously with intercardiac electrograms from the high right atrium, His bundle, and right ventricular apex. Standard definitions were used to determine the following electrophysiologic measures: corrected sinus node recovery time, atrial and atrioventricular nodal functional and effective refractory periods, and Wenckebach cycle length. The AH, HV, and QT intervals were measured during constant rate atrial pacing. S1 and S2 represent the stimulus artifacts of the last beat of ventricular pacing and the first extrastimulus, respectively. Corresponding ventricular electrograms resulting from these stimuli are designated V1 and V2. Ventricular effective refractory period was defined as the longest S2S3 interval at which S3 failed to produce a propagated response. The ventricular functional refractory period was the minimum V3S2 interval created during measurement of the ventricular effective refractory period. Ventricular effective refractory periods were measured at ventricular pacing cycle lengths of 600, 500, and 400 msec. Electrode catheters were not left in place for long periods but were replaced at each electrophysiologic study.

Assessment of Antiarrhythmic Efficacy

Ventricular tachycardia was induced with a previously described standard protocol. Briefly, single ventricular extrastimuli were applied at twice diastolic threshold during ventricular pacing cycle lengths of 600, 500, and 400 msec. Subsequently, double and triple extrastimuli were used. Finally, bursts of 5 and 15 beats of rapid ventricular pacing at cycle lengths of 300–240 msec were applied. Sustained ventricular tachycardia was defined as a continuous ventricular rhythm with a cycle length of less than 500 msec lasting for more than 30 seconds or requiring termination because of serious hemodynamic compromise. During drug therapy, completion of the entire stimulation protocol without induction of 5 or more consecutive ventricular depolarizations was considered to indicate a complete antiarrhythmic response. Recognizing that many other investigators use the potentially less rigorous definition of antiarrhythmic response of less than 15 induced repetitive ventricular responses, we will report efficacy rates with both of these endpoints.

In addition, the frequency of spontaneous ventricular arrhythmias was quantified by 24-hour ambulatory electrocardiographic monitoring of patients in the drug-free state. This study was prospectively designed to allow patients with an average of greater than 20 premature ventricular depolarizations per hour at baseline to undergo repeat 24-hour ambulatory electrocardiographic monitoring during amiloride treatments. Ambulatory electrocardiographic monitoring was performed while the patient received the highest well-tolerated dosage. The criteria for drug-induced suppression of spontaneous arrhythmias were 80% or more suppression of total ventricular premature depolarizations, 90% or more suppression of ventricular couplets, and 100% suppression of ventricular triplets and other longer repetitive forms. The criteria used to indicate drug inefficacy during ambulatory monitoring, which would preclude invasive electrophysiologic testing, was the presence of spontaneous ventricular tachycardia (>5 consecutive ventricular premature depolarizations at a cycle length of <500 msec) at steady-state amiloride treatment.

Long-term Therapy

Patients with a complete antiarrhythmic response, as assessed by programmed electrical stimulation, were discharged on amiloride therapy. Follow-up included clinical evaluation and 12-lead electrocardiographic and 24-hour ambulatory electrocardiographic monitoring at intervals of 3 months.

Assay

Serum samples were assayed for amiloride by a high-performance liquid chromatography.

Statistics

Continuous data are presented as mean±SD, and comparisons were made with one-way analysis of variance. The null hypothesis was rejected when p<0.05.

Results

The clinical characteristics of the 35 patients studied are presented in Table 1. All but two patients had coronary heart disease with a mean ejection fraction of 36±14%. Patients 2 and 11 had no identifiable structural heart disease. Sustained ventricular tachycardia was reproducibly inducible in all patients during the drug-free study. Patients
failed at least two and a mean of 3.6±1 trials of other antiarrhythmic drugs.

In Table 2, serum amiloride concentration, serum potassium, serum magnesium, body weight, and urinary electrolytes are shown at baseline and during amiloride treatment. Amiloride produced a significant increase in serum potassium from 4.6±0.4 at baseline to 5.1±0.4 mEq/L during the high-dose amiloride treatment (p<0.05). No significant difference occurred in the change in serum potassium in patients responding to or not responding to amiloride. In four patients, it was necessary to reduce the dosage of concomitant captopril therapy or oral potassium supplementation. No other significant changes were seen in serum, urinary electrolytes, or body weight. Radionuclide angiograms were obtained at baseline and during amiloride treatment. The mean ejection fraction was unchanged from 36±14% at baseline to 37±17% during amiloride therapy (Table 2). The mean concentration of amiloride in this patient group was 36±18 ng/ml (range, 10–70 ng/ml).

**Electrophysiologic Effects**

Amiloride caused a dose-dependent prolongation of ventricular functional refractory periods (Table 3). No significant change occurred in ventricular
effective refractory periods. Amiloride had no other effects on cardiac conduction or refractoriness. No differences were observed in the electrophysiologic effect of amiloride in patients with an antiarrhythmic response compared with those without a response. No significant linear correlation between serum concentration of amiloride and ventricular effective or functional refractory period was observed.

Antiarrhythmic Efficacy

Thirty-one of the 35 patients underwent electrophysiologic studies at baseline and during amiloride treatment. Four patients did not undergo an electrophysiologic study while receiving amiloride because of spontaneous recurrence of nonsustained ventricular tachycardia, which indicated drug inefficacy. Of the remaining 31 patients, six (19%) had a complete antiarrhythmic response to amiloride. Five of these six patients had a complete antiarrhythmic response at 20 mg/day, whereas one responded at 10 mg/day. An additional six patients had a partial antiarrhythmic response (<15 beats of nonsustained ventricular tachycardia were induced during amiloride treatment). All six of these additional patients had partial response at 20 mg/day. Therefore, 12 of the 31 (39%) patients had a complete or partial response to amiloride as assessed by programmed stimulation.

The amiloride concentration in patients with a complete antiarrhythmic response was significantly

<table>
<thead>
<tr>
<th>Measurement (msec)</th>
<th>Baseline</th>
<th>10 mg/day</th>
<th>20 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus CL</td>
<td>826±198</td>
<td>695±114</td>
<td>792±160</td>
</tr>
<tr>
<td>QRS</td>
<td>110±22</td>
<td>102±27</td>
<td>110±23</td>
</tr>
<tr>
<td>QT</td>
<td>445±31</td>
<td>443±29</td>
<td>440±26</td>
</tr>
<tr>
<td>AH</td>
<td>77±14</td>
<td>76±21</td>
<td>84±21</td>
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<tr>
<td>HV</td>
<td>46±13</td>
<td>45±13</td>
<td>43±12</td>
</tr>
<tr>
<td>CSNRT</td>
<td>350±199</td>
<td>337±110</td>
<td>372±210</td>
</tr>
<tr>
<td>WBCL</td>
<td>387±9</td>
<td>325±59</td>
<td>359±79</td>
</tr>
<tr>
<td>AERP</td>
<td>239±33</td>
<td>213±21</td>
<td>235±37</td>
</tr>
<tr>
<td>AVNERP</td>
<td>260±68</td>
<td>265±10</td>
<td>293±85</td>
</tr>
<tr>
<td>VERP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>257±25</td>
<td>247±22</td>
<td>260±27</td>
</tr>
<tr>
<td>500</td>
<td>244±25</td>
<td>232±19</td>
<td>245±28</td>
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<tr>
<td>400</td>
<td>232±27</td>
<td>222±17</td>
<td>237±26</td>
</tr>
<tr>
<td>VFRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>284±24</td>
<td>270±18</td>
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<tr>
<td>500</td>
<td>269±24</td>
<td>261±25</td>
<td>283±25*</td>
</tr>
<tr>
<td>400</td>
<td>260±22</td>
<td>265±18</td>
<td>270±25*</td>
</tr>
</tbody>
</table>

All values are mean±SD.

*CL, cycle length; QT, QT interval measured at constant rate atrial pacing of 500 msec; CSNRT, corrected sinus node recovery time; WBCL, Wenckebach cycle length; AERP, atrial effective refractory period measured at CL of 500 msec; AVNERP, AV node effective refractory period measured at CL of 500 msec; VERP, ventricular effective refractory period; VFRP, ventricular functional refractory period.

*p<0.05 vs. baseline.
greater than that in patients without a response (52±20 and 30±15 ng/ml, respectively; p<0.05). To assess whether antiarrhythmic efficacy correlated with serum concentration, the antiarrhythmic response to amiloride was graded. Patients whose tachyarrhythmias were noninducible during amiloride treatment received a zero grade; patients with less than 15 beats inducible received grade 1 and patients with greater than 15 beats induced received grade 2. The grade of antiarrhythmic response linearly correlated with amiloride concentration with an r value of 0.53, p<0.005.

The relations between clinical factors and antiarrhythmic efficacy were also assessed. Complete antiarrhythmic efficacy was not related to baseline left ventricular ejection fraction. Three of 13 patients with near normal ejection fractions (>40%) responded to amiloride, whereas three of 22 patients with reduced left ventricular ejection fractions (≤40%) responded (NS). Two of the six responding patients had low ejection fractions (15% and 21%). Amiloride treatment was associated with a significant increase in serum potassium. However, serum potassium at baseline in nonresponding patients (4.6±0.5 mM) was similar to that in responding patients (4.6±0.4 mM), and serum potassium during amiloride treatment in nonresponding patients (4.9±0.4 mM) was not significantly different from that in responding patients (5.3±0.4 mM). In one patient who had a complete antiarrhythmic response to amiloride, the serum potassium increased from 5.1 mM at baseline to 5.8 mM during amiloride therapy. To assess the possibility that this patient’s antiarrhythmic response was related to the change in serum potassium, a potassium resin-binding agent (Kayexolate) was administered with amiloride. The serum potassium returned to 4.8 mM. Nevertheless, a repeat electrophysiologic study documented that the complete antiarrhythmic response persisted.

Fifteen patients had greater than 20 premature ventricular complexes per hour in the drug-free state (Table 4). Amiloride therapy suppressed spontaneous ventricular arrhythmias in eight of these 15 patients (53%). In all but one of these patients, ambulatory electrocardiographic monitoring was performed during amiloride treatment at a dosage of 20 mg/day. In the one person who had ambulatory electrocardiographic data (Table 4) recorded during amiloride therapy at a dosage of 10 mg/day (patient 13), suppression of spontaneous arrhythmias occurred. To assess the concordance of results of programmed stimulation and suppression of spontaneous arrhythmia, the 13 patients with both baseline spontaneous and inducible ventricular arrhythmias were analyzed. Of these 13 patients, seven responded by suppression of spontaneous arrhythmias, of whom only one responded by programmed stimulation. Of the six patients not responding by suppression of spontaneous arrhythmia, none responded by programmed stimulation.

**Adverse Effects**

No somatic side effects of amiloride therapy were identified in this study. However, possible prodysrhythmic activity occurred in five patients. These five patients had low frequency, sporadic arrhythmias during their baseline 24-hour ambulatory electrocardiographic examination. After amiloride therapy in these patients, rare episodes (<3 episodes/24 hr) of asymptomatic nonsustained ventricular tachycardia occurred. One of these patients had an episode of nonsustained ventricular tachycardia on the
2nd day of amiloride treatment at 20 mg/day (before steady state was reached). On the 3rd day of therapy, no ventricular tachycardia occurred during 24-hour ambulatory monitoring. Therefore, invasive electrophysiologic studies were subsequently performed. In this individual, 15 beats of ventricular tachycardia were induced at electrophysiologic study.

**Long-term Follow-up**

Six patients had a complete antiarrhythmic response as assessed by electrophysiologic study. One patient also responded to sotalol. Because the antiarrhythmic activity of amiloride has not been previously reported in humans, the latter patient was discharged on sotalol therapy. Therefore, five patients were discharged on amiloride therapy. Amiloride was discontinued in two of these patients after an episode of asymptomatic nonsustained ventricular tachycardia was observed during follow-up (six beats and eight beats). Both patients subsequently died suddenly while receiving alternative empiric antiarrhythmic drug therapy (procainamide and amiodarone). The other three responding patients have been followed for a mean of 24±8 months and have not had a recurrence of symptomatic ventricular tachycardia. These three responding patients are not receiving any other antiarrhythmic drugs, including β-adrenoceptor blocking agents.

**Discussion**

An ideal antiarrhythmic drug to treat sustained ventricular tachycardia does not exist. However, the clinical features of such an antiarrhythmic drug would include a high degree of efficacy, a low incidence of adverse effects, pharmacokinetic characteristics that foster compliance, a low incidence of prodysrhythmic endpoints, and the absence of negative inotropic activity. Our results provide the first evidence that amiloride has antiarrhythmic efficacy in the treatment of drug-resistant sustained ventricular arrhythmias in humans. Complete suppression of inducible sustained ventricular tachycardia occurred in six of 31 patients on amiloride therapy. Furthermore, fewer than 15 beats of ventricular tachycardia could be induced in an additional six patients. Therefore, 12 of 31 (39%) patients had an antiarrhythmic response to amiloride as assessed by programmed stimulation. This antiarrhythmic efficacy rate is at least comparable to standard antiarrhythmic drugs. Moreover, adverse effects are common with most standard antiarrhythmic drugs. Adverse effects of amiloride during this study were uncommon. Four patients required reduction in the dosage of captopril or oral potassium supplementation secondary to hyperkalemia. However, no other somatic adverse effects were observed. Although spontaneous nonsustained ventricular tachycardia occurred in five patients receiving amiloride, arrhythmia exacerbation meeting standard definitions of prodysrhythmia were not observed. Finally, using radionuclide angiography, we could not show a negative inotropic effect of amiloride. This latter observation is more in keeping with in vitro studies that have reported amiloride to have positive inotropic activity.

**Other Electrophysiologic Effects**

The electrophysiologic effects of amiloride in this study are similar to those reported in a dog model of arrhythmia but are different from those reported in isolated Purkinje fibers from guinea pigs. In humans and in the dog model, amiloride prolonged ventricular refractoriness. In Purkinje fibers, amiloride markedly prolonged action potential duration. However, in the present study, we observed no change in the clinical correlate of action potential duration, the QT interval during atrial pacing. The different results in the in vivo and in vitro studies may relate to the stimulation frequencies used, the concentrations of amiloride assessed, and species differences. In the in vitro study of Marchese et al., amiloride prolonged the action potential duration in a frequency-dependent fashion. At a drive cycle length of 500 msec, prolongation of action potential duration was small, although that observed at a cycle length of 2,000 msec was significant. The cycle length of ventricular stimulation in humans and in our previous dog studies was performed at more rapid rates. The second difference between the in vivo and in vitro studies was the concentration of amiloride assessed. In the in vitro study, the range of concentrations assessed was 1–10 µM; little change in action potential duration occurred at a concentration of 1 µM. In the dog model and in humans, the concentration range was 0.1±0.3 µM. Usual serum amiloride concentrations in humans are at least 10-fold less than those concentrations studied in vitro.

**Potential Mechanisms of Antiarrhythmic Efficacy**

Unlike other antiarrhythmic drugs, the sole electrophysiologic effect of amiloride observed in humans was prolongation of ventricular functional refractoriness. This observation suggests the possibility that amiloride has a new and unique antiarrhythmic mechanism. This study does not address the cellular mechanisms of the electrophysiologic effects of amiloride. Nevertheless, a number of mechanisms can be postulated. Amiloride may alter potassium currents. Amiloride has been reported to substantially decrease intracellular pH. Intracellular acidification may block the inwardly rectifying potassium current (IK1) thereby prolonging action potential duration. Although no change in surface QT interval occurred in this study, regional changes are not excluded. We have reported such regional prolongation of refractoriness in the zone bordering an infarction in the dog without prolongation of refractoriness in other regions. Amiloride could also affect potassium currents by changing extracellular potassium concentration. However, we were unable to relate efficacy...
Potential Limitations

Random variability in ventricular tachycardiac induction does not explain the antiarrhythmic efficacy of amiloride. Patients entered into this study had failed 3.6±1 (range, 1–5) previous antiarrhythmic drug trials as assessed by programmed stimulation. Overall, including the drug-free study, these patients had tachyarrhythmia induced a mean of 4.6 times before amiloride treatment. Furthermore, suppression of spontaneous ventricular arrhythmias occurred, and a similar antiarrhythmic effect of amiloride was observed in a dog model of arrhythmia.4 Thus, the antiarrhythmic efficacy reported here is a true drug effect.

The antiarrhythmic activity of amiloride was assessed in patients with drug-resistant ventricular arrhythmias in this study. Therefore, the antiarrhythmic efficacy of amiloride may be even greater in populations of patients without demonstrated drug resistance. Because our observation on spontaneous arrhythmias are based on only 15 patients, further studies are necessary to confirm the findings.

Another potential limitation of this study is the relatively few (35) patients studied. A larger study would be necessary to allow follow-up of a substantial number of patients on amiloride treatment. Moreover, because this report is the first description of the antiarrhythmic efficacy of amiloride, the number of patients followed on a long-term basis was further reduced secondary to conservative indications for discontinuing amiloride therapy. The indications for discontinuing amiloride during follow-up were asymptomatic nonsustained ventricular tachycardia.

Conclusion

In conclusion, amiloride has significant antiarrhythmic activity in humans and has a low incidence of adverse effects. Further studies are warranted to address the mechanism(s) of this efficacy.

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References


KEY WORDS • ventricular tachycardia • amiloride • antiarrhythmic activity
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