The Potentiation of Warfarin Anticoagulation by Amiodarone

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MELVIN M. SCHEINMAN, M.D., and DONNA WEISS, R.N.

SUMMARY The potentiation of the anticoagulant effect of sodium warfarin by amiodarone is reported in 10 patients. Amiodarone appears to augment the depression of vitamin K–dependent coagulation factors caused by warfarin by an uncertain mechanism, and may lead to serious bleeding. The maintenance dose of warfarin should be halved when amiodarone and warfarin are prescribed together.

AMIODARONE, a benzoafuran derivative, is an effective drug in controlling supraventricular and ventricular arrhythmias, including the arrhythmias associated with the Wolff-Parkinson-White syndrome. It often controls arrhythmias when other drugs have failed. Its main reported side effects include reversible corneal opacities, changes in thyroid function, photosensitivity, and pulmonary infiltrates. The use of amiodarone in patients with cardiac disease may result in its therapeutic combination with coumadin derivatives prescribed for thromboembolic prophylaxis. Recently, Martinowitz et al. suggested an interaction between amiodarone and sodium warfarin. We report our experience in 10 patients who demonstrated the effect of amiodarone in potentiating the anticoagulant properties of the coumadin derivative warfarin, with the possibility of life-threatening consequences.

Patient Details, Warfarin Administration and Laboratory Monitoring

Ten patients were referred for the management of drug-resistant arrhythmias and were prescribed a single daily dose of amiodarone. The clinical details are summarized in table 1. Nine patients were already receiving sodium warfarin for thromboembolic prophylaxis after cardiac valve surgery or because of paroxysmal atrial fibrillation or transient cerebral ischemia; the remaining patient was prescribed warfarin after a pulmonary embolus and was already taking amiodarone. The dose of warfarin was monitored by weekly or monthly one-stage prothrombin times as indicated, expressed as a percentage of a control value (10.5–12.5 seconds) using a nomogram (prothrombin activity). The nomogram was constructed using saline dilutions of normal plasma and an exponential curve.

Acknowledgment

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References

3. Chesler E, Beck W, Schrire V: Selective catheterization of pulmonary or bronchial arteries in the preoperative assessment of pseudotruncus arteriosus and truncus arteriosus type IV. Am J Cardiol 26: 20, 1970
TABLE 1. Patient Details

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Indication for warfarin</th>
<th>Indication for amiodarone</th>
<th>Concurrent drug therapy</th>
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<tr>
<td>1</td>
<td>M</td>
<td>67</td>
<td>73</td>
<td>Transient cerebral ischemia</td>
<td>Ventricular tachycardia</td>
<td>Furosemide</td>
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<td>2</td>
<td>F</td>
<td>63</td>
<td>58</td>
<td>Mitral valve prosthesis</td>
<td>Atrial fibrillation</td>
<td>Digoxin, furosemide</td>
</tr>
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<td>3</td>
<td>M</td>
<td>71</td>
<td>67</td>
<td>Aortic valve prosthesis</td>
<td>Atrial, ventricular arrhythmias</td>
<td>Propanolol, quinidine, digoxin, furosemide, isosorbide dinitrate, colchicine, probenecid</td>
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<td>M</td>
<td>69</td>
<td>77</td>
<td>Mitral valve prosthesis</td>
<td>Supraventricular tachycardia</td>
<td>Digoxin, furosemide, procanamide</td>
</tr>
<tr>
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<td>M</td>
<td>56</td>
<td>75</td>
<td>Mitral valve prosthesis</td>
<td>Ventricular tachycardia</td>
<td>Procainamide, quinidine, digoxin, furosemide</td>
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<td>F</td>
<td>56</td>
<td>61</td>
<td>Mitral stenosis</td>
<td>Atrial fibrillation, ventricular arrhythmias</td>
<td>Digoxin, disopyramide</td>
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<td>7</td>
<td>F</td>
<td>47</td>
<td>71</td>
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<td>Atrial fibrillation</td>
<td>Digoxin, furosemide</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>68</td>
<td>59</td>
<td>Aortic and mitral valve prostheses</td>
<td>Atrial arrhythmias</td>
<td>Digoxin, furosemide</td>
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<td>F</td>
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<td>59</td>
<td>Pulmonary embolism</td>
<td>Ventricular arrhythmias</td>
<td>Digoxin, diphenylhydrantoin</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>70</td>
<td>58</td>
<td>Transient cerebral ischemia</td>
<td>Atrial fibrillation</td>
<td>Digoxin</td>
</tr>
</tbody>
</table>

through a series of derived points (prothrombin times) was drawn by a computer. The daily warfarin dose was constant in some patients; in others, it was varied in a regular pattern (e.g., alternating doses) with occasional dosage adjustments. Rabbit brain thromboplastin was used in the assay for prothrombin times, having a similar sensitivity for levels of factors II, VII, IX, and X, and being relatively insensitive to small changes in the daily warfarin dose. The average daily dose of warfarin (averaged over a week) for each patient is listed in table 2, together with prothrombin times in the control period (warfarin alone) and during amiodarone therapy.

**Case Reports**

**Patient 1**

A 71-year-old male who weighed 67 kg had an aortic valve prosthesis inserted in 1969. He had both rheumatic and ischemic heart disease. He had been taking warfarin since his operation, with a satisfactory prothrombin activity on an average daily dose of 5–5.7 mg/day. He had a 4-year history of atrial and ventricular arrhythmias, and had tried other antiarrhythmic drugs that had either failed to control his symptoms or produced significant side effects. Oral amiodarone, 600 mg/day, was prescribed in addition to his usual medications of propranolol, quinidine, digoxin, furosemide, isosorbide dinitrate, colchicine and probenecid. Nineteen days later, proranolol and quinidine were discontinued and the amiodarone dose was increased to 800 mg/day to maintain control of his arrhythmias. The next day he presented with bruising and bleeding from broken areas of his skin, associated with prothrombin activity of < 9%. The warfarin was discontinued immediately and the amiodarone dose halved 5 days later. Subsequently the prothrombin activity recovered and the average daily dose of warfarin required to maintain a satisfactory prothrombin activity was 2.5–3.7 mg/day. These events are summarized in figure 1, the time base starting 6 months before the commencement of amiodarone therapy.

**Patient 2**

A 67-year-old male (73 kg) was prescribed amiodarone, 600 mg/day, for recurrent ventricular tachycardia. A year earlier, he had suffered a transient cerebral ischemic attack after the implantation of a pacemaker, and warfarin was commenced. Subsequently, his prothrombin activity stabilized, and the day before commencing amiodarone his activity was 28.7% on 5 mg and 7.5 mg of warfarin on alternate days (average 6.25 mg/day). Two weeks after amiodarone was begun, the prothrombin activity was 14.7% on the same dose of warfarin. The warfarin dose was then reduced to 2.5 mg and 5 mg on alternate days (average 3.75 mg/day), but 4 weeks later his prothrombin activity was 13.4%. As a result, the warfarin was discontinued for 2 days, allowing the prothrombin activity to rise to 33%. The prothrombin activity was stabilized on a dose of 2.5 mg/day.

After 74 days of amiodarone therapy, he presented with diffuse pulmonary infiltrates and arterial hypoxia, without evidence of heart failure from right-heart catheterization or any infection. Amiodarone was ceased, and 15 days later the prothrombin activity was 49%. His warfarin was increased to 7.5 mg/day, resulting in a prothrombin activity of 24.5% and 26% at each of the next two 14-day visits. Two days after the second of these visits, he presented with an abrupt onset of weakness and pain in the right leg due to a femoral entrapment syndrome secondary to spon-
taneous hemorrhage into the groin, and his prothrombin activity was < 9%. Warfarin was discontinued permanently. Three months after amiodarone was ceased, his pulmonary infiltrate had cleared almost entirely.

### Patients 3–10

The commencement of amiodarone therapy in patients 3 and 4 caused a precipitous fall in the prothrombin activity to < 9% on an unchanged dose of warfarin. Patient 3 developed a hematoma of the foot after mild blunt trauma. The prothrombin activity in patient 5 fell to 16.5% after amiodarone, and bruising developed. The prothrombin activity in patient 6 fell to 14% before warfarin was temporarily discontinued and then recommenced at a lower daily dose. Thus, in patients 1–6, warfarin therapy was temporarily discontinued for 2–3 days because of a low prothrombin activity, and then restarted. Subsequently, the average daily dose of warfarin required to produce satisfactory prothrombin activity (similar to before amiodarone) was 40–70% of that used previously.

The fall in prothrombin activity after amiodarone was not as severe in patients 7 and 8, so a significant adjustment to the average daily dose of warfarin was not required. Patient 7 had prothrombin activities of 25–48% over a 6-month period on a constant dose of warfarin before amiodarone, which stabilized at 22–23% on several estimations after the drug. Similarly, prothrombin activities in patient 8 fell from 29–36% to 20% on two consecutive visits after amiodarone was commenced, although the effects of the drug were not seen until after 2 weeks of therapy.

Patient 9 was prescribed warfarin after she had already been taking amiodarone for several weeks, and her prothrombin activities were stabilized at an appropriate level. She then stopped taking her amiodarone because of side effects, and 3 weeks later, her prothrombin activity had increased from 25.5% to 77%, despite continuation of warfarin therapy at the same daily dose.

The precise laboratory details for patient 10 were not available, but her physician reported that she had required 5 mg/day of warfarin to achieve a prothrombin activity of approximately 20% before amiodarone was commenced. After starting amiodarone, she required an average daily dose of 2.4 mg/day to achieve similar prothrombin activities.

### Statistical Analysis

The prothrombin times of patients 1–8 were compared before and after the addition of amiodarone to a constant average daily dose of warfarin. While the dosage of each drug varied from patient to patient,

#### TABLE 2. Average Daily Warfarin Dose and Prothrombin Times Before and After Amiodarone

<table>
<thead>
<tr>
<th>Pt</th>
<th>Warfarin dose (mg/day)</th>
<th>Prothrombin times (warfarin alone) (seconds)</th>
<th>Amiodarone dose (mg/day)</th>
<th>Prothrombin times (warfarin + amiodarone) (seconds)</th>
<th>Adjusted warfarin dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5–5.7</td>
<td>18.5–25.5 (10)</td>
<td>600/800/400</td>
<td>85.0</td>
<td>2.5–3.3</td>
</tr>
<tr>
<td>2</td>
<td>6.25</td>
<td>20.9–22.6 (3)</td>
<td>600</td>
<td>33.0</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>6.25</td>
<td>17.9–26.3 (9)</td>
<td>600</td>
<td>52.0</td>
<td>2.5–3.4</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>20.8–22.0 (2)</td>
<td>800/400</td>
<td>42.0</td>
<td>3.75</td>
</tr>
<tr>
<td>5</td>
<td>7.5</td>
<td>18.8–24.5 (3)</td>
<td>800/600</td>
<td>30.3</td>
<td>5.0</td>
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<tr>
<td>6</td>
<td>5.8</td>
<td>16.0–22.0 (6)</td>
<td>800</td>
<td>34.1</td>
<td>5.0</td>
</tr>
<tr>
<td>7</td>
<td>4.3</td>
<td>19.8–22.5 (6)</td>
<td>800</td>
<td>24.1–25.8 (3)</td>
<td>4.3*</td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
<td>16.0–23.0 (4)</td>
<td>800</td>
<td>28.0–34.0 (2)</td>
<td>5.0*</td>
</tr>
</tbody>
</table>

Prothrombin times are single estimates unless the number of estimates in a given range is indicated in parentheses.

*No adjustment made.

Figure 1. The interaction between warfarin and amiodarone in patient 1. The daily warfarin dose and prothrombin activities are shown before and after amiodarone was commenced. Note the reduction in average daily warfarin dose required after amiodarone therapy is begun.
each patient served as his own control. To determine if the two treatment forms differed with respect to prothrombin times, a Wilcoxon matched-pairs signed-ranks test was conducted.

The maximum prothrombin time recorded in each patient was analyzed before and after amiodarone and the results of the group were found to be significantly prolonged, from a mean (± sd) of 23.6 ± 1.66 to 42.0 ± 19.1 (p < 0.01).

Other Investigations

Liver function tests were available in six of the 10 patients and in all cases were normal.

A blood sample from the first patient was analyzed when his prothrombin activity was < 9%. The partial thromboplastin time was prolonged at 88 seconds (control 37 seconds) and individual factor assays showed factor V = 85%, factor VII = 1%, factor IX = 11.8% and factor X was < 2.5%. Thus, three of the vitamin K-dependent factors were depleted but the blood level of another hepatic factor (factor V) was normal. Liver function tests (aspartate transaminase, alkaline phosphatase and bilirubin) were normal. The patient's prothrombin activity was returned to 100% with normal plasma, suggesting a direct effect of the drug on vitamin K activity and vitamin K-dependent factor production, rather than peripheral antifactor activity. In addition, a sample of plasma from this patient was added to plasma of another patient who was on warfarin, to assess whether any drug/coagulation factor complexes might be responsible for prolongation of the prothrombin time. The prothrombin time of the test patient prolonged from 22.1 seconds to 27.4 seconds, consistent with dilution by the severely factor-depleted plasma of the amiodarone patient and not suggesting such a drug mechanism.

Discussion

The 10 case studies provide evidence that amiodarone potentiates the anticoagulant effect of sodium warfarin. All of the patients were taking other medications during the period of observation. In three patients, these medications were changed about the time of the amiodarone/warfarin interaction, in that other antiarrhythmic drugs (propranolol in two patients and propranolol and quinidine in another) were discontinued as amiodarone was introduced. However, only quinidine is known to cause a significant interaction with warfarin, and although its cessation in patient 1 may have hastened the recovery of the prothrombin activity once warfarin therapy was discontinued, it probably did not play any other role in the interaction.

Amiodarone appears to augment the anticoagulant effects of warfarin by further lowering the levels of vitamin K-dependent coagulation factors. How this occurs is not known. It may involve (1) a reduction in warfarin metabolism; (2) displacement of warfarin from plasma protein (increasing free warfarin levels); (3) a reduction in vitamin K absorption; (4) increased vitamin K metabolism; (5) increased metabolism of the vitamin K-dependent coagulation factors; or (6) a direct coumadin-like effect of the drug on vitamin K-dependent factor production.

Amiodarone accumulates in the body, and 16–34% may be retained in the body 30 days after treatment has stopped. Rosenbaum et al. noted a persistent antiarrhythmic effect after cessation of therapy and a delayed onset of action (4–8 days) after beginning therapy as the accumulation process began. The earliest change in the prothrombin activity was recorded 6 days after the amiodarone was begun in patient 6, but no change was seen for 20 days in patient 4 and for 24 days in patient 8, when earlier estimations of prothrombin activity were available. The effect of cessation of amiodarone was recorded in two cases; it was noted at 2 weeks in patient 2.

The pharmacology of amiodarone is poorly understood, but its affinity for plasma protein appears to be high. The mechanism by which drugs that bind to plasma protein may displace warfarin has been described by Koch-Weser and Sellers, and experience with other drugs has shown that the time required for the development of the potentiation of the anticoagulant effects depends on the time for the displacing drug to accumulate, the half-life of warfarin in the presence of the displacing drug and the half-life of the vitamin K-sensitive clotting factors. Most displacing drugs cause observable potentiation of warfarin within 24 hours, and the effect reaches a maximum in 3–5 days. This is due to an increase in free, unbound warfarin levels, but enhanced metabolism of free warfarin causes the level to return to normal within 7–10 days despite continuation of the displacing drug. The prothrombin time returns to normal after 2 weeks. A single dose of warfarin may not have an exaggerated anticoagulant effect in this new steady state after the administration of the displacing drug, as transiently increased free warfarin levels are counteracted by increased warfarin metabolism. Thus, once the adjustment to a new steady state has been achieved, warfarin requirements may return to their former levels.

The experience with other displacing drugs does not match our experience with amiodarone, although we may have missed transient potentiation of warfarin activity in the first few days after beginning treatment in some of our patients. Amiodarone apparently had a delayed effect on the prothrombin activity in some patients, (e.g., patient 2), and most required a permanent reduction in warfarin dosage while on the drug. Although the effects of amiodarone on cardiac tissue may be delayed and may not reach a maximum level for days or weeks, oral absorption would lead to immediate blood levels of the drug. Thus, any effects of amiodarone on protein binding appear to be less important than some other mechanism whereby the effects of warfarin are potentiated, such as a direct effect on warfarin, vitamin K or clotting factor metabolism. Like its other tissue effects, these effects could be delayed in onset and offset.

The effect of amiodarone on the prothrombin activity appeared to be independent of the clinically effective doses used. A change in the amiodarone dosage or cessation of the drug is not appropriate
Deceleration-dependent Left Bundle Branch Block: A Spectrum of Bundle Branch Conduction Delay

CHARLES FISCH, M.D., AND WILLIAM M. MILES, M.D.

SUMMARY Two cases of deceleration (bradycardia)-dependent left bundle branch block showing varying degrees of bundle branch block are described. The degree of bundle branch delay related directly to the duration of preceding cycle lengths. These observations support spontaneous diastolic depolarization as the mechanism of deceleration-dependent aberrancy.

INTRAVENTRICULAR ABERRATION associated with acceleration of the heart rate is a well-recognized phenomenon that appears to be related to an inappropriate response of the refractory period to a change in heart rate. Dressler reported the first case of a bundle branch block occurring with deceleration of the heart rate. Deceleration-dependent aberrancy (DDA) is much less common than aberrancy due to acceleration of the heart rate, and its mechanism less clear. Massumi reported four additional cases and suggested criteria for diagnosis of DDA. In 1973, Rosenbaum and associates added 14 cases.

Enhanced phase 4 depolarization was proposed by Singer et al. as the mechanism of DDA. They suggested that with a longer cycle, the cell membrane depolarizes and activation is initiated from a reduced resting membrane potential resulting in slowing or block of conduction. This phenomenon has been referred to as diastolic or phase 4 block. If diastolic depolarization is indeed operative, one can assume that patients with incomplete bundle branch block at rates between those that cause complete bundle branch block and those with normal intraventricular conduction would be encountered. To our knowledge, no such cases have been reported. In this paper, we describe two patients who had DDA associated with varying degrees of bundle branch block.

Case Reports

Case 1
The tracings were recorded in a 20-year-old woman after surgery for congenital aortic stenosis, and represent DDA. The basic rhythm in figure 1 is a sinus arrhythmia with PP intervals of 680–1080 msec. The PR interval is constant at approximately 130 msec. In each lead the QRS complexes vary from 80–130 msec. The shortest RR cycles are followed by QRS complexes of normal duration, intermediate RR cycles by QRS complexes of intermediate duration (incomplete
The potentiation of warfarin anticoagulation by amiodarone.
A Hamer, T Peter, W J Mandel, M M Scheinman and D Weiss

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