Effects of Antiarrhythmic Drugs on Atrioventricular Conduction in Patients with Acute Myocardial Infarction

MELVIN M. SCHEINMAN, M.D., PETER REMEDIOS, B.S., MELVIN D. CHEITLIN, M.D.,
ROBERT W. PETERS, M.D., NICK HOLFord, M.D., JAWAHAR DESAI, M.D.,
AND JOSEPH A. ABBOTT, M.D.

SUMMARY Three hundred fifty-eight of 429 (83%) consecutive patients with acute myocardial infarction (MI) and a normal PR interval received various antiarrhythmic drugs (AD), including lidocaine and/or procainamide, quinidine, digoxin, propranolol or disopyramide. There was no significant difference in the incidence of progression to any degree of atrioventricular (AV) block or to higher degrees of AV block (Mobitz II or third-degree AV block) between those treated and not treated with AD: 38 of 358 (11%) and six of 358 (1.7%) with AD vs 11 of 71 (15%) and two of 71 (2.8%) in the untreated group, respectively. Similarly, there was no significant difference in progression between treated and untreated patients with anterior MI, 14 of 144 (10%) vs five of 32 (16%); inferior MI, 21 of 111 (19%) vs five of 26 (19%), or subendocardial MI, three of 103 (3%) vs one of 12 (8%). Bundle branch block (BBB) (without AV block) was initially present in 89 of 249 (21%). The incidence of AV block (seven of 24, 30%) was higher in treated patients with newly acquired BBB (27 patients) than in the untreated patients (none of three, p < 0.05). The commonly used ADs did not adversely affect AV conduction in patients with acute MI with narrow QRS and either normal, first-degree, or Mobitz I AV block. Moreover, no subset of patients grouped by infarct location, specific AD used, or BBB (except perhaps for those with newly acquired BBB) appeared to be at risk of development of AV block during AD therapy.

PATIENTS with acute myocardial infarction (MI) are usually treated with antiarrhythmic drugs, especially i.v. lidocaine. The effects of these agents on atrioventricular (AV) conduction in patients with acute MI has not been assessed critically. Recent in vitro studies, for example, clearly showed that lidocaine depresses conduction in ischemic cells of the specialized cardiac conduction system.1,2 Gerstenblith et al.3 reported that lidocaine increases the incidence of AV block in an intact ischemic canine preparation. Although AV block associated with antiarrhythmic drug therapy has been reported occasionally, no comprehensive studies have been carried out on the effects of the commonly used antiarrhythmic drugs in patients with acute MI. In this study we assessed retrospectively the effects of frequently used antiarrhythmic agents on AV conduction in patients with acute MI. We also attempted to define a subset of patients with acute MI who appear to be at high risk of developing AV block when treated with these drugs.

Materials and Methods

Fourteen hundred thirty-seven patients were admitted to the coronary care unit at the San Francisco General Hospital Medical Center from January 1976 through July 1978. The medical records of 485 consecutive patients with the diagnosis of acute MI were reviewed. Fifteen patients with cardiogenic shock in whom AV block developed as a terminal rhythm disturbance were excluded from the study; however, data before the shocked state or in those with shock not showing terminal AV conduction arrhythmias were included in the study. Our detailed criteria for diagnosis of acute MI and location of the infarction have been reported previously.4,5 In brief, the diagnosis of acute MI was based on a compatible history, characteristic electrocardiographic changes, and presence of positive creatine phosphokinase (CPK)-MB fraction. In our laboratory only CPK-MB concentrations > 2% of the total CPK (as determined by area under the electrophoretic curves) are considered positive.6 The upper limits of normal of the total CPK are 50 IU.7 All of the patients received intramuscular injections after entry into the emergency ward or coronary care unit. Four patients who died within 6 hours of admission (in whom CPK-MB determinations were negative) were included in the study because they showed characteristic electrocardiographic or anatomic changes of acute MI.

Transmural infarction was diagnosed on the basis of development of q waves and evolutionary ST-T abnormalities, whereas subendocardial infarction was diagnosed in the presence of evolutionary ST-T changes. Location of the infarction site was based upon analysis of leads showing the electrocardiographic abnormalities. For this study, patients who had characteristic changes in the precordial or lateral (lead I, aVL) leads were included in the anterior infarction group; those who had similar changes in the inferior leads (2, 3, aVF) were categorized as showing inferior MI. Eight patients with characteristic changes
of true posterior MI were included in the latter group. Patients in whom ST-T changes were present in either anterior or inferior leads or those in whom the site of infarction was indeterminate were placed in the subendocardial infarction category. Because the incidence of AV block in the subendocardial infarction group was extremely low and none developed high-grade AV block, the group as a whole was subdivided into three groups: those with transmural anterior, inferior or subendocardial MI.

In all patients, an initial 12-lead ECG was obtained in the emergency room and continuous electrocardiographic monitoring was used en route to the coronary care unit. The following data were recorded for each patient: age, sex, infarct location, and the status of AV or intraventricular conduction. The time, dose, and duration of treatment with antiarrhythmic agents (i.v. lidocaine and/or procainamide or oral quinidine, digoxin, propranolol or disopyramide) were noted. An i.v. bolus injection of 50–100 mg of lidocaine was administered to 261 patients. The initial bolus was followed by a lidocaine infusion of 2–4 mg/min and repeat 50-mg boluses were injected at 5- to 10-minute intervals to control ventricular arrhythmias. If arrhythmia control was not achieved after administration of a total of 250–300 mg of lidocaine i.v. (89 of the 261 treated patients required more than 200 mg of lidocaine), lidocaine was stopped and i.v. infusion of procainamide was initiated. The latter agent was infused in 50 patients at a rate of 20 mg/min to a total dose of 700–1000 mg. Then the infusion rate was reduced to 2–5 mg/min. Repeated bolus infusions of 200–600 mg of procainamide were required in 18 of the 50 patients. We attempted to discontinue lidocaine but concurrent use of both lidocaine and procainamide was required in 29 patients to control ventricular arrhythmias. Treatment with oral antiarrhythmic preparations was as follows: quinidine sulfate (200–400 mg four times a day) in 29 patients, disopyramide (150–200 mg four times a day) in four patients, propranolol (20–80 mg four times a day) in 36 patients, and digoxin (0.125–0.25 mg/day) in 72 patients. Before admission 17 patients had been taking quinidine orally, 21 had been taking propranolol orally and 47 had been taking digoxin orally. For purposes of the study, patients with possible drug-related AV block included those in whom AV block occurred either while taking the drug or within one half-life of the drug after cessation of the drug. AV block was considered less likely to be drug- (or drug-metabolite) related if the block occurred two half-lives (β) after termination of the drug.12, 13 None of the patients developed AV block between one and two half-lives of the drug after termination of the specific agent.

Patients with acute MI and bundle branch block (BBB) were divided into three categories: (1) preexistent BBB — patients with electrocardiographic documentation of BBB before the present admission; (2) new BBB — patients with acute MI whose ECG on admission showed BBB and whose previous ECGs showed normal intraventricular conduction or those in whom BBB developed during the hospital course; and (3) unknown — patients whose initial ECG showed BBB but no previous ECGs were available. Our criteria for fascicular blocks have been detailed previously.14 In brief, right bundle branch block (RBBB) was diagnosed when the QRS duration was ≥ 0.12 second with terminal forces directed rightward and anteriorly. Left bundle branch block (LBBB) was defined in the presence of a wide QRS duration ≥ 0.12 second with terminal QRS forces directed leftward and posteriorly. Left anterior fascicular block (LAFB) was diagnosed when initial forces were directed rightward and inferiorly and terminal forces were directed leftward and superiorly with a mean frontal plane QRS vector of greater than −30°. Left posterior fascicular block (LPFB) was diagnosed when initial forces were directed leftward and superiorly and terminal forces were directed rightward and inferiorly with a mean frontal plane QRS vector of greater than 90°. The last diagnosis was made only in the absence of pulmonary hypertension or anterolateral infarction.

The following definitions of AV block were used: (1) first-degree AV block (1° AV block) — prolongation of the PR interval > 0.20 second for heart rates between 60–100 beats/min; (2) second-degree AV block (2° AV block) — nonconducted P waves during sinus rhythm (Mobitz I or Wenckebach conduction was differentiated from Mobitz II types of block); (3) third-degree AV block (3° AV block) — complete AV block in which no atrial impulses are conducted to the ventricles; (4) low-degree AV block — 1° AV block and Mobitz type I block; and (5) high-degree AV block — Mobitz type II block or 3° AV block.

The following values for drug β half-lives were used12, 13: lidocaine, 4.5 hours; procainamide, 3 hours; quinidine, 7 hours; digoxin, 42 hours; phenytoin, 22 hours; disopyramide, 7 hours; and propranolol, 6 hours.

Data were analyzed by nonpaired t test using two-way tables (one degree of freedom) and the standard chi-square distributions;16 p values < 0.05 were considered to be significant.

Results

Group Characteristics

Four hundred twenty-nine of 470 patients had normal AV conduction on admission, and 358 of 429 patients (83%) (group 1) received one or more of the following antiarrhythmic drugs: lidocaine (344 of 429, 80%), digoxin (94 of 429, 22%), procainamide (65 of 429, 15%), propranolol (45 of 429, 10%), quinidine (38 of 429, 9%) and disopyramide (six of 429, 1%). Seventy-one patients (group 2) did not receive any of these drugs. There was no significant difference in sex distribution, mean age, time from onset of symptoms to coronary care unit admission, time in coronary care unit, incidence of Killip class III and IV,14 peak serum CPK, serum K+ or creatine concentrations, or mortality between groups 1 and 2 (table I). Similarly, there was no significant difference in location of infarct or incidence of BBB between the two groups.
TABLE 1. Clinical and Electrocardiographic Parameters for Treated (Group 1) and Untreated (Group 2) Patients with Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 358)</th>
<th>Group 2 (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (years)*</td>
<td>270 (75%)</td>
<td>51 (72%)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>62 ± 13</td>
<td>61 ± 13</td>
</tr>
<tr>
<td>Time from onset of symptoms to</td>
<td>3 ± 1.8</td>
<td>2.8 ± 1.7</td>
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<tr>
<td>coronary care unit admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in coronary care unit (days)</td>
<td>5.2 ± 1.9</td>
<td>4.9 ± 1.6</td>
</tr>
<tr>
<td>Peak serum creatine</td>
<td>433 ± 1230</td>
<td>988 ± 548</td>
</tr>
<tr>
<td>phosphokinase (CPK)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days of elevated CPK</td>
<td>22 ± 0.43</td>
<td>2.7 ± 0.52</td>
</tr>
<tr>
<td>Serum K+ (mEq/l)†</td>
<td>3.8 ± 0.9</td>
<td>4.1 ± 0.7</td>
</tr>
<tr>
<td>Serum creatinine (mg/l)†</td>
<td>1.2 ± 0.6</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>Bundle branch block (no. of</td>
<td>75 (21%)</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior myocardial</td>
<td>144 (40%)</td>
<td>32 (45%)</td>
</tr>
<tr>
<td>infarction (no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior myocardial</td>
<td>111 (31%)</td>
<td>27 (38%)</td>
</tr>
<tr>
<td>infarction (no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subendocardial myocardial</td>
<td>103 (29%)</td>
<td>12 (17%)</td>
</tr>
<tr>
<td>infarction (no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killip class III or IV</td>
<td>82 (23%)</td>
<td>14 (20%)</td>
</tr>
<tr>
<td>(no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (no. of patients)</td>
<td>57 (16%)</td>
<td>10 (14%)</td>
</tr>
</tbody>
</table>

*Mean ± SD.
†Mean ± SD of highest recorded value.

Development of AV Block

Data relating to development of AV block are summarized in figure 1. AV block developed in 38 of 358 (11%) patients in group 1. It occurred either while the drug was being administered or within one half-life of the drug after drug termination in 30 patients and two half-lives after drug termination in eight. Even if the latter eight cases are considered drug-related AV block, there was no significant difference in the incidence of AV block between treated (38 of 358, 11%) and untreated (11 of 71, 15%) groups. Similarly, there was no significant difference in the incidence of progression to high-grade AV block between the groups (six of 358 vs two of 71). Moreover, no higher risk for development of AV block was encountered in those who received the larger doses of lidocaine (≥ 200 mg) (12 of 89, 13%) or in those who received combinations of lidocaine and procainamide therapy (two of 29, 7%). Similarly, use of other drug combinations (fig. 2) did not appear to be an important factor in development of AV block. In addition, there was no significant difference in time between hospital admission and onset of AV block between group 1 (46 ± 73 hours [mean ± SD]) and group 2 (38 ± 35 hours).

Infarct Location, Antiarrhythmic Drugs and AV Block

Data relative to the relationship of infarct site and specific antiarrhythmic agents are summarized in figures 2 and 3 and table 2. Although there was no significant difference in the incidence of AV block in patients with transmural anterior, inferior or subendocardial MI between the two groups, the incidence of AV block in patients with transmural MI as a group...
The incidence of various degrees of atrioventricular (AV) block, infarct location, and specific drug therapy are detailed for 358 patients with normal AV conduction on admission. The type of AV block is listed on the left column, and the numbered boxes refer to the number of patients in a given category. A branch diagram is used to detail the course of 38 treated patients in whom AV block developed. For example, of the 38 patients with initial normal AV conduction, 30 developed 1° AV block (left arm of branch); of these, 22 remained in that category, while seven progressed to 2° AV block and one of the seven progressed to 3° AV block. The site of infarction and specific drug(s) therapy are also detailed for each subgroup. Only three of the patients who developed AV block received more than one drug. Abbreviations: MI = myocardial infarction; Inf = inferior; Ant = anterior; Sub = subendocardial; L = lidocaine; D = digoxin; Pc = procainamide; Pr = propranolol. Q = quinidine.

(45 of 311, 15%) was higher than that in patients with subendocardial infarction (four of 115, 3.4%) (p < 0.05) (table 2). The antiarrhythmic drugs were divided into two general categories based on their major presumed site of action: His-Purkinje system — lidocaine, procainamide, quinidine; AV node — digitalis and propranolol (table 2). The incidence of AV block was similar for patients with anterior transmural MI treated with lidocaine, procainamide or quinidine (10 of 107, 9%) compared with that in the
untreated group (five of 32, 16%). Similarly, there was no significant difference in the incidence of AV block between patients with inferior MI and AV block treated with digitalis and/or propranolol (four of 29, 14%) and the untreated patients with inferior MI (five of 27, 19%). Therefore, neither infarct location nor specific categories of antiarrhythmic drugs appeared to influence the development of AV block between the two groups.

**BBB and AV Block**

Eighty-nine of the 100 patients with BBB showed normal AV conduction on admission to the hospital. All except three, who had RBBB, had anterior MI, whereas the site of infarction was indeterminate in four with LBBB. The incidence of AV block was higher in those with BBB (20 of 89, 23%) compared with those who had narrow QRS complexes (29 of 340, 9%) ($p < 0.025$). Of the 89 patients with BBB and normal conduction, AV block developed in 14 of 75 (19%) treated with antiarrhythmic drugs, compared with six of 14 (43%) in the untreated group ($p < 0.05$) (fig. 4). There was no significant difference between treated and untreated patients with BBB with regard to age, sex, amount of drug or drug combination, infarct location, or peak CPK concentration. In addition, the incidence of patients with Killip class III or IV was similar in the treated (52 of 75, 69%) and untreated (eight of 14, 56%) groups with BBB. Progression to high-grade AV block occurred in seven of 89, but there was no difference in incidence of high-grade block between treated (five of 75, 7%) and untreated (two of 14, 14%) groups. Although the incidence of AV block was higher in those with newly acquired BBB (seven of 27, 26%) or indeterminate BBB (12 of 43, 28%) than in those with preexistent BBB (one of 19, 5%), these differences were not statistically significant. Of the 27 patients with newly acquired BBB, 24 received antiarrhythmic drugs (17 received lidocaine), and AV block developed in seven of the 24. In three of these seven, AV block developed two half-lives after termination of the drug. In contrast, AV block did not develop in any of the three untreated patients with new BBB. The relationships among specific BBB pattern, drug treatment, and incidence of AV block are detailed in table 3. All seven patients with BBB who progressed to high-grade AV block had new or indeterminate BBB, anterior transmural MI, and either left BBB or right BBB plus left anterior hemiblock. The risk of developing AV block appeared to be more related to the extent of the disease of the conduction system and whether or not the BBB was newly acquired than to specific drug intervention.

**Natural History and Effects of Drugs in Patients with Spontaneous AV Block**

Forty-one patients had varying degrees of AV block at the time of admission to the hospital, whereas AV block developed in 11 untreated patients during hospitalization. Forty-three of these 52 patients had

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**Table 2. Infarct Location, Type of Antiarrhythmic Drug Therapy and Atrioventricular Block**

<table>
<thead>
<tr>
<th>Myocardial infarction location</th>
<th>Total incidence of AV block</th>
<th>Incidence of high-grade AV block</th>
<th>Type of drug* and AV block</th>
<th>Total incidence of AV block</th>
<th>High-grade AV block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>14/144 (10%)</td>
<td>54/144 (3.5%)</td>
<td>L, Pr, Q</td>
<td>5/32 (16%)</td>
<td>3/32 (9%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>215/111 (19%)</td>
<td>2/111 (2%)</td>
<td>L, Pr, Q</td>
<td>5/27 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Subendocardial</td>
<td>3/103 (3%)</td>
<td>0</td>
<td>0</td>
<td>1/12 (8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*The numerator denotes the number of patients who developed AV block and the denominator refers to the number of patients with a specific infarct pattern treated with at least one of the indicated drugs. The total incidence of AV block for treated (column 1) and untreated (column 5) is also detailed.

†Three developed AV block more than two half-lives after termination of drug treatment.

‡One developed AV block more than two half-lives after termination of drug treatment.

§Five developed AV block more than two half-lives after termination of drug treatment.

¶Two of three who had AV block received lidocaine only and the third was treated with lidocaine and procainamide.

Abbreviations: AV = atrioventricular; L = lidocaine; P = procainamide; Q = quinidine; D = digoxin; Pr = propranolol.

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**Figure 4. Incidence of atrioventricular (AV) block for 89 patients with bundle branch block (BBB) and normal AV conduction on admission. Eleven patients developed AV block either while taking a drug or within one half-life (1/2) after termination of drug therapy, whereas AV block developed in three patients two or more half-lives after termination of drug treatment.**
Table 3. Type of Intraventricular Conduction Delay and Incidence of Atrioventricular Block

<table>
<thead>
<tr>
<th>Type of intraventricular conduction delay</th>
<th>No. of patients</th>
<th>Patients treated with drugs</th>
<th>Treated patients with AV block</th>
<th>Nondrug related AV block</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB</td>
<td>29</td>
<td>26</td>
<td>5*</td>
<td>3</td>
</tr>
<tr>
<td>RBBB</td>
<td>20</td>
<td>18</td>
<td>5*</td>
<td>0</td>
</tr>
<tr>
<td>RBBB and LAH</td>
<td>14</td>
<td>13</td>
<td>4*</td>
<td>1</td>
</tr>
<tr>
<td>RBBB and LPH</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alternating LBBB and RBBB</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IVCD</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>LAH</td>
<td>12</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LPH</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*One patient in each of these categories developed AV block after more than two half-lives of drug after termination of drug treatment.

Abbreviations: AV = atrioventricular; LBBB = left bundle branch block; RBBB = right bundle branch block; LAH = left anterior hemiblock; LPH = left posterior hemiblock; IVCD = intraventricular conduction delay (QRS duration > 0.12 second) without right or left bundle branch block pattern.

Discussion

Limitations

Although a rigidly controlled prospective drug-placebo trial is required to assess conclusively the effects of antiarrhythmic drugs, such a study would present serious ethical problems. A retrospective study may suffer from biases that may be difficult to discern. However, it should be emphasized that administration of lidocaine (the most commonly used drug) was usually initiated by the coronary care nurses under standing orders. In addition, patient care was carefully supervised by a single attending physician, providing a greater degree of treatment uniformity than might occur in a unit in which patients are cared for by many attending physicians. Similarly, aside from frequency of premature ventricular depolarizations, we could not detect any significant bias relating to infarct location, degree of heart failure, or peak CPK concentration between treated and untreated patients.

The lack of blood concentration of drug data poses a serious limitation. Clearly, accumulation of drug and/or drug metabolite to toxic levels might have occurred in those with heart failure or renal or hepatic disease. Although we did not find a correlation between the development of AV block and the amount of drug administered, use of drug combinations, incidence of heart failure, or peak serum creatinine concentration for treated and untreated groups, our studies do not preclude the possibility that AV block was related to toxic blood concentrations of drug. The thrust of our study, however, was to assess the effects of those drugs used to achieve the desired objectives of rhythm or rate control on AV conduction.

His bundle recordings were not obtained, so precise location of the site of AV block was impossible. If one assumes that the majority of those with inferior MI had AV nodal block and that those with anterior MI had infranodal block, then again no significant difference in incidence of AV block was apparent for treated vs untreated patients. Similarly, no specific drug or group of drugs appeared to be related to development of AV block in patients with anterior vs inferior transmural or subendocardial MI.

Our monitoring techniques were limited in that very transient episodes of AV block may not have been recognized. We have no data correlating the incidence of AV block determined in the coronary care unit with 24-hour taped recordings; therefore, the incidence for AV block cited in our study is likely a minimal figure. Although previous reports of presumed drug-related AV block describe periods of block lasting as little as 10 seconds, the clinical significance of these transient episodes is unclear. In addition, although transient episodes of AV block may have been missed, we find no a priori reason for assuming a systematic differing

Figure 5. Comparison of 52 treated and untreated patients with varying degrees of spontaneous atrioventricular (AV) block.

*Three patients with inferior myocardial infarction and complete AV block were given lidocaine and no adverse effects occurred.
incidence of omission between treated and untreated groups.

We found that patients with acute MI treated with the commonly used antiarrhythmic drugs designed to achieve the desired therapeutic end points of rate or rhythm control had no greater tendency to develop AV block than the untreated patients.

Moreover, we could not define a subset of patients prone to develop AV block on the basis of infarct location or use of specific drug categories. We divided the antiarrhythmic drugs into two broad categories based largely on their presumed site of action. Based on experimental observations, quinidine, procainamide, and disopyramide would be expected to depress conduction in normal or ischemic His-Purkinje tissue2.3,18–20 or ventricular muscle1,18,19,21 Similarly, clinical studies have shown that these agents prolong infranodal and intraventricular conduction and increase His-Purkinje and ventricular muscle refractoriness20–27. Lidocaine and phenytoin appear to have similar effects on ischemic His-Purkinje tissue1 and/or ventricular muscle.28,29

In our study, we found no evidence that patients with transmural anterior MI treated with these drugs had a greater risk of developing AV block than untreated patients with anterior MI. We presumed that patients with inferior MI would be expected to have a higher incidence of latent or overt AV nodal dysfunction, in view of the common blood supply to these areas.30 Moreover, because digitalis31,32 and propranolol33 exert major effects on AV nodal function (by depressing conduction and increasing refractoriness), we tested the hypothesis that subjects with inferior MI treated with these drugs would be more susceptible to the development of AV block. However, we could not detect a subset of patients with inferior MI that have an increased risk of developing AV block on the basis of specific drug therapy. We recognize that patients with acute MI may have changes in autonomic tone that may influence drug effects on AV conduction. Similarly, changes in blood pressure may be associated with changes in baroreceptor influence on AV nodal conduction. We could not demonstrate significant drug effects either for the treated group as a whole or when specific drug categories were analyzed according to the major presumed site of action (table 2).

BBB and AV Block

The incidence of AV block was higher in those with BBB than in those with normal intraventricular conduction, which was similar to recently reported series in which preterminal AV block was excluded.14,34,35 The higher incidence of AV block in the untreated group with BBB was somewhat surprising. Although a protective effect of drugs appears unlikely, it is equally unlikely that these findings should be ascribed to physician bias, because the patterns of antiarrhythmic drug use were similar for patients with anterior MI with or without BBB. Similarly, the incidence of heart failure was similar in treated and untreated BBB patients. A similar "protective" effect was observed in a recent study of patients with acute MI in whom prophylactic disopyramide therapy was compared with placebo.36 Regardless of the explanation of this finding, antiarrhythmic agents clearly did not exert a deleterious effect on this patient subgroup.

We observed a trend toward a higher incidence of AV block in those patients with either newly acquired BBB (seven of 27, 26%) or BBB of indeterminate age (12 of 43, 28%) compared with those with preexistent BBB (one of 19, 5%). These findings were similar to those reported by Hindman et al.,34 who found that newly acquired BBB in the setting of acute MI was a definite risk factor in the development of higher grades of AV block. Therefore, we examined the relationship of drug therapy to development of AV block in this high-risk subgroup, and although there was a significant difference between treated (seven of 24) and untreated (none of three) patients in terms of progression to AV block, the small numbers involved precluded definitive conclusions. Similarly, attempts to detect a specific high-risk subgroup among BBB patients based on infarct location and specific BBB pattern was impossible in view of the relatively small numbers of patients for each subgroup (table 3). All of the subjects with BBB (both treated and untreated) who progressed to high-grade AV block had anterior MI and newly acquired or indeterminate BBB and either left BBB or right BBB plus left anterior hemiblock. These data suggest that the site of infarction and severity of the underlying disease of the conduction system is a more important determinant of development of high-grade AV block than specific drug intervention for patients with BBB.

Effects of Drugs on Patients with Impaired AV Conduction

Because none of the patients with Mobitz II AV block and only three of those with complete block (due to inferior MI) received drugs without temporary cardiac pacing, the effects of drugs on those with impaired AV conduction could only be tested for those with 1° or Mobitz I AV block. There was no evidence that antiarrhythmic drug therapy further depressed AV conduction in those with either spontaneous or drug-related low-grade AV block. The small numbers of subjects with complete AV block (three patients) who were treated with drugs (lidocaine) clearly preclude any definitive statement regarding safety of drug therapy in this patient subgroup. The effects of drugs in patients with anterior MI and 2° or 3° AV block were not assessed because these patients underwent temporary pacemaker insertion before initiation of drug therapy. In addition, sparse data were available in our study relative to the underlying rhythm or conduction disturbance in these patients when intermittent demand ventricular pacing was operative.

Previously Related Observations

Our results are somewhat surprising in view of recent experimental and clinical observations of the
effects of antiarrhythmic drugs on AV conduction. Roos and Dunning assessed the effects of an i.v. injection of 100-mg bolus of lidocaine in 39 patients (10 of whom had recent MI) with AV conduction disturbances. In three patients (one with recent MI), lidocaine administration was associated with transient deterioration of AV conduction. The investigators found extremely high blood concentrations of the drug shortly after the injection (maximum of 26.6 μg/ml at 60 seconds) and noted that the depression of AV conduction disappeared 30-200 seconds after administration of lidocaine. Similar results were reported by Gupta et al. in three of 21 patients with intraventricular conduction delay. Many of the patients reported in these studies who showed deterioration in AV conduction after lidocaine had episodic Mobitz II or 3° AV block before lidocaine administration. In our study, none of the patients with Mobitz II or 3° AV block (except for three with inferior MI) were treated with antiarrhythmic drugs, and progression of AV block within minutes after an i.v. bolus injection of lidocaine occurred in only two patients. Although a subgroup of patients with acute MI and BBB might be especially vulnerable to progressive AV block after lidocaine, this phenomenon appears to be uncommon.

Clinical Significance

We found no evidence that the commonly used antiarrhythmic agents (used to achieve therapeutic end points of rate or rhythm control) exert deleterious effects on AV conduction in patients with normal intraventricular conduction with either normal AV conduction or 1° or Mobitz I AV block. The need for antiarrhythmic agents in these patients does not necessarily require insertion of a temporary pacemaker. In addition, we found that the incidence of AV block was small (3.4%) in patients with subendocardial infarction, and none developed high grade AV block. Thus, the need for prophylactic pacing in these patients appears to be uncommon. Although patients with BBB have a higher risk of developing AV block again, frequently used antiarrhythmic drugs did not in general appear to exert deleterious effects on AV conduction. Progression in these patients appeared to be more related to the extent of underlying disease of the conduction system and site of the infarct than to specific drug intervention. Caution should be exercised, however, in the use of these agents in patients with acute MI and newly acquired BBB. Detection of a subset of patients with acute MI and specific BBB pattern (or HQ prolongation) who have an increased risk of developing AV block is still unsettled. Finally, our limited data preclude definitive conclusions relative to the safety of very high doses of type I antiarrhythmic agents in the setting of acute MI.

References


Effects of Amrinone on Myocardial Energy Metabolism and Hemodynamics in Patients with Severe Congestive Heart Failure Due to Coronary Artery Disease

JOSEPH R. BENOTTI, M.D., WILLIAM GROSSMAN, M.D., EUGENE BRAUNWALD, M.D., AND BLASE A. CARABELLO, M.D.

SUMMARY Amrinone has been shown to exhibit a potent inotropic effect in patients with heart failure secondary to congestive cardiomyopathy, but its effects on myocardial oxygen consumption (MVO₂) and coronary blood flow (CBF) are unknown. Accordingly, the hemodynamic, myocardial metabolic and ECG responses to amrinone (2.5 mg/kg i.v. over 1 hour) were measured in nine patients with congestive heart failure secondary to coronary artery disease. Increases were observed in cardiac index (1.3 ± 0.4 to 2.2 ± 0.7 l/min/m²) and left ventricular stroke work (10.6 ± 3.0 to 19.2 ± 6.3 g-m/m²), and decreases in mean pulmonary wedge (31 ± 5 to 26 ± 4 mm Hg), mean pulmonary artery (44 ± 8 to 36 ± 7 mm Hg) and mean right atrial pressures (18 ± 4 to 10 ± 4 mm Hg), myocardial arteriovenous oxygen difference (129 ± 19 to 109 ± 17 ml/l), CBF (215 ± 117 to 178 ± 84 ml/min) and MVO₂ (27 ± 14 to 19 ± 9 ml/min). All changes were significant (p < 0.01). No significant changes occurred in aortic mean pressure, heart rate, myocardial lactate extraction or ECG, and no patient developed angina. In explaining the decline in MVO₂, it is possible that the increase in contractility was more than offset by the reductions in preload and afterload. The amrinone-induced hemodynamic improvement in patients with congestive heart failure secondary to coronary artery disease was associated with reductions in MVO₂ and CBF and no evidence of myocardial ischemia.

AMRINONE, a bipyridine derivative, exerts a strongly positive, inotropic action in a variety of in vitro and in vivo preparations.1, 2 In experimental models of congestive heart failure, amrinone consistently elevated cardiac output and lowered ventricular filling pressure.2 Amrinone's mechanism of action has not been established. Its inotropic action is not blocked by propranolol or modified by pretreatment with reserpine. It apparently does not alter adenosine 3'-5'-cyclic monophosphate, phosphodies- terase or Na⁺-K⁺-activated adenosine triphosphatase activity in cardiac muscle.1, 2

We previously reported the hemodynamic effects of amrinone in a group of patients with nonischemic congestive cardiomyopathy.3 Amrinone consistently raised cardiac output and left ventricular peak dP/dt, while reducing both right and left ventricular filling pressures. Acute intravenous administration of this agent caused no discernible adverse effects. These findings have been corroborated.4 A major concern, however, has been that administration of such a potent inotropic agent might be deleterious in patients with congestive heart failure in the setting of extensive coronary artery disease. An increase in contractility, if accompanied by a rise in myocardial oxygen consumption (MVO₂), might precipitate myocardial

From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts.

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Dr. Grossman is an Established Investigator of the American Heart Association.

Address for correspondence: William Grossman, M.D., Department of Medicine, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115.

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