Aggravation and Provocation of Ventricular Arrhythmias by Antiarrhythmic Drugs

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SUMMARY Antiarrhythmic drugs may aggravate or even induce ventricular arrhythmias. This type of adverse reaction is becoming more prevalent as the use of antiarrhythmic agents becomes more widespread. In a retrospective analysis of antiarrhythmic drug action, a worsening of arrhythmia was observed in 80 of 722 (11.1%) antiarrhythmic drug tests in 53 of 155 patients being treated for ventricular tachyarrhythmias. Aggravation of arrhythmias was defined by occurrence of a fourfold increase in the frequency of ventricular premature complexes, a 10-fold increase in repetitive forms, or the first emergence of sustained ventricular tachycardia coincident with time course of action of the particular drug under study. Such aggravation was noted with each of nine drugs tested: quinidine, procainamide, disopyramide, propranolol, metoprolol, aprindine, mexiletine, tocainide and pindolol. The frequency of this complication for a specific drug ranged from 5.9–15.8%. Blood drug concentrations were consistently in the therapeutic range. A study of the variability of ventricular arrhythmia during 48-hour Holter monitoring and exercise stress testing in no instance showed arrhythmia enhancement commensurate with that defining aggravation.

Our data suggest that this potentially serious complication is not readily predictable and requires a systematic approach to antiarrhythmic drug testing before a patient is prescribed a long-range maintenance program.

THE MEDICAL MANAGEMENT of patients with serious ventricular arrhythmias is a challenging problem. Frequently, drug therapy fails to control the disordered rhythm, even when "therapeutic" blood levels have been achieved. Less well appreciated is the potential of antiarrhythmic drugs to aggravate and even provoke arrhythmias. Quinidine in therapeutic doses may induce ventricular tachycardia (VT) and ventricular fibrillation (VF), but few studies implicate other antiarrhythmic agents in the precipitation of these potentially life-threatening disorders. Adverse effects have usually involved idiosyncratic reactions or have been associated with toxic levels of drug.

The problem of adverse antiarrhythmic drug reactions is of growing clinical importance. The introduction of precise monitoring methods to expose the presence of ventricular ectopic activity, as well as the association of such arrhythmia with a heightened risk for sudden cardiac death, compels the physician ever more frequently to prescribe these drugs. An increase in drug-induced complications therefore is to be expected. The majority of untoward effects are readily recognizable; but this is not the case when the very arrhythmia being treated is enhanced rather than suppressed. Recognition is further complicated by the fact that the ventricular arrhythmia is sporadic. When more or worse ectopic activity emerges, it is unclear whether an ineffective agent has been chosen, an inadequate dose has been administered, or the augmented arrhythmia is the result of random variability.

Our policy of discontinuing all drugs in patients with arrhythmias who are admitted to hospital has highlighted this problem. In some patients, ventricular ectopic activity completely stopped when antiarrhythmic drugs were discontinued. The present retrospective study is prompted by this observation and aims to determine the frequency of this phenomenon with many of the antiarrhythmic agents being used and to suggest an approach for recognizing these potentially life-threatening complications.

Materials and Methods

The study population consisted of 155 consecutive patients referred because of ventricular arrhythmias. One hundred twenty-eight males and 27 females, average age 53 years (range 16–78 years), were studied. Ninety-seven patients had coronary heart disease, 19 cardiomyopathy, 12 valvular heart disease, and 22 no demonstrable heart disease. Five patients had congenital heart disease, including one with a prolonged QT syndrome. The presenting arrhythmia was VF in 65 patients, VT in 55, and symptomatic ventricular premature complexes (VPCs) without repetitive forms in 35.

After hospital admission and a 24–48-hour washout period off antiarrhythmic drugs, three phases of study were conducted. Phase 0 consisted of a 48-hour control period to determine the prevalence of arrhythmia while the patient was not taking antiarrhythmic agents. Digitalis drugs to treat cardiac decompensation were continued. During this phase, Holter monitoring was carried out, as was maximal symptom-limited exercise testing on a motorized treadmill. Phase I consisted of a series of acute drug tests with various antiarrhythmic agents to assess drug efficacy, as previously described. Phase 2 involved administration, for 48 hours, of a drug proved to be effective during phase 1 to establish whether a main-
The antiarrhythmic drug dosages used in phases 1 and 2 are summarized in Table 1. During acute drug testing, usually half of the usual daily maintenance dose of the antiarrhythmic agent was given as a single dose. During phase 2 testing, the selected drug was administered at a fixed dosing schedule for 48 hours. In the case of tocainide and mexiletine, the dose was increased at daily intervals based on antiarrhythmic response, development of side effects, or changes in PR interval or QRS complex duration. During the initial 24 hours, aprindine was given in a total dose of 400 mg and maintained at 100–200 mg daily. The emergence of a therapeutic or toxic end point, in some patients, required 96 hours of drug administration.

A total of 722 phase 1 and phase 2 tests were evaluated for aggravation of antiarrhythmic drug action. Three criteria were accepted as evidence of drug-induced aggravation of arrhythmia: (1) A fourfold increase in the hourly frequency of VPCs compared with the control period; (2) A 10-fold increase in the hourly frequency of repetitive forms (couplets or ventricular tachycardia) compared to the control period; or (3) the first occurrence of sustained VT not present during control studies. VT was defined as sustained if it lasted for 1 minute or longer.

The initial frame of reference for judging aggravation of arrhythmia during phase 1 testing was the control period of 30 minutes before drug administration, consisting of continuous trendscription recording.\textsuperscript{18} For a drug to be implicated during phase 1, three other criteria had to be met: (1) The increase in ventricular arrhythmia had to occur at least 1 hour after drug administration; (2) augmentation of arrhythmia had to be sustained for at least 60 minutes; and (3) the level of arrhythmia judged to represent aggravation should not have occurred during 48-hour monitoring or maximal exercise stress testing of phase 0.

In the case of phase 2 testing, the initial 48 hours of monitoring and the exercise tolerance test performed while the patient was without antiarrhythmic drugs constituted the control period. Repeat monitoring and exercise testing were compared to these same studies obtained during the control period. A drug was considered to exhibit arrhythmia aggravation if criteria were met during either monitoring or exercise.

### Determination of Variability of Ventricular Arrhythmia

The spontaneous variability in prevalence of ventricular ectopic activity is critical. Judgment as to drug-induced aggravation was based on a comparison of pre- to postdrug monitoring intervals. The presence of variability equal to that constituting the criteria for aggravation necessarily would confound the data and preclude a meaningful conclusion. Thus, we examined the incidence of VPCs and repetitive forms during a control 24-hour monitoring session. For each patient the mean number of hourly VPCs and repetitive forms, standard deviation and standard error of the mean were calculated. The coefficient of variation (CV) for VPCs and repetitive forms for each patient was determined as sp/mean. To assess whether spontaneous variation in frequency of ventricular arrhythmia could account for the enhancement ascribed to drug action, two groups were compared for variability in ventricular ectopic activity. Group 1 consisted of 78 patients who had not shown aggravation of arrhythmia with any of the drugs, and group 2 consisted of 32 patients who had shown aggravation of arrhythmia. A coefficient of variations for VPCs and repetitive forms for each group was determined. The two groups were compared to each other as to mean hourly frequency of VPCs and repetitive forms. A comparison of the coefficient of variations between the two groups was also determined.

Bloods for serum drug levels were obtained from each patient at the time that aggravation of arrhythmia was observed. In the case of mexiletine, tocainide, aprindine, propranolol and pindolol, determinations were carried out by the sponsoring drug company.* Quinidine, procainamide and disopyramide assay determinations were performed by established methods.\textsuperscript{19–21} Additional statistical analysis was performed by the \textit{t} test for paired values and chi-square test with Yates correction. Significance was considered to be $p < 0.05$. Values are mean ± SEM.

### Results

Aggravation of ventricular arrhythmia was noted in 80 of the 722 drug tests (11.1%). Among the 155 patients, at least one drug worsened the arrhythmia in 53 patients (34.2%) (42 males and 11 females, average age 51 years, age range 17–76 years). The distribution

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*Mexiletine, Boehringer Ingelheim, Ltd.; tocainide, Astra Pharmaceuticals; aprindine, Eli Lilly & Company; propranolol, Ayerst Laboratories; and pindolol, Sandoz, Inc.
of cardiac diagnoses is listed in Table 2. There was an equivalent prevalence of patients who experienced aggravation among the 34 whose presenting mechanism was frequent VPCs compared with the 120 patients whose referral was for malignant ventricular arrhythmia. Thus, in the former there were 10 patients (expected 12); of the latter group there were 43 (expected 41). A difference was noted when patients presenting with VT were compared with those with VF. Thus, aggravation of arrhythmia was observed in 25 patients with VT (expected 19), and in 18 patients with VF (expected 22); however, the difference was not significant ($p > 0.05$).

During phase 1, the worsening of arrhythmia was recorded in 51 of 476 tests (10.7%). In 246 phase 2 maintenance tests, 29 (11.8%) demonstrated arrhythmia aggravation; of these, 14 were noted in the 24-hour monitoring, two occurred during exercise (sustained VT in both) and the remaining 13 were recorded during both procedures (Fig. 1).

In all of these cases, phase 1 study had not been performed before phase 2. During phase 1, the enhancement of arrhythmia was observed after the expected onset of drug effect, and this consistently correlated with the known time course of drug action (Table 3). The severity of arrhythmia gradually increased and then progressively abated in parallel with the presumed changes in serum drug concentration. In no instance were blood levels in a toxic range at the time of arrhythmia aggravation (Table 3).

In eight studies (10.0%), there was a fourfold increase in VPC frequency; in 31 studies (38.7%), a 10-fold increase in repetitive forms; and in 41 studies (51.3%), the emergence of VT. The VT had not been previously observed in 18 patients during 23 of the 41 drug testing studies demonstrating VT. The drugs involved and the frequency of this complication with each are shown in figure 2 and ranged from 5.9-15.8%.

**Table 2. Characteristics of Patients with Aggravation of Arrhythmia**

<table>
<thead>
<tr>
<th>Type of heart disease</th>
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<td>Coronary</td>
<td>32</td>
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<td>Valvular</td>
<td>6</td>
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<tr>
<td>Cardiomyopathy</td>
<td>2</td>
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<tr>
<td>Congenital</td>
<td>3</td>
</tr>
<tr>
<td>Prolonged QT syndrome</td>
<td>1</td>
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<tr>
<td>None demonstrable</td>
<td>10</td>
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</table>

Quinidine had an incidence of aggravation of 15.4%. Procainamide, not thought to be arrhythmogenic, was associated with aggravation in 9.9%. In 38 patients, arrhythmia was aggravated by one drug only; in 15, multiple drugs aggravated the arrhythmia (Table 4). During our earlier studies, eight patients were rechallenged with the antiarrhythmic drug that caused aggravation because it was initially unclear whether the augmented arrhythmia was drug related or merely the result of random variability. In each case, arrhythmia again worsened.

The results with quinidine deserve additional com-

**FIGURE 1. (A) Control period of an acute quinidine test. Frequent ventricular premature complexes and occasional couplets are provoked by exercise. (B) Three hours after 600 mg of quinidine. Ventricular tachycardia occurs spontaneously at rest. Exercise to the same heart rate as during control provokes ventricular tachycardia that lasts 60 seconds. ETT = exercise treadmill test; HR = heart rate.**
TABLE 3.  Time of Onset of Aggravation of Arrhythmia After Drug Administration and the Serum Drug Level at the Time of Its Occurrence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time of onset</th>
<th>Average drug concentration (μg/ml)</th>
<th>Therapeutic concentration (μg/ml)</th>
</tr>
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<tbody>
<tr>
<td>Quinidine</td>
<td>(A) 131 minutes (60–180)*</td>
<td>3.1 (1.1–5.0)</td>
<td>2–5.5</td>
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<td>(B) 228 minutes (195–240)*</td>
<td>8 (5.9–10.5)</td>
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<tr>
<td>Procaainamide</td>
<td>105 minutes (75–120)</td>
<td>3.5 (3.4–3.6)</td>
<td>2–5</td>
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<tr>
<td>Disopyramide</td>
<td>110 minutes (60–150)</td>
<td>30 (19–41)</td>
<td>Variable</td>
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<tr>
<td>Propranolol</td>
<td>137 minutes (60–165)</td>
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<tr>
<td>Metoprolol</td>
<td>100 minutes (60–120)</td>
<td>0.6 (0.4–0.9)</td>
<td>0.7–1.6</td>
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<tr>
<td>Mexiletine</td>
<td>100 minutes (60–120)</td>
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<tr>
<td>Tocainide</td>
<td>96–120 hours</td>
<td>8.6 (5.3–15)</td>
<td>6–30</td>
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<tr>
<td>Aprindine</td>
<td>60–120 minutes (i.v.)</td>
<td>1.16 (0.36–2.10)</td>
<td>1–2</td>
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<td>72–120 hours (oral)</td>
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<tr>
<td>Pindolol</td>
<td>105 minutes (75–135)</td>
<td>66.8 (43.9)</td>
<td>Variable</td>
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Values in parentheses are ranges.
*Two patterns were observed: Type A represented a progressive increase in ectopy and B was a rebound aggravation of arrhythmia.

The most frequent pattern of aggravation — a progressive increase in ectopic activity — was observed in 15 tests. However, a second pattern occurred in five studies which we termed "rebound aggravation." At 1–2 hours after oral administration, arrhythmia was suppressed, but at 2–4 hours there was an abrupt exacerbation to a level of ectopic activity far in excess of that observed during the control period, which met the criteria for arrhythmia aggravation (fig. 3). At the time of this rebound, drug levels were within a therapeutic range, but lower than the peak levels obtained at the time of arrhythmia suppression.

Electrocardiographic changes coincident with aggravation were infrequent and occurred only in six patients receiving quinidine. The QT interval was lengthened significantly in these six cases, from 0.40 to 0.49 second (p < 0.01); in four tests the QT exceeded 0.52 second. An adverse arrhythmic response with a drug from one class in no way predicted the action of other agents with similar electrophysiologic properties. Thus, of the 20 patients in whom quinidine aggravated arrhythmia, 13 were successfully treated with another membrane-active drug (disopyramide, procaainamide, tocainide, mexiletine or aprindine), and seven were treated with a β-adrenergic blocking agent (propranolol or metoprolol). Of 16 patients who showed enhancement of arrhythmia with one β-blocking drug, in three a similar drug was without adverse effect, while in 12 a membrane-active drug controlled the arrhythmia without complication.

**Variability of Arrhythmia**

The variability in VPCs and repetitive forms during 24-hour Holter monitoring was determined in two groups. The first, consisting of 78 patients, had symptomatic ventricular arrhythmia but no drug-induced aggravation of arrhythmia. Mean hourly VPC frequency was 547 ± 57 (CV 0.34 [range 0.05–0.95]) (fig. 4). The mean number of hourly repetitive forms was 5.4 ± 1.5 (CV 0.64 [range 0.004–2.0]). Group 2, composed of 32 patients with aggravation of arrhythmia, had a mean hourly VPC frequency of 523 ± 54 (CV 0.30 [range 0.17–0.59]). The mean rate of repetitive forms was 10.1 ± 4.1 per hour (CV 0.85 [range 0.05–1.40]). The variability in arrhythmia during monitoring hours was not different between these two groups (p > 0.05). At a confidence level of 99% the greatest increase in VPC frequency based on random variability is 72% and greatest increase in frequency of repetitive forms is 194%. However, the increase in ar-
**Figure A**

- **Control:**
  - Rest: Grade 2
  - Exercise: Grade 4
  - Post Exercise: Grade 4

- **2 Hours:**
  - Rest: Grade 2
  - Exercise: Grade 4
  - Post Exercise: Grade 2

**Figure B**

- **4 Hours:**
  - Rest: Grade 2
  - Exercise: Grade 4
  - Post Exercise: Grade 4

**Legend:**
- LEVEL: 2.2 μg/ml
- 15 sec

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rhythmia required to meet criteria for aggravation were strikingly different from the spontaneous variability encountered during 24-hour Holter monitoring. Thus, the compared variability had a p value of < 0.001 for VPCs and < 0.001 for repetitive forms (fig. 5).

**Discussion**

The present study documents that nine currently used antiarrhythmic drugs, with blood levels at presumed therapeutic concentrations, worsened ventricular arrhythmia. They caused a spectrum of adverse responses, ranging from augmentation of VPC frequency to potentially malignant VT. The incidence of this serious drug complication has not been established. In our series, aggravation of arrhythmia was noted in 11% of drug tests and in 34% of patients who had been treated with multiple antiarrhythmic agents. This frequency probably understates the magnitude of the problem. Criteria for aggravation selected were stringent so as to preclude confounding by the random variability in the incidence of ventricular arrhythmia. No single drug was completely free of this type of adverse reaction. The presence or absence of heart disease, the degree of cardiac impairment, the type of ventricular arrhythmia or the response to other antiarrhythmic agents gave no clues to the likelihood of this complication. Of the commonly used antiarrhythmic agents, only quinidine has been implicated as a cause of ventricular tachyarrhythmia in the absence of either other toxic manifestations or of elevated blood levels. Numerous case reports of paroxysmal VT and VF in patients taking quinidine (quinidine syncope) have appeared since this adverse reaction was first described in 1921. Rarely has quinidine-induced syncope been found in patients being treated for ventricular ectopic activity. In the largest review of this quinidine complication, Reynolds and Vander Ark²⁷ reported that in 59 of 61 patients, quinidine had been administered for control of atrial arrhythmias. This may have been related to the concomitant use of digitalis glycosides. However, Koster and Wellens¹ recorded the occurrence of quinidine syncope in three patients who had not received digitalis drugs.

Procainamide has received considerably less attention than quinidine as a potentially arrhythmogenic drug. Castellanos and Salhanick²⁸ noted widening of the QRS complex and VF after 700 mg of procainamide administered intravenously over a 28-minute period to a 63-year-old man in an attempt to terminate VT. McCord and Taguchi¹ reported the occurrence of short paroxysms of VT in two of 25 pa-

**TABLE 4. Drugs Involved in Patients Who Had Aggravation with Two or More Drugs**

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Quin = quinidine; PCA = procainamide; Diso = disopyramide; Apr = aprindine; Mex = mexiletine; Toc = tocinide; Prop = propranolol; Metop = metoprolol; Pind = pindolol.

**FIGURE 3.** (A) Quinidine drug test. Arrhythmia is not present at rest, but two brief salvos of ventricular tachycardia are provoked by exercise. Two hours after drug administration, arrhythmia is suppressed. (B) "Rebound" aggravation of arrhythmia 4 hours after quinidine. Frequent paroxysms of ventricular tachycardia occur at rest and the duration of paroxysm is increased during exercise and in the exercise recovery period. The drug level is lower than that at 2 hours, but still in a therapeutic range.
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FIGURE 4. Average variability of ventricular premature complexes (VPCs) in 110 patients. The mean number of VPCs/hour and the standard error of the mean for each third hour during the 24-hour control monitoring are shown. There was no difference in variability between group 1 (coefficient of variations 0.34) and group 2 patients (coefficient of variations 0.30) (p > 0.05).

patients receiving procainamide for control of atrial arrhythmias. Epstein28 reported VF in three patients after i.v. procainamide. Though procainamide and quinidine have similar electrophysiologic properties, there are few reports of arrhythmogenic complications with procainamide, in contrast to quinidine. Another so-called membrane-stabilizing agent, disopyramide, though only recently introduced, has already been implicated in the provocation of malignant ventricular arrhythmias in some case reports.9, 10, 80 Propranolol, the most widely used of the β-adrenergic blocking drugs, has been recorded only once to have caused this complication.81 No information is available on the arrhythmic effects of the other five agents tested in the present study.

The conclusion that antiarrhythmic drugs in current use may be progenitors of ventricular arrhythmia depends on a temporal comparison between the prevalence of ectopic activity during a control interval and during the period of presumed drug action. Morganroth et al.92 and Winkle93 argued that because of the intrinsic variability in incidence of ventricular arrhythmia, no brief monitoring period, even when extending to 24 hours, permits judgment of drug action unless substantial changes are recorded.92, 93 A critical question is whether random variability may account for the observed changes in our study. Several reasons make such a conclusion improbable. First, the emergence and subsidence of arrhythmia aggravation closely paralleled the known pharmacokinetics of the particular drug. Second, the criteria selected for assessing aggravation of arrhythmia were not encountered in these patients during extensive control monitoring. Indeed, the average hourly variability of VPCs in this population was only 30% and a 13-fold increase was required to meet the criterion of aggravation. In the case of repetitive forms, the observed variability was less than threefold, while the criterion for aggravation demanded a 10-fold increase. Third, in patients who had lessening of arrhythmia during a phase 2 study, only discontinuation of the agent being tested resulted in return to baseline arrhythmia levels. For these reasons, we believe that the augmentation in ventricular ectopic activity is the result of adverse drug action and not the consequence of sporadic ventricular ectopic variability.

It may be questioned whether the enhancement of arrhythmia that we observed is largely the result of our method of drug usage; specifically, the acute drug testing.12, 15, 16 In this test, a single large oral dose of an antiarrhythmic drug is administered. However, 40% of the aggravation of arrhythmia was noted during phase 2 testing, during which customary maintenance doses were administered. Likewise, aggravation of arrhythmia occurred with equal prevalence during both phases; 10.7% of phase 1 studies and 11.8% of phase 2 studies. Doses in phase 1 testing of procainamide, disopyramide, propranolol and mexiletine are not exceptional and have been prescribed in maintenance regimens. Also, the blood levels reached with the dosing schedules in the present study were consistently within a therapeutic range. Furthermore, there appeared to be a dissociation between cardiac and generalized toxicity, for few if any other adverse reactions were encountered, though these are common with antiarrhythmic drugs. These considerations indicate that the augmentation of arrhythmia was not due to the method of drug dosing, but rather, was the result of unique drug-patient interaction.

This study would have been enhanced had we been able to rechallenge each patient who exhibited what was considered a drug-induced arrhythmia aggravation. This was accomplished in eight patients, and the arrhythmia worsened in each. However, in a retrospective analysis, one does not have the option of rechallenging all patients. Were it possible to do so, one would confront serious ethical problems. The objective of administering an antiarrhythmic drug is to control a disordered heart rhythm. There is no medical

Figure 5. The average coefficient of variations of ventricular premature complexes (VPCs) and repetitive forms in the 110 patients compared with the criteria for aggravation of arrhythmia used in this study (fourfold increase in VPC frequency or 10-fold increase in repetitive forms). The aggravation is greater than can be accounted for by random variability.
justification for exposing the patient to an ineffective drug, especially when it may have been implicated in an adverse reaction.

The electrophysiologic basis for antiarrhythmic drug arrhythmogenesis in man is not known. In animal models, Fabargas and co-workers showed that procainamide in “therapeutic” concentrations (4–9 µg/ml) can incite ventricular echo beats by favoring reentry within the atroventricular node. Procainamide is also known to depress conduction and enhance refactoriness in the His-Purkinje network and may therefore favor reentry within this system as well. The electrophysiologic action of the membrane stabilizing drugs is to slow conduction through the His-Purkinje system and ventricular muscle, decreasing membrane excitability and responsiveness. In certain situations, this may result in an enhancement of reentry and an increase in ventricular ectopy. Catecholamines speed conduction through the ventricular myocardium. The β-blocking drugs, by preventing this action, may favor disparity in conduction velocity and thereby predispose to reentry. These speculations leave unaccounted the clinical fact that drugs with nearly identical electrophysiologic properties have markedly dissimilar actions. Thus, in some patients in the present study, while a membrane-stabilizing drug like procainamide aggravated the arrhythmia, disopyramide suppressed the arrhythmia; quinidine was without therapeutic or toxic effect. These findings suggest either the existence of as yet undiscovered electrophysiologic differences or that these drugs exert distinctive metabolic effects that cause their diverse clinical actions.

Ventricular arrhythmias are being observed more frequently because of the increasing use of ambulatory monitoring and exercise stress testing. The clinical objective is to identify the patients at risk for sudden death. Once a patient is found to have advanced grades of VPCs, treatment is instituted for their suppression by the use of an ever-increasing number of antiarrhythmic agents. The possibility that these drugs may, instead of suppressing, augment ventricular arrhythmia remains inadequately documented. It constitutes a significant threat to the patient with arrhythmias and no doubt has already accounted for preventable iatrogenic fatalities.

The very occurrence of such a complication eludes ready recognition, represents a highly individual response and is tantamount to an idiosyncratic reaction. The clinician is therefore without clues for identifying the susceptible patient. This phenomenon is of sufficient frequency, mandating prompt action whenever an unexpected augmentation in ventricular arrhythmia occurs while a patient is receiving antiarrhythmic drugs. While there exists no easy method for predicting individual risk, the methods of antiarrhythmic drug usage used in the present study is one approach for identifying some of the susceptible patients.

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The Effects of a Cardioselective (Metoprolol) and a Nonselective (Propranolol) Beta-adrenergic Blocker on the Response to Dynamic Exercise in Normal Men

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SUMMARY We compared the effects of a cardioselective β-adrenergic blocking drug, metoprolol, with a nonselective β-adrenergic blocker, propranolol, on the response of 10 normal men to dynamic treadmill exercise. The volunteers underwent a standard graded exercise test to exhaustion while receiving placebo; propranolol, 40 mg every 6 hours; propranolol, 80 mg every 6 hours; metoprolol, 50 mg every 6 hours; or metoprolol, 100 mg every 6 hours. The drugs were given in a double-blind fashion for 48 hours before exercise. Five days were allowed between successive drug administrations and the order of drug administration was randomized. Heart rate, arterial pressure, oxygen consumption, minute ventilation and CO2 production were monitored. Plasma drug concentrations were measured at the time of exercise. Judged by plasma levels, propranolol was about three times more potent than metoprolol in attenuating heart rate. Both drugs produced a wide variation in plasma levels after a given oral dose, and both drugs attenuated the systolic blood pressure response to exercise. Neither drug affected diastolic blood pressure or maximum oxygen consumption, maximum minute ventilation or the anaerobic threshold. We conclude that there is no evidence that the cardioselective drug metoprolol is superior to propranolol in terms of the ability to perform or respond to short-term maximal exercise. In addition, the fact that maximal oxygen consumption and the anaerobic threshold were unaffected implies that fatigue during exercise while on β-adrenergic blocking drugs is not due to an effect of these drugs in limiting blood flow to the exercising extremities.

THE β-ADRENERGIC blocking drugs propranolol and metoprolol are used widely in the treatment of patients with hypertension, ischemic heart disease and a variety of other conditions. Metoprolol is cardio-selective, presumably avoiding the unnecessary and undesirable effects of β-adrenergic blockade in the lung and peripheral vasculature. Patients with reactive airway disease may thus tolerate metoprolol therapy better than propranolol.

However, it is not clear whether there is any advantage of cardioselective, β1-adrenergic blockade in preserving the ability to perform or respond to exercise.1-7 The cardiac effects of metoprolol and propranolol should be similar at equipotent doses, but during exercise the sympathetic nervous system is activated and epinephrine is released from the adrenal medulla. In the presence of peripheral, β2-adrenergic blockade produced by propranolol, circulating epinephrine can produce unopposed, α-adrenergically mediated vasoconstriction in skeletal muscle.8 This
Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs.
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