Reversal of Proarrhythmic Effects of Flecainide Acetate and Encainide Hydrochloride by Propranolol

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The use of membrane-active antiarrhythmic agents may be complicated by aggravation of existing arrhythmias or development of new drug-induced arrhythmias. Four patients, referred because of out-of-hospital cardiac arrest or symptomatic sustained ventricular tachycardia, were receiving class IC antiarrhythmic agents in an attempt to prevent inducibility of sustained ventricular tachycardia. New or worsening spontaneous arrhythmias developed while they were on flecainide acetate (n=3) or encainide hydrochloride (n=1) therapy. Spontaneous runs of rapid nonsustained and sustained ventricular tachycardia developed in two. Increased frequency of premature ventricular contractions and repetitive forms of ventricular ectopic activity developed in one, despite the fact that inducibility of sustained ventricular tachycardia had been prevented. Salvos and nonsustained ventricular tachycardia developed in the fourth patient. Propranolol had failed to prevent inducibility of sustained ventricular tachycardia during previous programmed stimulation studies in three of the four patients, but it reproducibly suppressed drug-induced arrhythmias that appeared only after administration of the IC agents in each patient. Suppression of the proarrhythmic effects by β-adrenergic blockade suggests a possible interaction of these drugs with autonomic function in the genesis of the observed proarrhythmic effects. Direct pharmacologic control of proarrhythmic drug effects has not previously been reported. (Circulation 1989;80:1571–1579)

The use of antiarrhythmic drugs is limited by the risk of inducing or aggravating arrhythmias,1–7 in addition to their potential metabolic and toxic side effects. The manifestation of “proarrhythmic effects” of these agents may be only an increase in the frequency of premature ventricular contractions (PVCs) or induction of repetitive forms. However, they also may provoke malignant ventricular arrhythmias such as torsades de pointes, ventricular fibrillation (VF), or resistant uniform morphology rapid ventricular tachycardia (VT). Among nine patients in whom proarrhythmic events developed during dose titration of class IC antiarrhythmic agents for treatment of inducible sustained ventricular tachycardia, four patients were tested with propranolol in an attempt to suppress the proarrhythmic events. The drug-induced arrhythmias were suppressed by propranolol in all four of the patients tested.

Methods

The patients included in this report were referred to the University of Miami/Jackson Memorial Medical Center for management of potentially lethal cardiac arrhythmias. Each patient was admitted to the coronary care unit, which had a monitoring system with capacity for full storage and recall of anomalous impulses and editing capability allowing the generation of edited 8-hour trend records (CAMS, American Optical, Bedford, Massachusetts). The system has been previously documented to be more than 95% sensitive for PVC recognition,8 and the edited trend graphs can be used to estimate total ectopic impulse frequency (impulses/min), from which hourly or daily mean frequencies can be calculated.
TABLE 1. Patients Tested for Effects of β-Adrenergic Blockade on Proarrhythmic Responses to Class IC Drugs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/gender</th>
<th>Structure/presentation</th>
<th>EF (%)</th>
<th>Baseline PVC forms* (no drugs)</th>
<th>Drug (dosage)</th>
<th>PVC forms</th>
<th>IC drug + propranolol (PVC forms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63/M</td>
<td>LVH/CA</td>
<td>45</td>
<td>A</td>
<td>F (150 q12h)</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>62/M</td>
<td>CAD/CA</td>
<td>30</td>
<td>A</td>
<td>F (150 q12h)</td>
<td>E</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>63/M</td>
<td>CAD/VT</td>
<td>20</td>
<td>A</td>
<td>E (25 q8h)</td>
<td>E</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>79/M</td>
<td>CM/VT</td>
<td>35</td>
<td>A</td>
<td>F (100 q12h)</td>
<td>D</td>
<td>A</td>
</tr>
</tbody>
</table>

Forms of ventricular ectopy: Class A, single, unifocal premature ventricular contractions (PVCs); class B, single, multifocal; class C, couplets, salvos (2–5); class D, nonsustained ventricular tachycardia (VT) (6 impulses, less than 30 seconds); class E, sustained VT (more than 30 seconds). EF, ejection fraction; LVH, left ventricular hypertrophy; CA, cardiac arrest; CAD, coronary artery disease; VT, sustained VT; CM, nonischemic cardiomyopathy; F, flecainide; E, encainide.

Patients were initially monitored for up to 48 hours off of antiarrhythmic agents to calculate baseline spontaneous arrhythmia frequency (number of ectopic impulses) and forms (e.g., singles, couplets, salvos, nonsustained VT), and then underwent invasive electrophysiologic testing to determine baseline inducibility of sustained VT or VF. The induction protocol included incremental pacing and programmed stimulation using up to three extrastimuli at up to two drive cycle lengths (between 600 and 400 msec) from up to two right ventricular pacing sites (apex and outflow tract). All patients were reproducibly inducible into their clinical tachycardia at baseline study and then underwent at least one intravenous drug trial of procainamide, lidocaine, or propranolol. Each patient subsequently received one or more oral preparations, including a class IC antiarrhythmic agent (flecainide, three; encainide, one).

Propranolol was administered intravenously to one patient whose drug-related arrhythmia was a rapid, poorly tolerated sustained VT that repeatedly recurred after DC cardioversion. It was given orally to the patients in whom increased frequency of PVCs developed, with new salvos, nonsustained VT, or well-tolerated sustained VT. The oral protocol consisted of a single oral dose of 40 mg propranolol, followed by a regimen of 20–60 mg q6h by dose titration. The intravenous protocol consisted of 1-mg boluses given at 1-minute intervals until the arrhythmia was suppressed. Efficacy of propranolol was defined as follows: 1) eradication of spontaneous sustained VT, 2) 100% suppression of new salvos or nonsustained VT, and 3) reduction of PVC frequency to levels present before proarrhythmic manifestations. Clinical effect of the β-adrenergic blocker was defined as a reduction of baseline sinus rate by at least 15% and to less than 70 per min and more than 15% reduction in systolic blood pressure. The first patient in the series was treated empirically; subsequent patients were tested on propranolol based on a prospective trial plan.

For patients tested on flecainide, plasma concentrations of the drug were measured at times noted in the "Results" by a fluorescence polarization immunnoassay technique, using the Abbott TDx instrumentation. Plasma concentrations of propranolol were measured with high-performance liquid chromatography with an ultraviolet detector.

Results

During a 2 1/2-year period, spontaneous proarrhythmic events were observed in nine in-hospital patients evaluated for the effect of a class IC antiarrhythmic drug on inducible VT and VF. In four patients (three receiving flecainide and one receiving encainide after previously receiving flecainide; see Table 1), propranolol was administered in an attempt to suppress the new spontaneous proarrhythmic events, and in each it was successful. In the other five, the class IC drug had been stopped at the option of the primary physician or because of restrictions in a study protocol without an attempt to control the proarrhythmic event pharmacologically. Details of each of the four patients managed by β-adrenergic blockade follow.

Patient 1

N.C., a 63-year-old man, was referred to the University of Miami/Jackson Memorial Medical Center after surviving out-of-hospital cardiac arrest. He had had no known history of heart disease, and a rapid heart rate and weakness had developed while he was playing tennis. Emergency rescue personnel recorded sustained VT, which degenerated to VF, and he was immediately defibrillated.

Cardiac catheterization revealed minor coronary artery disease, an ejection fraction of 45%, and left ventricular hypertrophy. A treadmill stress test did not induce arrhythmias. During programmed electrical stimulation, sustained VT was reproducibly induced by two extrastimuli (see Figure 1A). Intravenous procainamide (900-mg infusion with a 2-mg/min continuous drip) failed to prevent VT induction but increased the tachycardia cycle length. The
peak plasma concentration was 12.8 μg/ml. Addition of 10 mg propranolol i.v. had no effect. After administration of oral procainamide to a plasma concentration of 11.0 μg/ml, the patient remained inducible, and addition of lidocaine (75-mg bolus, 2-mg/min infusion) had no effect (see Figure 2 for flow diagram). Flecainide acetate (100 mg q12h) was started and increased to 150 mg q12h after 48 hours. Repeat programmed stimulation (plasma level, 810 ng/ml) revealed that VT could no longer be induced, even with a more aggressive protocol (drive cycle length, 400 msec; three extrastimuli; see Figure 1B). Continuous bedside monitoring while the patient was off of antiarrhythmic drug therapy, during administration of procainamide, propranolol, and lidocaine, and during initiation of flecainide therapy revealed mean daily PVC frequencies of 5 or less PVCs/min and no repetitive forms (see Table 1 and Figure 3A), with minimal variation in day-to-day PVC frequency (Figure 2). The mean daily heart rate during this period was 71 impulses/min. However, continuous monitoring after the higher dose of flecainide was started revealed that the heart rate had increased to 87/min and that an increasing frequency of PVCs and a new onset of repetitive forms was developing in the patient (Figure 2, compare days 1–10 with days 12–14; Figure 3, compare Panel A [no drugs] and Panel B [flecainide, 150 mg q12h]). A single 40-mg oral test dose of propranolol was administered, and the increased frequency and advanced forms of PVCs were suppressed over a 2-hour period (Figure 2, Figure 4A). After washout, the PVCs recurred, and oral propranolol (20 mg q6h) was started 1 day later. The PVCs and salvos again disappeared, and the heart rate decreased to 61/min. Both flecainide and pro-

**Figure 1.** Programmed electrical stimulation studies in patient 1. Panel A demonstrates inducibility of sustained ventricular tachycardia in absence of antiarrhythmic therapy. Initiating program included a drive cycle length of 500 msec (S2-S1), with two extrastimuli (S2-S2, S3-S3), coupled at 290 and 220 msec, respectively. Panel B demonstrates repeat study while patient was receiving flecainide acetate, 150 mg q6h (plasma level, 810 ng/ml). With a more aggressive protocol (drive cycle, 400 msec, and triple extrastimuli [S2, S3, S4] at coupling intervals of 280, 250, and 230 msec, respectively), two repetitive ventricular responses occur but no nonsustained or sustained ventricular tachycardia was induced. HRA, high right atrium; RVA, right ventricular apex.
pranolol were subsequently stopped, and only low grade PVCs persisted. On rechallenge with flecainide, the PVCs and repetitive forms reappeared, and another single 40-mg oral dose of propranolol again suppressed the arrhythmia transiently. Long-term oral propranolol was restarted (20 mg q6h) and PVCs and repetitive forms remained suppressed (Figure 4B). The patient had exercise-induced arrhythmias during treadmill testing while receiving flecainide, which a 40-mg oral dose of propranolol prevented on repeat testing on the same day. He was discharged on flecainide and propranolol therapy and has had no recurrences of VT or VF for 36 months.

Approximately 18 months after discharge, the primary physician stopped propranolol therapy for 1 month but restarted it because frequent PVCs and repetitive forms had reappeared on ambulatory monitoring. Thus, on multiple challenges, advanced forms of ventricular ectopy were observed only in the presence of flecainide and were suppressed by concomitant therapy with propranolol.

**Patient 2**

R.M., a 62-year-old man, was referred after surviving out-of-hospital cardiac arrest. He had a prior history of recurrent sustained VT associated with symptoms of hemodynamic compromise and had recurrent VT on quinidine and on tocainide therapy. During continuous monitoring, he had only low frequency unifocal PVCs and no repetitive forms more advanced than couplets. At the time of cardiac arrest, he was receiving tocainide.

Cardiac catheterization revealed three-vessel coronary artery disease and a 30% left ventricular ejection fraction. During electrophysiologic study (see Table 2), incremental pacing in the right ventricular outflow tract induced sustained VT, which accelerated into ventricular flutter (cycle length, 210 msec) and required cardioversion. After 800 mg procainamide intravenously, followed by a continuous infusion at a rate of 2 mg/min, the patient remained inducible to sustained VT (cycle length, 265 msec); the procainamide plasma level was 11.6 µg/ml. Propranolol (5 mg i.v.) was infused, and no arrhythmias were induced by triple extrastimuli delivered to both the right ventricular apex and outflow tract. The propranolol plasma level at that time was 150 µg/l. Oral propranolol (30 mg q.i.d.) was started, and the dose was titrated to 60 mg q.i.d. to achieve adequate β-adrenergic blockade. VT again was induced by triple extrastimuli delivered during a drive cycle length of 400 msec (Table 2). The VT cycle length was 220 msec, and the propranolol level at the time was 133 µg/l.

Because of failure of both procainamide and propranolol to prevent inducibility of sustained VT,
flecainide acetate was started at a dose of 100 mg q12h. The sinus rate increased progressively from a range of 65–80 impulses/min before flecainide therapy to 90–105/min during the third day, but the patient remained free of angina pectoris or clinical evidence of heart failure. After 72 hours, the trough plasma level was 300 ng/ml, and the dose was increased to 150 mg q12h. Shortly after the first 150-mg dose (Figure 5), the patient began to have frequent PVCs and runs of nonsustained VT, as well as repetitive episodes of sustained VT at a cycle length of 300 msec. The sinus rate approached 100/min between episodes of VT (Figure 5), but no chest pain occurred and no changes in baseline ST segment deviation were recorded. Because of his previously demonstrated tolerance of propranolol, a single 40-mg oral dose was given, and both the sustained VT and frequent PVCs were suppressed (Figure 6) and remained suppressed on 40 mg q6h (see Tables 1 and 2). Flecainide plasma level at the time of the arrhythmia was 600 mg/ml. When both flecainide and propranolol were stopped, the patient had only infrequent PVCs and no repetitive forms; but nonsustained VT recurred when flecainide therapy was restarted (see Table 2). The patient was inducible into a slow, stable tachycardia on this regimen (cycle length, 480 msec; see Table 2). Reinstitution of propranolol again suppressed the spontaneous arrhythmias. However, the flecainide level was 1,400 ng/ml at that time, possibly because of a propranolol-related increase in flecainide level. It was decided that the high flecainide level required to achieve a partial effect and concomitant requirement for β-adrenergic blockade did not warrant continuing this therapy. Flecainide was stopped, and the patient received an automatic implantable cardioverter-defibrillator.

**Patient 3**

E.W., a 63-year-old man with a history of myocardial infarctions 16 and 11 years previously, had an episode of symptomatic sustained VT approximately 7 months before referral to our institution. He had been managed empirically with quinidine until approximately 1 week before admission when he had a recurrent episode of sustained VT (VT-1; cycle length, 330 msec). He was admitted to another hospital and received procainamide but had another episode of sustained VT at a plasma concentration of 14 μg/ml. Procainamide therapy was stopped and he was started on flecainide therapy (100 mg q12h) and subsequently multiple episodes of a different tachycardia developed (VT-2; cycle length, 220–240 msec) that recurred after each of multiple cardioversions (Figure 7). He received 4 mg propranolol intravenously, and the tachyarrhythmia converted to nonsustained runs and then stopped. He was then transferred to our institution for further management.

During invasive electrophysiologic testing while on no antiarrhythmic drug therapy, the patient was induced into sustained VT (VT-1; Figure 7B) at a cycle length of 310 msec by two extrastimuli delivered during a drive cycle of 600 msec. He was hypotensive during the VT and was converted by burst pacing. During a trial of propranolol (11 mg i.v.), he remained inducible into VT-1 by the same protocol (plasma level, 152 μg/l); the addition of intravenous lidocaine (plasma level, 2.3 μg/ml) did not prevent inducibility. Because of failure of multiple antiarrhythmic drugs, an automatic implantable cardioverter-defibrillator was implanted and his initial postoperative course was stable. He then began having multiple episodes of sustained VT (VT-1; Figure 7) and was started on encainide therapy. After an initial 25-mg dose, PVC frequency increased from a baseline of 9±6 PVCs/hr

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**Table 2. Spontaneous and Induced Ventricular Arrhythmias and Antiarrhythmic Drugs in Patient No. 2**

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug</th>
<th>Dose</th>
<th>Level</th>
<th>Frequency of PVCs</th>
<th>Forms of PVCs</th>
<th>PES results</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/3</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Class II</td>
<td>Class A</td>
<td>I-VT</td>
</tr>
<tr>
<td>PR (i.v.)</td>
<td>800 mg</td>
<td>2 mg/min</td>
<td>11.6 μg/ml</td>
<td>Class II</td>
<td>Class A</td>
<td>I-VT (CL, 210 msec)</td>
</tr>
<tr>
<td>12/11</td>
<td>PR (p.o.)</td>
<td>60 mg q6h</td>
<td>133 μg/l</td>
<td>Class II</td>
<td>Class A</td>
<td>I-VT (CL, 220 msec)</td>
</tr>
<tr>
<td>12/15</td>
<td>FL (p.o.)</td>
<td>100 mg q12h</td>
<td>300 ng/ml</td>
<td>Class II</td>
<td>Class A</td>
<td>I-VT (CL, 220 msec)</td>
</tr>
<tr>
<td>12/16</td>
<td>FL (p.o.)</td>
<td>150 mg q12h</td>
<td>...</td>
<td>Class IV</td>
<td>Class C,D,E</td>
<td>I-VT (CL, 480 msec)</td>
</tr>
<tr>
<td>12/17</td>
<td>FL (p.o.)</td>
<td>150 mg q12h</td>
<td>600 ng/ml</td>
<td>Class II</td>
<td>Class A</td>
<td>I-VT (CL, 480 msec)</td>
</tr>
<tr>
<td>12/21</td>
<td>FL (p.o.)</td>
<td>150 mg q12h</td>
<td>660 ng/ml</td>
<td>Class IV</td>
<td>Class C,D</td>
<td>I-VT (CL, 480 msec)</td>
</tr>
</tbody>
</table>

Frequency of PVCs: Class I, less than 1/hr; class II, 1–9/hr; class III, 10–29/hr; class IV, 30/hr or more.

Forms of ventricular ectopy: class A, single, unifocal premature ventricular contractions (PVCs); class B, single, multifocal; class C, couplets, salvos (2–5); class D, nonsustained ventricular tachycardia (VT) (6 impulses, 29 seconds); class E, sustained VT (30 seconds or more).

PES, programmed electrical stimulation; PA, procainamide; CL, cycle length; PR, propranolol; FL, flecainide; I-VT, inducible ventricular tachycardia.
(mean±SD) during the 3 hours before the dose to 94±18 PVCs/hr during the 3 hours after the drug was started (Table 1). The spontaneous ventricular ectopy then decreased, and he was given a second dose of 25 mg encainide 8 hours after the first. Within 45 minutes, he began to have spontaneous episodes of sustained VT accompanied by hypotension. The tachycardias occurred at a cycle length of approximately 290–300 msec initially and then accelerated to 210–240 msec and had a sinusoidal configuration (VT-2). He was cardioverted twice, both times followed by prompt recurrence of the tachyarrhythmia. After the second cardioversion, he was given 1-mg boluses of propranolol to a total dose of 5 mg. After the second milligram, the bursts of VT became nonsustained, and after the fourth milligram, spontaneous ectopy was reduced to infrequent PVCs. Salvos and nonsustained VT recurred approximately 3 hours later. An additional 3 mg propranolol intravenously again suppressed the arrhythmia. No further episodes of encainide were given, and the patient had no further episodes of the rapid sinusoidal tachycardia.

Approximately 10 days later, he had multiple episodes of his clinical sustained VT at a cycle length of 320–330 msec (VT-1) that were not suppressed by propranolol, and he was started on amiodarone. After 3 days on amiodarone therapy, no further episodes of sustained VT occurred, and his automatic implantable cardioverter-defibrillator was activated. He has remained free of clinically significant arrhythmias since that time. This patient demonstrated two patterns of VT. VT-1 occurred spontaneously when he was receiving no drugs and while receiving quinidine, procainamide, lidocaine, or propranolol. It was also induced in the laboratory. VT-2 was a more rapid, sinusoidal VT that occurred only when exposed to flecainide or encainide and was suppressed by propranolol.

**Patient 4**

W.W., a 79-year-old man, was referred for long-term management of sustained VT. Prior cardiac catheterization had revealed a moderately severe cardiomyopathy of unknown origin with normal coronary arteries and an ejection fraction of 35%. Approximately 12 months before admission, ambulatory monitoring revealed that he had salvos and long runs of nonsustained VT. Five antiarrhythmic agents were tried, all of which either failed to control the arrhythmia or resulted in unacceptable side effects. Subsequently, antiarrhythmic drug therapy was discontinued for approximately 10 months and then episodes of presyncope began to occur. During one of these events, sustained VT accompanied by hypotension was documented. He was referred for evaluation for experimental antiarrhythmic drugs, an automatic implantable cardioverter-defibrillator, or possible catheter ablation.
Before automatic implantable cardioverter-defibrillator (AICD) implantation, the patient had VT-1 induced on no antiarrhythmic therapy, and again after receiving intravenous propranolol (PR) and lidocaine (LI). After receiving AICD, VT-1 again occurred spontaneously and required external cardioversion (*) because AICD was off. Encainide hydrochloride (EN) was started with arrhythmia evolution described in text. After second dose of EN, VT-2 occurred spontaneously, required cardioversion (*), and recurred immediately after cardioversion. After total dose of 5 mg propranolol i.v., arrhythmia abated. (See text for details.)

At baseline electrophysiologic testing while on no antiarrhythmic drug therapy, he was reproducibly inducible into sustained VT by two extrastimuli at a drive cycle length of 500 msec. The cycle length of the VT was 400 msec and required cardioversion during one of the two inductions. Procainamide (1,200-mg infusion i.v.; 2 mg/min continuous drip) was administered, but he remained inducible into sustained VT at a plasma concentration of 7.8 μg/ml. The VT cycle length on procainamide was 420 msec. A trial of propranolol (10 mg i.v.) failed to slow the tachycardia. The patient was then started on flecainide therapy (100 mg q12h) in an attempt to achieve at least sufficient slowing of the VT to carry out intracardiac catheter mapping.

During baseline continuous monitoring for 72 hours before the administration of flecainide, the patient had single PVCs (mean frequency, 4±6 PVCs/min) and no couplets, salvos, or nonsustained VT (Table 1). After the third dose of flecainide, PVC frequency increased to more than 20 PVCs/min, frequently in a bigeminal pattern, with occasional couplets. Over the next 1–2 hours, the arrhythmia worsened to include runs of nonsustained VT lasting up to a maximum of 17 beats. A single 40-mg oral dose of propranolol was administered, and after 1 to 1½ hours the repetitive forms of PVCs were suppressed and the frequency of PVCs decreased to pretreatment levels (Figure 8A). After 4 hours, the advanced forms of spontaneous ectopy recurred, and a second dose of 40 mg propranolol was administered. Again, the spontaneous ectopy was suppressed, and propranolol (20 mg q6h) was started. At this dose, only single PVCs were recorded within the first 4 hours after a dose, with emergence of couplets and salvos during the last 2 hours. The dosage was increased to 30 mg q6h with uniform control of spontaneous ectopy. The plasma concentration of flecainide before the sixth dose was 520 μg/ml. Withdrawal of propranolol and subsequent rechallenge with the drug reproduced the observation of the flecainide–propranolol relation (Figure 8B).

**Discussion**

Aggravation of arrhythmias is an important factor limiting the use of almost all antiarrhythmic drugs. Although there is considerable variability in the forms, incidence, and clinical significance of proarrhythmic effects produced by individual drugs, it appears that such effects may limit as many as 10–15% of attempted drug uses. Furthermore, it has been suggested, with good argument, that some of the many out-of-hospital cardiac arrest events recorded each year may be related to the use of drugs intended to prevent arrhythmias. Potentia-
tion of proarrhythmic effects has been observed. The development of the typical torsade de pointes pattern associated with class IA and class III drugs is favored by slow heart rate, electrolyte disturbances (e.g., hypokalemia, hypomagnesemia), or concomitant use of digitalis. Sinusoidal VT due to class IC agents is commonly associated with left ventricular dysfunction, rapid changes in dosing schedules, and high plasma concentrations.6,13,14

Aggravation of spontaneous or induced clinical tachycardias is also included among the possible proarrhythmic events.15 In this regard, the distinction between true proarrhythmic effects and spontaneous variation of arrhythmias must always be considered because spontaneous variations can confound conclusions based on data from continuous monitoring. In each of the cases in this report, the frequency of PVCs while the patient was on no drug, therapy or on non-class IC antiarrhythmic drugs was low; and day-to-day variability during multiple days of continuous monitoring was insignificant. In each patient, there was a close and reproducible temporal relation between administration of class IC agents and appearance of the new arrhythmias. In addition, in two patients in whom sustained VT developed while receiving class IC agents, the cycle length and QRS axis of the drug-related tachycardias were different than the clinical VTs or those induced while the patient was on other antiarrhythmic drug therapy. Furthermore, even if the spontaneous VTs associated with the class IC drugs were accelerated and more resistant forms of the clinical tachycardias, they still fall within the realm of proarrhythmic responses.1,4--7,15 Thus, the data supporting proarrhythmia, rather than spontaneous variation, is compelling in these patients.

In this report, we cite four instances in which proarrhythmic events associated with use of a class IC drug were reversed by a β-adrenergic-blocking agent. It should be noted that the patients treated with propranolol had different forms of proarrhythmic effects. Patient 1 had increased frequency of PVCs and development of repetitive forms (salvos), but drug-related spontaneous or induced sustained VT did not develop. In contrast, the more serious spontaneous recurrent rapid sustained VT and longer runs of nonsustained VT developed in patients 2 and 3. Patient 4 had increased frequency of PVCs and development of multiple runs of nonsustained VT. All patterns were dramatically reversed by β-adrenergic blockade. New PVCs and salvos, which were suppressed by propranolol, developed in one additional patient who had no structural heart disease and was receiving a class IC drug for recurrent atrial fibrillation. Her data are not included in this report, however, because she refused rechallenge to document reproducibility.

We have previously suggested that pharmacologic effects of antiarrhythmic drugs against sustained VT and various forms of background spontaneous ectopy were not predictably concordant, either quantitatively or qualitatively, based on both clinical8 and experimental16 data. In this report, we extend these conclusions to include discrepancies between target and drug-induced arrhythmias. Propranolol was not effective against the induced VTs in the three patients in whom it was tested but was effective against the arrhythmias provoked by class IC drugs in each patient. Finally, because the myocardial depressant effects of flecainide and propranolol are additive,12 it is necessary to be cautious in the use of this combination; but clinical evidence of hemodynamic intolerance was not observed, even in patients 2 and 3 who had markedly reduced ejection fractions.

The mechanism responsible for our observations is not yet established. Two of our patients demonstrated a tendency for the sinus rate to increase during dose titration of flecainide, in the absence of clinical evidence of ischemia or worsening of left ventricular function, or of changes in baseline ST segment deviations. The increased rate may have enhanced pharmacologic effects by use dependency, resulting in adverse electropharmacologic effects at faster heart rates. It is further possible that the sinus rate changes represented autonomic adjustments induced by flecainide. If so, increased sympathetic tone may have caused increased susceptibility to arrhythmias, a possibility supported by recent observations that the β-adrenergic agonist, isoproterenol, may reverse the beneficial effects of flecainide on accessory pathways in the Wolff-Parkinson-White syndrome.17 This response was also prevented by propranolol. In yet another report, two patients receiving flecainide for atrial fibrillation had development of new VT during exercise testing,18 also suggesting a role for enhanced sympathetic activity or use dependency in the genesis of these adverse responses. There is no other literature to our knowledge on the direct effects of flecainide or encainide on central or sympathetic nervous system function. Concomitant long-term oral propranolol and flecainide therapy have been noted to increase the plasma concentrations of both drugs,12 but there are no pharmacologic studies that would predict the observations cited in this report. The initial observation was serendipitous—the propranolol trial in patient 1 was carried out incidentally as part of an evaluation of the efficacy of β-adrenergic blockade for treatment of nonsustained and sustained ventricular arrhythmias. The other three patients were studied by protocol because of the pharmacodynamic similarities to patient 1, although the arrhythmias induced by flecainide and encainide were more severe in patients 2 and 3, the patients with the lowest ejection fractions. We were unable to test the effect of other membrane-active antiarrhythmic agents on the flecainide-induced arrhythmia aggravation. Nonetheless, the effect of propranolol occurred in the β-blocking dosing and plasma level range and is unlikely to be due to a membrane-active effect of the drug.
The value of these observations is threefold: 1) They suggest a possible autonomic mechanism for proarrhythmic effects of class IC drugs, 2) they point to avenues of investigation for a relation between class IC drugs and the autonomic axis, and 3) they raise questions about the ability to expand use of antiarrhythmic drugs by pharmacologic blockade of undesirable electrophysiologic effects. There are no previous reports of antiproarrhythmic effects by pharmacologic means that potentially could be used long-term. However, such use may be limited by hemodynamic intolerance in patients with extensive disease and significantly reduced ejection fractions.

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References


KEY WORDS • flecainide • encainide • propranolol • arrhythmias • ventricular tachycardia
Reversal of proarrhythmic effects of flecainide acetate and encainide hydrochloride by propranolol.
R J Myerburg, K M Kessler, M M Cox, H Huikuri, E Terracall, A Interian, Jr, P Fernandez and A Castellanos

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