JACC Vol. 14, No. 1
July 1989:209–15

Arrhythmogenic Effects of Antiarrhythmic Drugs: A Study of 506 Patients Treated for Ventricular Tachycardia or Fibrillation

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Antiarrhythmic therapy in 506 consecutive patients undergoing 1,268 antiarrhythmic drug trials for ventricular tachycardia or ventricular fibrillation was reviewed for evidence of arrhythmogenic drug effect defined as the occurrence of a new form of ventricular tachyarrhythmia temporally associated with initiation of drug therapy or dosage increase. Arrhythmogenic effects occurred in 6.9% of patients and 3.4% of drug trials. This ranged from a high of 11.8% caused by encainide to none occurring with procainamide, tocainide or beta-adrenergic blocking drugs. The incidence of arrhythmogenesis was significantly greater in patients whose presenting arrhythmia was sustained ventricular tachycardia than it was in those who presented with nonsustained ventricular tachycardia or ventricular fibrillation ($p = 0.02$).

Decreased systolic function measured echocardiographically at the base of the left ventricle was associated with an increased incidence of arrhythmogenic effects ($p = 0.006$) whereas global left ventricular ejection fraction was not. Age, gender, cardiac diagnosis, location of prior myocardial infarction and New York Heart Association functional class for heart failure were not related to the occurrence of drug-induced arrhythmias. These findings emphasize the need for in-hospital cardiac monitoring during initiation of antiarrhythmic drug therapy for ventricular tachyarrhythmias.

(J Am Coll Cardiol 1989;14:209–15)

Since its introduction into clinical practice, quinidine has been noted to be associated with syncope and sudden death due to ventricular tachyarrhythmias (1,2). In recent years, arrhythmogenic actions have been attributed to virtually all antiarrhythmic drugs. However, most reports either have been anecdotal or have focused on the arrhythmogenic potential of a single drug or a specific arrhythmia. Velebit et al. (3) determined the overall incidence of arrhythmogenic effects of antiarrhythmic therapy in a large series of patients treated for ventricular arrhythmia during a protocol of short-term drug testing. No other study has been published on the frequency of arrhythmogenic effects of a variety of antiarrhythmic drugs used in a large population of patients.

In the present study, arrhythmogenic drug effects were defined as the new occurrence of ventricular fibrillation or of a form of ventricular tachycardia not previously experienced by that patient. The purpose of the study was to define the incidence of these arrhythmogenic drug effects in a large patient group treated for recurrent ventricular tachycardia or ventricular fibrillation and to analyze the association of these effects with clinical variables that might predict their occurrence.

Methods

Study group (Table 1). The study group consisted of 506 consecutive patients (388 men and 118 women aged 13 to 88 years [mean 56 ± 13]) evaluated and treated for recurrent ventricular tachycardia or ventricular fibrillation at Indiana University Medical Center. Before therapy, 184 patients had sustained ventricular tachycardia, 130 had ventricular fibril-

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Manuscript received July 26, 1988; revised manuscript received January 6, 1989, accepted February 8, 1989.

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0735-1097/89/$3.50

JACC Vol. 14, No. 1
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Table 1. Clinical Characteristics of 506 Study Patients

	n	
Clinical arrhythmia		
Nonsustained ventricular tachycardia	192	
Sustained ventricular tachycardia	184	
Ventricular fibrillation	130	
Cardiac diagnosis		
Ischemic heart disease	308	
Anterior infarction		99
Inferior infarction		103
Anterior + inferior infarction		25
Non-Q wave infarction		16
No infarction		65
Dilated cardiomyopathy	69	
Primary electrical disease	69	
Mitral valve prolapse	30	
Other valvular heart disease	14	
Wolff-Parkinson-White syndrome	7	
Congenital heart disease	5	
Hypertensive heart disease	4	

lation and 192 had nonsustained ventricular tachycardia. Primary electrical disease was defined as the absence of structural heart disease on clinical examination, echocardiography and catheterization. Endomyocardial biopsy was not systematically performed in this subgroup. Patients with Wolff-Parkinson-White syndrome were included if they had documented ventricular tachycardia or ventricular fibrillation that was not associated with atrioventricular reciprocating tachycardia or atrial fibrillation with a rapid ventricular response.

Left ventricular function. Three hundred thirty-eight patients had baseline assessments of left ventricular size and function. Left ventricular (LV) ejection fraction was determined by contrast or radionuclide ventriculography or two-dimensional echocardiography. Echocardiograms were further analyzed to derive the fractional shortening, which was calculated as the ratio of systolic change in left ventricular internal diameter (LVID) to the diastolic diameter: $(LVID_{diastole} - LVID_{systole})/LVID_{diastole}$. Fractional area change was similarly calculated from the measurements at the mid-ventricular level as $(LV\ area_{diastole} - LV\ area_{systole})/LV\ area_{diastole}$.

Antiarrhythmic drug treatment. Each patient was hospitalized and the cardiac rhythm was continuously monitored during a drug-free period of ≥2 days and during administration of all antiarrhythmic drugs. Twenty-four hour monitoring of the patients' cardiac rhythm was accomplished by telemetry with use of a commercially available computerized arrhythmia detection system (Hewlett-Packard 78525) and was continuously observed by experienced cardiac intensive care unit nurses. Rhythm tracings were reviewed daily by physicians. The choice of specific antiarrhythmic drugs was individualized and based on each patient's previous drug history and clinical state and the availability of specific drugs. A previously administered drug was not reevaluated if limiting side effects or recurrent arrhythmia had occurred during prior exposure to that agent. Drugs with significant negative inotropic effects, such as disopyramide or beta-adrenergic blocking agents, were not administered to patients who had overt congestive heart failure. Drugs that were investigational when the patient entered the study were tested after drugs approved by the Food and Drug Administration were evaluated. Each drug, except for amiodarone, which was given for 7 to 14 days, was administered for 2 to 4 days at each dose and, if discontinued because of adverse effects or lack of efficacy, administration of another drug was not begun for at least another 24 h. If single drug therapy appeared ineffective, drug combinations were employed using the same guidelines as for single drugs. Each drug combination was evaluated as a separate, unique drug trial and was not included in the individual analysis of single drugs. The most frequent combinations involved amiodarone, which was paired with quinidine in 20 trials, encainide in 13, aprindine in 13 and mexiletine in 12.

Definition of arrhythmogenic effects. An arrhythmogenic effect of antiarrhythmic drug therapy was defined as the spontaneous occurrence of a new symptomatic ventricular tachyarrhythmia that occurred in temporal association with the start of drug administration or a new increase in dosage and that abated once administration of the drug was discontinued. Drug-induced arrhythmias were analyzed solely on the basis of spontaneous arrhythmias observed during electrocardiographic (ECG) monitoring. Whereas electrophysiologic testing was employed to evaluate drug efficacy, these data were not used to define arrhythmogenic drug effects. Arrhythmogenic effects were categorized further into: 1) repetitive nonsustained ventricular tachycardia, defined as recurrent salvos (usually of 3 to 10 complexes) of ventricular tachycardia separated by brief periods of sinus rhythm; 2) sustained ventricular tachycardia, defined as ventricular tachycardia lasting >30 s or requiring termination because of hemodynamic compromise; 3) incessant ventricular tachycardia, defined as continuous ventricular tachycardia that could not be terminated by electrical cardioversion or pacing or that recurred immediately after termination; 4) polymorphic ventricular tachycardia; 5) ventricular fibrillation, which was primary (that is, was not a result of degeneration of ventricular tachycardia). To be noted as an arrhythmogenic response, the arrhythmia had to be *new* for that patient. Therefore, patients who had sustained ventricular tachycardia or ventricular fibrillation as their primary arrhythmia would not be included as having an arrhythmogenic event if that same arrhythmia occurred during drug therapy. Likewise, a change in the rate or configuration of sustained or nonsustained ventricular tachycardia during arrhythmia recurrence was not considered as an arrhyth-

Table 2. Antiarrhythmic Drug Doses and Number of Study Trials

Drug	Dose (mg/day)	Number of Trials
Amiodarone	800 to 1,600 load	256
Quinidine	1,200 to 1,600	167
Propafenone	450 to 900	162
Encainide	75 to 300	110
Disopyramide	400 to 600	95
Aprindine	75 to 200	88
Mexiletine	450 to 900	79
Procainamide	2,000 to 6,000	77
Beta-blockers	—	43
Tocainide	1,200 to 1,800	29
Flecainide	100 to 400	25
Cibenzoline	195 to 293	23
Combinations	—	114

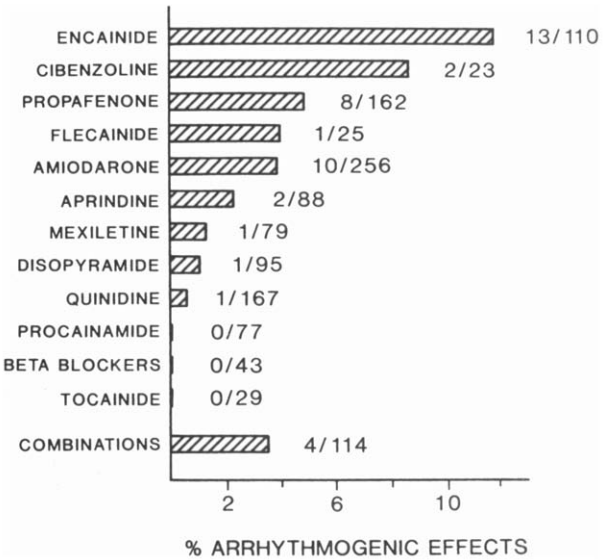

Figure 1. Incidence of arrhythmogenic effects for each drug. The numbers to the right of the bars represent the number of arrhythmogenic drug trials per total number of trials for that drug.

mogenic response if the sustained or nonsustained ventricular tachycardia occurred before drug treatment.

Electrocardiographic intervals. QRS, QT and corrected QT (QTc) intervals were obtained in the control state before antiarrhythmic drug therapy and on the day of the arrhythmogenic event. These intervals were compared with those obtained from a subgroup of patients from our study group not experiencing an arrhythmogenic event. This latter subgroup was matched to the former one with respect to age, gender, left ventricular size and function and antiarrhythmic drug. For analysis, patients experiencing arrhythmogenesis while receiving amiodarone were compared with those having an uneventful amiodarone drug trial. Likewise, patients receiving flecainide, encainide or propafenone were grouped together to compare those with and without arrhythmogenic drug effects. The number of patients having arrhythmogenesis while receiving other drugs was too small to perform meaningful analysis.

QT intervals were measured from the onset of the QRS complex to the termination of the T wave. The QTc intervals were calculated as $QT/\sqrt{RR}$. JT intervals were calculated as QT − QRS. JTc intervals were calculated as $(QT - QRS)/\sqrt{RR}$.

Statistical analysis. Data are presented as mean values ± 1 SD. Comparisons between patients who did or did not experience arrhythmogenic effects were made with use of the Student's *t* test for continuous variables such as fractional shortening. Categorical variables, such as presenting arrhythmia, were analyzed by the chi-square test for contingency tables. Electrocardiographic intervals were analyzed by two-way repeated measures analysis of variance. Statistical significance was assigned to probability values ≤ 0.05.

Results

Incidence of arrhythmogenesis (Table 2). Arrhythmogenic drug effects were identified in 35 (6.9%) of 506 patients and in 43 (3.4%) of 1,268 drug trials (Fig. 1). Each of the 35 patients who experienced an arrhythmogenic effect while receiving one drug received at least one additional drug trial. Four patients had arrhythmogenic responses during more than one drug trial (two patients had two arrhythmogenic drug responses and one each had three and five such responses). Encainide produced the highest incidence rate (11.8%) of arrhythmogenic effects, and this incidence rate was statistically greater than that for all other drugs combined by the chi-square test ($p < 0.001$). Of the 13 drug trials with encainide, 4 were in patients treated during early investigational trials that used an incremental dosing regimen that exceeded the current recommendations for dose escalation. The incidences of arrhythmogenesis varied among the remaining drugs, but these differences did not attain statistical significance. Drug combinations produced arrhythmogenic responses in four trials. A combination of amiodarone and flecainide was arrhythmogenic in two of the three trials in which it was used whereas amiodarone plus propafenone had arrhythmogenic effects in one of nine trials and amiodarone plus quinidine in one of 20 trials.

Type of arrhythmogenic effect. The specific categories of arrhythmogenic responses for each drug are presented in Figure 2. Incessant ventricular tachycardia accounted for 23 of the 43 drug-induced arrhythmias. Polymorphic ventricular tachycardia and ventricular fibrillation occurred in six instances and were only associated with amiodarone therapy in this series.

Arrhythmogenic effects occurred at a mean of 4.9 ± 3.8 days (median 3; range 1 to 17) after drug initiation. For all drug trials, therapy during continuous ECG monitoring

	Enc	Amio	Propf	Flec	Quin	Comb	Other	TOTALS
REPETITIVE VT-NS	2		5	1	1			9
VT-S	3	1	1					5
INCESSANT VT-S	8	3	2			4	6	23
POLYMORPHIC VT		2						2
VF		4						4

Figure 2. Type of arrhythmogenic response seen for each drug. Amio = amiodarone; Comb = combination therapy; Enc = encainide; Flec = flecainide; Propf = propafenone; Quin = quinidine; VF = ventricular fibrillation; VT-NS and VT-S = nonsustained and sustained ventricular tachycardia, respectively.

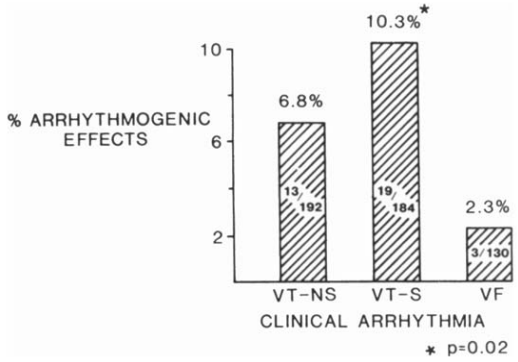

Figure 3. Incidence of arrhythmogenic effects as related to presenting arrhythmia. Abbreviations as in Figure 2.

lasted a mean of 6.6 ± 6.5 days and ranged from a mean of 4.7 ± 2.8 days for trials of disopyramide to a mean of 11.7 ± 6.1 days for trials of amiodarone. Arrhythmias associated with amiodarone treatment occurred 3 to 17 days after drug initiation and resolved within 24 h, except in two patients in whom incessant ventricular tachycardia lasted for 2.5 and 3 days, respectively; the latter patient was receiving amiodarone in combination with flecainide.

Treatment. Therapy consisted of discontinuing the offending drugs and administering intravenous antiarrhythmic agents or electric cardioversion as indicated. Four patients required extraordinary treatment. Two of these patients required vasopressor drugs, one of whom additionally had placement of an intraaortic balloon pump. Another patient required prolonged cardiopulmonary resuscitation intermittently for 6 h. The fourth patient died as a result of cardiogenic shock related to incessant ventricular tachycardia.

Factors associated with arrhythmogenesis. Clinical and demographic factors were compared between the 35 patients with and the 471 patients without arrhythmogenic drug effects. Age, gender, cardiac diagnosis, location of prior infarction and functional class were not different between the two groups. Serum potassium concentrations in 20 patients at the time of the drug-induced arrhythmia ranged from 3.5 to 5.4 mEq/dl (mean 4.2 ± 0.5). Digitalis was being used concurrently in 14 of 35 patients and in 14 of 43 drug trials with arrhythmia exacerbation.

The nature of the presenting arrhythmia appeared to influence the likelihood of a patient experiencing an arrhythmogenic effect during drug therapy. Arrhythmogenic effects occurred in 19 (10.3%) of 184 patients presenting with sustained ventricular tachycardia, compared with only 3 (2.3%) of 130 patients with ventricular fibrillation and 13 (6.8%) of 192 patients with nonsustained ventricular tachycardia (p = 0.02) (Fig. 3).

Echocardiographic and ventriculographic data concerning left ventricular function and ejection fraction are pre-

Table 3. Comparison of Variables of Left Ventricular Size and Function Between Patients With and Without Arrhythmogenic Effects

	Arrhythmogenic Effects (n = 23)	No Arrhythmogenic Effects (n = 280)	Normal Range
LV diameter (cm)			
Diastole	5.7 ± 0.2	5.4 ± 0.1	3.6 to 5.2
Systole	4.5 ± 0.2	4.2 ± 0.1	2.3 to 3.9
Fractional shortening	0.16 ± 0.02*	0.22 ± 0.01	0.18 to 0.42
LV area (cm^2)			
Diastole	24.5 ± 2.1	24.2 ± 0.7	9.5 to 22.3
Systole	16.7 ± 1.9	16.3 ± 0.7	4.0 to 11.6
Fractional area change	0.36 ± 0.03	0.35 ± 0.01	0.36 to 0.64
LV ejection fraction (%)	37.9 ± 3.2 (n=25)	38.2 ± 1.8 (n=91)	

*p = 0.006 for fractional shortening of patients with arrhythmogenic effects versus those without. LV = left ventricle.

Table 4. Left Ventricular Size and Function in Patients Receiving Flecainide, Disopyramide or Beta-Blockers (F, D, BB) and in Patients Receiving Other Drugs.

Variable	F.D. BB (n)	Other (n)	p Value
LV diameter (cm)			
Diastole	5.1 ± 0.1 (111)	5.6 ± 1 (192)	<0.001
Systole	3.8 ± 0.1 (109)	4.5 ± 0.1 (169)	<0.001
Fractional shortening	0.25 ± 0.01 (108)	0.19 ± 0.01 (169)	<0.001
LV Area (cm^2)			
Diastole	21.5 ± 0.9 (88)	25.8 ± 0.9 (145)	0.002
Systole	13.0 ± 0.8 (89)	18.5 ± 0.9 (144)	0.001
Fractional area change	0.42 ± 0.01 (88)	0.31 ± 0.01 (144)	0.001
LV ejection fraction (%)	44 ± 4 (32)	36 ± 2 (84)	0.045

Data are given as mean values ± SE. n = number of patients having that measurement. Abbreviations as Table 3.

sented in Table 3. The mean value for echocardiographic fractional shortening, an index of systolic ventricular wall motion at the base of the heart, was abnormal for patients who had arrhythmogenic effects and was significantly less than that obtained in patients without drug-induced arrhythmias (0.16 ± 0.02 versus 0.22 ± 0.01, p = 0.006). Other measurements of left ventricular chamber size and ejection fraction were not significantly different between the two groups. A further analysis by specific drug revealed that echocardiographic measurements of left ventricular size and systolic function were significantly better in those patients who were given trials of flecainide, disopyramide and beta-adrenergic blocking agents than in patients who did not receive these drugs (Table 4).

Electrocardiographic intervals. There were no differences between those patients experiencing arrhythmogenic events and the matched subgroup in those receiving amiodarone with regard to the QRS, QT or QTc intervals in the control period or during treatment with the drug. The groups receiving flecainide, encainide or propafenone showed no differences in QT, QTc, JT, JTc or control QRS. However, the group *not* experiencing an arrhythmogenic effect had a greater drug-induced QRS lengthening (124 ± 26 versus 108 ± 21 ms; p = 0.004).

Discussion

Definition. The definition of arrhythmia exacerbation in this study was based entirely on the clinical observation and recording of a new form of ventricular tachyarrhythmia that occurred during drug therapy and disappeared after drug discontinuation. It is unlikely that these arrhythmias represented the natural evolution of the clinical arrhythmia pattern of each patient because, in each patient, the arrhythmia designated as drug-induced had not been noted previously and resolved after the drug was discontinued except in one patient who died with incessant ventricular tachycardia. Furthermore, a treatment regimen was eventually found that prevented the clinical arrhythmia and was not associated with the previously noted drug-associated arrhythmia. A more certain diagnosis might have been possible if the patients had been rechallenged with each potentially arrhythmogenic drug, but this procedure was neither practical nor safe in the present context. Limiting the designation of arrhythmogenic effects to the time period of in-hospital continuous ECG monitoring and to the stated arrhythmia categories was designed to provide more certainty to the diagnosis. The occurrence of an arrhythmia later in drug therapy would more likely reflect progression of disease or result from other precipitating factors. The definition of arrhythmogenic effects in this study was derived so as to avoid the natural variability in extrasystole frequency (4) that can simulate antiarrhythmic (5) or arrhythmogenic (6) effects.

Other studies. Velebit et al. (3) reported an overall incidence of drug-associated arrhythmias greater than that in the present series. Whereas the study groups were largely comparable, these authors used short-term drug testing and identified arrhythmogenic effects as an increase in the frequency of ventricular extrasystoles or the occurrence of ventricular tachycardia as compared with control period monitoring of up to 48 h. In the present study, only new forms of ventricular tachycardia or ventricular fibrillation not previously present in that patient were designated as drug-induced. In addition, our study has added an analysis of the arrhythmogenic potential of several newer drugs such as encainide, flecainide and amiodarone. Previous reports (7–9) of the arrhythmogenic potential of either encainide or flecainide agree with our findings. Whereas 4 of the 13 instances of arrhythmia aggravation with encainide in our series may have been related to rapid dose increases, current guidelines, which were followed in the other nine cases, did not obviate the arrhythmogenic potential of encainide. Similar results have been noted with flecainide, with a much higher arrhythmogenic potential reported in patients treated for sustained ventricular tachyarrhythmias (9).

Several reports (10–12) have identified the potential of amiodarone, during the early phase of drug loading, to

produce polymorphic ventricular tachycardia, ventricular flutter or ventricular fibrillation. The reported incidence rates of arrhythmia aggravation with amiodarone have ranged as high as 3.9% (13), which is the same as that in our report.

Drug combinations. Drug combinations are usually employed to obtain added antiarrhythmic efficacy but also have the risk of enhancing potential toxicity. Because in our experience combination drug therapy has usually involved amiodarone as one of the agents, it is not surprising that all four cases of arrhythmia aggravation we reported involved amiodarone in combination with another drug. The potential danger of drug combinations with amiodarone has been reported by others (14,15). The noted pharmacokinetic interactions between amiodarone and other antiarrhythmic drugs may be a contributing factor (14,16). However, in our series, careful dose adjustments and plasma concentration monitoring did not prevent this complication.

Clinical correlates. Of the clinical variables assessed, the presenting arrhythmia and left ventricular function at the base of the heart were statistically associated with the occurrence of drug-induced arrhythmia. As noted by others (17,18), patients who presented with sustained ventricular tachycardia more commonly experienced arrhythmogenic effects than did those who had ventricular fibrillation or nonsustained ventricular tachycardia. However, these latter diagnoses did not imply that drug therapy was safe—they accounted for nearly half of the episodes of potentially life-threatening drug-induced arrhythmia. Left ventricular ejection fraction did not distinguish between the patient groups perhaps because a large majority of patients in the study had significantly impaired left ventricular function. There was a small but significant difference between groups in systolic function at the base of the heart, measured as fractional shortening by echocardiography. This measurement has been found to be useful in other clinical settings (19), but the mechanism for this relation is not known.

The finding that both groups of patients receiving type IC agents (flecainide, encainide, propafenone) had lengthening of the QRS interval but that the magnitude of effect was greater in those not having an arrhythmogenic event was surprising and cannot be readily explained.

Arrhythmogenesis occurred early during treatment in this study. This finding agrees with the data of Minardo et al. (20), who studied a separate group of patients referred to our institution after they experienced ventricular fibrillation as outpatients while receiving antiarrhythmic drugs. The median duration of drug therapy before ventricular fibrillation in that group was 4 days compared with 3 days in our current report.

Limitations. In our study the choice of specific drug therapy was influenced by each patient's hemodynamic status, but this precaution did not preclude completely the arrhythmogenic potential of these drugs. We did not systematically record plasma drug concentrations because they were unavailable for certain investigational drugs (e.g., propafenone and aprindine) and because the correlation between drug concentration and electrophysiologic effect is unknown in others (e.g., amiodarone and encainide). Furthermore, plasma drug concentrations have been shown not to correlate with arrhythmogenesis (2,12,18).

Conclusions. Potentially life-threatening arrhythmias induced by antiarrhythmic drugs were found in 6.9% of patients and 3.4% of drug trials in this group of patients treated for ventricular tachycardia and ventricular fibrillation. The incidence varied with the drug employed, and although there was an association with sustained ventricular tachycardia as the presenting clinical arrhythmia and reduced left ventricular systolic function at the base of the heart, the occurrence of arrhythmogenic drug effects was generally unpredictable. Moreover, these effects occurred despite careful attention to correction of underlying heart failure and electrolyte imbalance and careful individual drug selection. These data should argue strongly for careful in-hospital arrhythmia surveillance to detect and treat a potentially fatal but reversible complication of antiarrhythmic drug therapy in this patient group.

References

1. Kerr WJ, Bender WL. Paroxysmal ventricular fibrillation with cardiac recovery in a case of auricular fibrillation and complete heart-block while under quinidine sulphate therapy. Heart 1922;9:269–81.
2. Selzer A, Wray HW. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. Circulation 1964;30:17–26.
3. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982;65:886–94.
4. Pratt CM, Delclos G, Wierman AM, et al. The changing baseline of complex ventricular arrhythmias: a new consideration in assessing long-term antiarrhythmic drug therapy. N Engl J Med 1985;313:1444–9.
5. Winkle RA. Antiarrhythmic drug effect mimicked by spontaneous variability of ventricular ectopy. Circulation 1978;57:1116–21.
6. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: the CAPS. Am J Cardiol 1988;61:501–9.
7. Winkle RA, Mason JW, Griffin JC, Ross D. Malignant ventricular tachyarrhythmias associated with the use of encainide. Am Heart J 1981;102:857–64.
8. Soyka LF. Safety of encainide for the treatment of ventricular arrhythmias. Am J Cardiol 1986;58:96C–103C.
9. Morganroth J, Anderson JL, Gentzkow GD. Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. J Am Coll Cardiol 1986;8:607–15.
10. McComb JM, Logan KR, Khan MM, Geddes JS, Adgey AAJ. Amiodarone-induced ventricular fibrillation. Eur J Cardiol 1980;11:381–5.
11. Cui G, Huang W, Urthaler F. Ventricular flutter during treatment with amiodarone. Am J Cardiol 1983;51:609–10.
12. Brown MA, Smith WM, Lubbe WF, Norris RM. Amiodarone-induced torsades de pointes. Eur Heart J 1986;7:234–9.

13. Fogoros RN, Anderson KP, Winkle RA, Swerdlow CD, Mason JW. Amiodarone: clinical efficacy and toxicity in 96 patients with recurrent, drug-refractory arrhythmias. Circulation 1983;68:88–94.

14. Tartini R, Kappenberger L, Steinbrunn W, Meyer UA. Dangerous interaction between amiodarone and quinidine. Lancet 1982;1:1327–9.

15. Keren A, Tzivoni D, Gavish D, et al. Etiology, warning signs and therapy of torsade de pointes. Circulation 1981;64:1167–74.

16. Windle J, Prystowsky EN, Miles WM, Heger JJ. Pharmacokinetic and electrophysiologic interactions of amiodarone and procainamide. Clin Pharmacol Ther 1987;41:603–10.

17. Morganroth J, Horowitz LN. Flecainide: its proarrhythmic effects and expected changes on the surface electrocardiogram. Am J Cardiol 1984; 53:89B–94B.

18. Tordjman T, Podrid PJ, Raeder E, Lown B. Safety and efficacy of encainide for malignant ventricular arrhythmias. Am J Cardiol 1986; 58:87C–95C.

19. Ryan T, Petrovic O, Armstrong WF, Dillon JC, Feigenbaum H. Quantitative two-dimensional echocardiographic assessment of patients undergoing left ventricular aneurysmectomy. Am Heart J 1986;111:714–20.

20. Minardo JD, Heger JJ, Miles WM, Zipes DP, Prystowsky EN. Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. N Engl J Med 1988;319:257–62.