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Congestive Heart Failure Induced by Six of the Newer Antiarrhythmic Drugs

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The incidence of drug-induced congestive heart failure with several newer antiarrhythmic agents including encainide, ethmozine, lorcainide, mexiletine, propafenone and tocainide was determined in a group of 407 patients who underwent 1,133 drug tests. The incidence rate ranged from 0.7% with lorcainide to 4.7% with propafenone. Congestive heart failure was present in 167 patients (41%) who underwent 491 drug trials. Congestive failure was induced in 15 (9%) of these 167 patients and involved 19 (3.9%) of the 491 tests. Left ventricular ejection fraction was 20 ± 8% in patients who developed congestive failure, in contrast to 39 ± 19% in those who did not ($p < 0.001$).

It is concluded that each of the six antiarrhythmic drugs examined has the potential to aggravate congestive heart failure in patients with reduced left ventricular ejection fraction or a history of congestive heart failure, but the incidence rate is low and its occurrence unpredictable.

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Ever larger numbers of patients are being resuscitated from sudden cardiac arrest and identified as having ventricular tachycardia. The major therapeutic intervention for prophylaxis involves the use of antiarrhythmic drugs (1–3). A majority of these patients have significant left ventricular dysfunction. Additionally, many patients with severely depressed left ventricular function and congestive heart failure have frequent complex ventricular arrhythmias (4–6) that may be harbingers of sudden death and for which antiarrhythmic drugs are prescribed. However, antiarrhythmic drugs exert negative inotropic effects, with the potential of precipitating or aggravating congestive heart failure (7,8).

The purpose of this retrospective study was to determine the incidence of aggravation or provocation of congestive failure by antiarrhythmic drugs in a large group of patients with serious ventricular arrhythmias. The six drugs evaluated were the newer antiarrhythmic agents mexiletine, tocainide, ethmozine, lorcainide, encainide and propafenone. An additional objective was to identify, if possible, the risk factors for drug-induced congestive heart failure.

Methods

Study patients (Table 1). Data were collected by reviewing hospital and arrhythmia clinic records. The clinic had a close follow-up of all patients evaluated for arrhythmias, and recorded any symptom or finding. Patients were instructed to report to the clinic any change in their symptoms, and all patients were telephoned within 1 month of discharge from the hospital.

The study group consisted of 407 patients (303 male and 104 female), with a mean age of 56 years (range 15 to 83), representing all patients referred for therapy of recurrent ventricular tachyarrhythmias during a 6 year period. In each patient, conventional antiarrhythmic drugs including quinidine, disopyramide, procainamide and a beta-adrenergic blocking agent were not effective or poorly tolerated. The majority of patients (62%) had coronary artery disease; the remaining patients had valvular heart disease (10%), cardiomyopathy (8%) or other cardiac conditions (20%). The presenting arrhythmia was ventricular fibrillation in 26% of patients, sustained ventricular tachycardia in 42% and nonsustained ventricular tachycardia in 26%; the remaining 6%

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Table 1. Clinical Characteristics of the Study Group

No. of patients	407
No. (%) male	303 (74)
No. (%) female	104 (26)
Age (yr)	
Mean	56
Range	15 to 83
No. (%) with cardiac diagnoses	
Coronary artery disease	252 (62)
Dilated cardiomyopathy	33 (8)
Valvular disease	41 (10)
Other	81 (20)
No. (%) with presenting arrhythmias	
VF	104 (26)
Sustained VT	172 (42)
Nonsustained VT	105 (26)
Symptomatic VPCs	26 (6)
No. (%) with history of CHF	167 (41)
LVEF (%) (n = 232 patients)	38 ± 19

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; VF = ventricular fibrillation; VPBs = ventricular premature compheres; VT = ventricular tachycardia.

of patients had symptomatic and frequent ventricular premature beats. A history of congestive failure was present in 167 patients (41%). Clinically significant congestive heart failure was diagnosed if the patient had a history of typical symptoms and physical findings in association with a chest X-ray study consistent with heart failure.

Drug evaluation protocol. The determination of the effects of drugs on arrhythmias involved four phases of study, which have been described previously (3,9). After patients were admitted to the hospital, antiarrhythmic drugs were discontinued. Digitalis, diuretic drugs, beta-blockers, vasodilators and calcium channel blocking agents were continued if clinically indicated for treatment of heart failure or angina. Patients with overt congestive heart failure were treated until compensated, and their condition had to have been stable for at least 1 week before they entered the protocol for evaluating antiarrhythmic drugs. During the control period of observation, patients were in stable condition and free of congestive heart failure for at least 10 to 12 days before antiarrhythmic drugs were administered. Phase 0 began after a drug-free period of at least four half-lives of the prior antiarrhythmic drug. During this phase, patients underwent control studies that included 48 h of ambulatory electrocardiographic (ECG) monitoring and symptom-limited exercise testing on a motorized treadmill. Baseline left ventricular function was assessed by radionuclide ventriculography with the use of gated blood pool scanning in 232 (57%) of the 407 patients. This group included 109 of the 167 patients with a history of congestive heart failure.

At the conclusion of control studies, drugs were evaluated by previously described invasive or noninvasive techniques (9,10). Phase 1 investigations involved acute drug testing. After a 30 min control period, a single large dose of drug was administered orally and ECG monitoring by trendscription continued for 3 h. At the completion of a series of acute drug tests, those drugs determined to be of benefit were evaluated during a short period of maintenance therapy (phase 2). Drugs possessing active metabolites or those with a long accumulation time (for example, encainide or lorcainide) were not tested acutely, but only during short-term maintenance therapy. During phase 2, which lasted for 48 to 96 h, the dose of drug was titrated to its effect on arrhythmia or the occurrence of side effects. At the completion of this period, response to the antiarrhythmic drug was assessed by repeat ambulatory ECG monitoring and exercise testing. Long-term maintenance therapy with a selected drug was defined as phase 3.

Patients with a low density of spontaneously occurring ventricular arrhythmias or those who demonstrated significant day to day variability in ventricular arrhythmia frequency underwent electrophysiologic study to assess drug efficacy. The protocol for electrophysiologic study has been previously described (10). Drug evaluation involved both acute testing and maintenance therapy.

An effective response, as determined with both ECG monitoring and exercise testing, was defined as (9): 1) total elimination of runs of nonsustained ventricular tachycardia; 2) reduction of couplets by ≥90%; and 3) >50% reduction in ventricular premature beats. When drug selection was guided by electrophysiologic testing, the criterion for efficacy was the inability to induce three or more repetitive ventricular premature beats when up to three extrastimuli were added during ventricular pacing at cycle lengths of 600 and 500 ms (10). If the antiarrhythmic drug was effective and well tolerated, the patient continued to take it as part of a long-term treatment program (phase 3).

Drugs evaluated. The newer antiarrhythmic drugs evaluated were those administered to and evaluated in ≥100 patients and included encainide, ethmozine, lorcainide, mexiletine, propafenone and tocainide. Flecainide was not evaluated because experience with this agent was limited during this period of time. No patient was excluded from treatment with a particular drug on the basis of left ventricular ejection fraction or a history of congestive heart failure. Table 2 lists the doses of each drug administered. There were a total of 1,133 drug studies; 246 (22%) were acute drug tests and 887 (78%) involved short-term maintenance. In each case, acute drug testing was followed by a short period of maintenance therapy unless side effects occurred. Noninvasive techniques were used in 895 drug studies (79%), and 238 studies (21%) involved electrophysiologic testing. The 167 patients with a history of congestive heart failure underwent 491 antiarrhythmic drug trials (2.9/patient); the 240 patients without heart failure underwent 642 drug studies (2.7/patient) (p = NS).

Table 2. Incidence of Congestive Heart Failure Induction After Antiarrhythmic Drug Administration

Drug	No. of Drug Tests	Dose (mg)		No. of Inductions of CHF (%)	No. of Patients With a History of CHF (%)	No. of Cases of CHF Worsening in the CHF Group (%)
		Acute Drug Testing	Daily Maintenance			
Encainide	153	NP	75 to 200	4 (2.6)	70 (46)	4 (5.7)
Ethmozine	125	600	600 to 1200	3 (2.4)	62 (50)	3 (4.8)
Lorcainide	144	NP	200 to 400	1 (0.7)	63 (44)	1 (1.6)
Mexiletine	352	400	300 to 1200	3 (0.9)	146 (41)	3 (2.0)
Propafenone	108	450	450 to 900	5 (4.7)	43 (40)	4 (9.3)
Tocainide	251	800	600 to 2400	4 (1.6)	107 (43)	4 (3.7)
Total	1,133			20 (1.8)	491 (43)	19 (3.9)

NP = not performed; other abbreviations as in Table 1.

Induction of congestive heart failure. Antiarrhythmic drug-induced congestive heart failure was defined as the emergence of appropriate symptoms (cough, shortness of breath, dyspnea on exertion, paroxysmal nocturnal dyspnea and reduced exercise tolerance) associated with either new radiologic findings consistent with congestive heart failure or the development of physical signs including pulmonary rales, S_3 gallop sound and weight gain. So as to minimize the influence of other factors or progression of disease, a drug was implicated only if these findings developed within the first 2 weeks of therapy. Also, heart failure had to 1) be established by direct contact with and physical examination of the patient by one of the investigators, and 2) resolve completely after drug discontinuation or reduction of dose, 3) appear in the absence of other causes of heart failure, such as new onset ischemia, dietary sodium indiscretion, use of other medications or intercurrent illness.

Statistical analysis. Statistical analyses were performed by Student's *t* test for paired values and by the chi-square analysis for categorical data. Significance was defined as a p value ≤ 0.05. Results are expressed as mean values ± SD.

Results

Incidence of drug-induced congestive heart failure (Table 2). Congestive heart failure developed during 20 (1.8%) of the 1,133 antiarrhythmic drug trials. In 19 of these cases, the patient had a prior history of heart failure. Therefore, congestive failure was aggravated in 19 (3.8%) of 491 drug studies performed in patients with and in only 1 (0.16%) of the 642 tests in patients without congestive failure ($p < .001$). Thus, patients with a history of congestive heart failure have a nearly 24-fold greater risk of experiencing this adverse reaction than that of patients without prior cardiac decompensation. For any tested drug, the incidence rate of induction of congestive heart failure was twice as high in those with as in those without a history of failure (range 1.6% with lorcainide to 9.3% with propafenone).

Clinical characteristics of patients who developed heart failure (Table 3). The 20 episodes of new or worsened congestive heart failure involved 16 patients, or 3.9% of the total study group. These patients underwent 63 drug studies (range 2 to 7 [mean 3.9]/patient). Thus, aggravation of heart failure in these 16 patients occurred in 20 (32%) of the 63 drug trials. Exacerbation of congestive heart failure with one drug did not predict this complication with another drug. The only patient without a history of congestive heart failure who developed heart failure with an antiarrhythmic drug had severe coronary artery disease, two previous myocardial infarctions and a left ventricular ejection fraction of 30%. Each of the 16 patients who had drug-induced congestive heart failure was being treated with digoxin, 14 with diuretic

Table 3. Clinical Characteristics of 16 Patients With Drug-Induced Congestive Heart Failure

	No. (%)
No. (%) male	9 (56)
No. (%) female	7 (44)
Age (yr)	
Mean	62
Range	46 to 76
No. (%) with cardiac diagnoses	
CAD	6 (37)
CDM	10 (63) ($p < 0.001$)*
No. (%) with presenting arrhythmias	
VF	2 (12)
Sustained VT	7 (44)
Nonsustained VT	7 (44)
Other	0
No. (%) with history of CHF	15 (94) ($p < 0.001$)*
LVEF (%)	20 ± 8 ($p < 0.001$)*
No. of drug tests	63
No. of tests inducing CHF	20 (32)
No. of patients with CHF induction with one drug	12
No. of patients with CHF induction with two drugs	4

*Compared with the 391 patients who did not develop congestive heart failure on antiarrhythmic drug therapy. Abbreviations as in Table 1.

Table 4. Clinical Characteristics of 167 Patients With a History of Congestive Heart Failure

	Total	No. With CHF Induced	No. Without CHF Induced	p Value
No.	167	15	152	
No. (%) male	127 (77)	8 (53)	119 (80)	NS
No. (%) female	40 (23)	7 (47)	33 (22)	<0.02
Age (yr)	61	62	61	NS
No. (%) with cardiac diagnoses				
CAD	119 (71)	5 (33)	114 (75)	NS
CDM	23 (14)	10 (67)	13 (9)	<0.001
Valvular disease	15 (9)	0 (0)	15 (9)	NS
Other	10 (6)	0 (0)	10 (7)	NS
No. (%) with presenting arrhythmias				
VF	50 (30)	2 (13)	48 (31)	NS
Sustained VT	69 (41)	6 (40)	63 (41)	NS
Nonsustained VT	40 (24)	7 (47)	33 (21)	NS
Other	8 (5)	0 (0)	8 (7)	NS
LVEF (%) (n = 109)	27 ± 14	19 ± 8	28 ± 15	<0.04

Abbreviations as in Table 1.

drugs and 6 with vasodilators. At the time of drug testing, all 16 patients were in sinus rhythm, 9 had an underlying conduction delay and 6 had left ventricular hypertrophy; all 6 patients with coronary artery disease had Q waves consistent with old myocardial infarction. In 3 of the 16 patients, pulmonary edema developed within the first 24 h after administration of the new antiarrhythmic drug. The left-sided congestion resolved with diuretic therapy. In 12 patients, congestive heart failure developed gradually over 2 to 14 days after initiation of drug therapy and resolved completely when the dose was decreased or the agent discontinued. One patient with a left ventricular ejection fraction of 23% developed cardiogenic shock after 3 days of propafenone administration at a dose of 900 mg/day. The patient needed intensive supportive care and recovered 3 days after the drug was discontinued.

Patients in whom congestive failure was provoked (Table 3) did not differ significantly from the study group as a whole (Table 1) with respect to age, gender, renal or liver function and presenting arrhythmia. There was no significant difference in dose of the antiarrhythmic drug used. In each patient, the blood level was in the defined therapeutic range. Left ventricular ejection fraction in those who developed congestive heart failure was 20 ± 8% compared with 39 ± 19% among the patients who did not. Although this difference was significant ($p < 0.001$), there was much overlap. A history of heart failure was present in 94% of those who developed congestive heart failure but in only 41% of those who did not develop failure ($p < 0.001$). Ten patients (63%) with compared with 23 patients (6%) without exacerbation of congestive heart failure had cardiomyopathy ($p < 0.001$).

Role of preexisting left ventricular dysfunction. Marked left ventricular dysfunction, defined as a left ventricular ejection fraction <35%, was present in 120 patients of whom 15 (12.5%) had drug-induced congestive heart failure. In contrast, only 1 (0.9%) of 12 patients with an ejection fraction ≥35% (mean 37%) had this complication ($p < 0.001$). Those who developed congestive heart failure did not differ significantly with respect to age, presenting arrhythmia, renal or liver function or dose of antiarrhythmic drug administered from other patients with a history of congestive heart failure (Table 4). However, the group that developed heart failure had a lower ejection fraction (19 ± 8% versus 27 ± 15%, $p < 0.04$) and a greater prevalence of cardiomyopathy (67% versus 9%, $p < 0.001$) and included more women (47% versus 22%, $p < 0.02$).

Discussion

This study documents that each of six of the newer antiarrhythmic drugs has the potential to aggravate congestive heart failure. The overall incidence rate of this complication was low (1.8%). However, when these drugs were administered to patients with a history of heart failure the incidence rate doubled (3.8%). Similar findings had been reported with disopyramide; this complication was noted in 5% of patients without a history of failure in contrast to 55% among those who had experienced heart failure (11).

Predisposing factors. Our attempt to define features that would identify patients predisposed to antiarrhythmic drug-induced congestive failure was only partially successful. Although a history of congestive heart failure and preexisting significant left ventricular dysfunction were predisposing factors, the majority of patients with these clinical features tolerated the antiarrhythmic drugs without further decompensation. Thus, the provocation of congestive heart failure was unpredictable, even among these high risk patients.

Patients were tested with several antiarrhythmic drugs; however, the negative inotropic effect caused by one drug did not predict such susceptibility with other agents, even those of a similar class. Other factors, such as the effect of the drug on peripheral vascular resistance, are also important and may account for differences among these agents. The significantly higher incidence of exacerbation of congestive heart failure among patients with cardiomyopathy is of some interest, but the number of the patients with cardiomyopathy was too small for this finding to be conclusive. The greater prevalence of women among those with worsening congestive heart failure may relate to a greater prevalence of women among patients with cardiomyopathy, in contrast to their low prevalence among patients with coronary artery disease.

Reported incidence of drug-induced congestive heart failure. The incidence of antiarrhythmic drug-induced congestive heart failure has been inadequately documented, especially in patients with serious arrhythmias who have significant left ventricular dysfunction. Soyka (12) reviewed the experience with encainide in 1,245 patients enrolled in several comparative drug trials. Among the 386 patients with a history of congestive failure, possible encainide-induced worsening occurred in 13 (4.1%) in contrast to 7 (0.8%) among 859 patients without preexisting failure. Horn et al. (13) evaluated the safety of tocainide among 369 patients; 5 (1.4%) experienced worsening of heart failure and all were in functional class IV. Reports (14–16) relating the hemodynamic effects of propafenone and mexiletine in patients with left ventricular dysfunction are limited to small numbers of patients, but the conclusions are not dissimilar to the findings of the present study.

Limitations of the study. Our findings are subject to limitations inherent in any retrospective study design. The patient group is variable and there is a possibility of bias in drug selection for individual patients. However, as seen in Table 2, the percent of patients with a history of congestive failure undergoing testing with each drug was similar to the percent of patients with a history of congestive heart failure in the study group as a whole, suggesting that drug selection was not affected by clinical bias. Each patient who developed congestive heart failure was seen by one of the physicians associated with the cardiovascular laboratory and, in each case, resolution of congestive heart failure after drug discontinuation was confirmed by reexamination.

A small number of drug trials involved only short-term drug therapy. It is, therefore, possible that the incidence of congestive failure would have been higher had therapy been extended for longer periods of time. Also, we defined drug-induced congestive heart failure as that which occurred within 2 weeks of initiating therapy. The duration of drug exposure for expression of a negative inotropic effect is unknown and probably variable. Therefore, in some patients, a longer period of drug administration may have been required to precipitate congestive failure. This would be especially true for those drugs that have active metabolites or that require a prolonged period of dosing before therapeutic blood levels are achieved. However, extending the period of observation would introduce numerous confounding factors, thereby reducing the certainty of the role of antiarrhythmic drugs in inducing congestive heart failure.

Conclusions and clinical implications. Antiarrhythmic drugs possess negative inotropic effects and peripheral vascular actions that can aggravate or precipitate congestive heart failure. This complication appears to be more common in patients with significantly impaired left ventricular function, a history of congestive heart failure or cardiomyopathy, but the incidence is low and unpredictable, even among patients at risk. Congestive heart failure is reversible when the drug is discontinued or the dose reduced. Although careful monitoring is advised when these antiarrhythmic drugs are administered to patients with reduced left ventricular ejection fraction and a history of congestive heart failure, they are not contraindicated, even in these high risk patients.

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