Effect of Chronic Amiodarone Therapy on Defibrillation Energy Requirements in Humans

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Amiodarone Effect on Defibrillation Energy Requirement. ***Introduction:*** **The effect of oral amiodarone therapy on defibrillation energy requirements in patients with an implantable defibrillator has not been established.**

Methods and Results: **Twenty-one consecutive patients with implantable biphasic waveform defibrillators underwent a step-down determination of the defibrillation energy requirement 211 ± 12 days before and 73 ± 22 days after initiation of amiodarone therapy (mean total dose 26.7 ± 11.1 g). Serum amiodarone and desethylamiodarone concentrations were measured at the time of defibrillation energy requirement determination. The mean defibrillation energy requirement before amiodarone therapy was 9.9 ± 4.6 J. After initiation of amiodarone therapy, the mean defibrillation energy requirement increased to 13.7 ± 5.6 J ($P = 0.004$). A linear relationship between the amiodarone ($P = 0.02$, $r = 0.6$), desethylamiodarone ($P = 0.02$, $r = 0.6$), and combined amiodarone-desethylamiodarone concentrations ($P = 0.01$, $r = 0.6$) and the defibrillation energy requirement was noted. Stepwise regression analysis demonstrated that the combined amiodarone-desethylamiodarone concentration was the only independent predictor of increase in the defibrillation energy requirement.**

Conclusion: **Chronic oral amiodarone therapy increases the defibrillation energy requirement by approximately 62% in patients with an implantable defibrillator. The combined amiodarone-desethylamiodarone concentration is directly related to the increase in the defibrillation energy requirement.** *(J Cardiovasc Electrophysiol, Vol. 11, pp. 736-740, July 2000)*

implantable defibrillator, ventricular fibrillation, defibrillation threshold

Introduction

Amiodarone is commonly prescribed for patients with an implantable defibrillator who receive frequent shocks for atrial or ventricular arrhythmias.[1-4] The effect of amiodarone on the defibrillation energy requirement is unclear. Indirect evidence suggests that amiodarone elevates monophasic defibrillation energy requirements.[5-8] However, a prospective comparison of defibrillation energy requirements before and after chronic amiodarone administration in patients with an implantable defibrillator has not been reported. The purpose of this study was to determine prospectively the effect of chronic amiodarone therapy on the defibrillation energy requirement in patients with an implantable defibrillator.

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Manuscript received 13 December 1999; Accepted for publication 28 March 2000.

Methods

Patient Population

The study population consisted of 21 patients (19 men and 2 women, mean age 64 ± 15 years) with an implantable defibrillator having biphasic waveforms who were treated with amiodarone (Table 1). Mean left ventricular ejection fraction was 0.31 ± 0.13. Coronary artery disease was present in 13 patients, nonischemic cardiomyopathy was present in 7 patients, and 1 patient had no structural heart disease. The indication for implantable defibrillator placement was aborted sudden cardiac death in 8 patients, sustained ventricular tachycardia in 6, syncope in 4, and nonsustained ventricular tachycardia in 3. The indication for amiodarone therapy was atrial fibrillation in 13 patients and frequent symptomatic ventric-

TABLE 1
Patient Characteristics

Pt. No.	Age (years)	Gender (M/F)	Heart Disease	Ejection Fraction	ICD Indication	Active Can	Baseline DER (J)	Amiodarone Indication	Daily Dose (mg/day)	Duration of Amiodarone Therapy (days)
1	51	M	CAD	0.33	VT	0	5	AF	200	83
2	66	M	CAD	0.27	NSVT	0	14	AF	200	97
3	67	M	CAD	0.24	SCD	0	10	AF	200	24
4	45	M	NICM	0.20	VT	+	10	AF	200	72
5	58	M	NICM	0.18	Syncope	0	8	AF	200	—
6	67	M	CAD	0.32	SCD	0	5	AF	200	68
7	54	M	NICM	0.30	SCD	0	15	AF	400	52
8	52	M	CAD	0.21	VT	+	8	AF	200	43
9	25	M	None	0.60	SCD	0	15	VT	400	89
10	70	M	CAD	0.20	VT	+	6	VT	400	78
11	75	M	CAD	—	NSVT	+	6	AF	200	89
12	46	M	NICM	0.30	NSVT	+	15	VT	400	85
13	74	M	CAD	0.35	VT	0	6	VT	400	70
14	47	M	NICM	0.25	VT	+	15	AF	200	57
15	78	F	NICM	0.35	Syncope	+	4	VT	400	—
16	83	F	CAD	0.25	SCD	+	11	VT	400	—
17	71	M	NICM	0.20	SCD	+	15	AF	200	61
18	84	M	CAD	0.41	Syncope	+	6	VT	400	91
19	82	M	CAD	0.25	Syncope	+	12	AF	200	112
20	70	M	CAD	0.60	SCD	+	5	AF	200	78
21	78	M	CAD	0.55	SCD	+	7	VT	400	74

AF = atrial fibrillation; CAD = coronary artery disease; DER = defibrillation energy requirement; F = female; ICD = implantable cardioverter defibrillator; M = male; NICM = nonischemic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death; VT = ventricular tachycardia; + = present; 0 = absent; — = unavailable.

ular arrhythmias in 8. Nineteen patients had a defibrillator manufactured by Cardiac Pacemakers, Inc. (St. Paul, MN, USA) and 1 patient each had a defibrillator manufactured by Medtronic (Minneapolis, MN, USA) and by Intermedics (Angelton, TX, USA). A transvenous lead with 1 (n = 2; Medtronic, Intermedics) or 2 (n = 18; Cardiac Pacemakers, Inc.) defibrillator coils was used in 20 patients. Epicardial defibrillation and sensing leads were used in the remaining patient. Total time from arrhythmia detection to delivery of shock was 9.5 ± 3.0 seconds. The charging time of the defibrillator after detection was 5.2 ± 2.8 seconds. The generator functioned as a defibrillation electrode in 13 patients. Among the 20 patients with a transvenous lead, 1 required a subcutaneous patch and 1 patient required a single epicardial defibrillation lead.

Defibrillation Energy Requirement Determinations

In the study patients, the defibrillation energy requirement was determined during the implantation procedure, 1 to 2 days after implant, 2 months later, and 2 months after amiodarone therapy was initiated. The most recently determined defibrillation energy requirement before the initiation of amiodarone was defined as the baseline defibrillation energy requirement. The mean time between defibrillator implantation and baseline defibrillation energy requirement determination was 409 ± 450 days. The mean time interval between the baseline defibrillation energy requirement and initiation of amiodarone therapy was 211 ± 212 days.

At each defibrillation energy requirement determination, a step-down protocol was used (15, 10, 8, 6, 4, 3, 2, and 1 J). After ventricular fibrillation was induced using 60-Hz pacing, the implantable defibrillator sensed, charged, and delivered the defibrillation shock. If normal rhythm was restored with the first shock, then the step-down protocol was continued until the first shock was ineffective. When the first shock failed during implantation testing, the programmed shock energy for the next ventricular fibrillation induction was 20 J. If the 20-J shock failed, then a subcutaneous defibrillation electrode was added to the system, and the step-down protocol was repeated. At least 5 minutes elapsed between each ventricular fibrillation induction.

Amiodarone Administration

The mean total dose of amiodarone before the amiodarone defibrillation energy requirement determination was 26.7 ± 11.1 g. The mean total dose of amiodarone consisted of a mean amiodarone loading dose of 680 ± 166 mg/day for 12.6 ± 5.9 days, and a total mean loading dose of 9.1 ± 5.2 g. This was followed by a maintenance dose of amiodarone 276 ± 100 mg/day. The total duration of amiodarone therapy before the amiodarone defibrillation energy requirement determination was 73 ± 21 days.

At the time of defibrillation energy requirement determination 2 months after the initiation of amiodarone therapy, a venous blood sample was obtained and the serum amiodarone and desethylamiodarone concentrations determined using high-performance liquid chromatography.

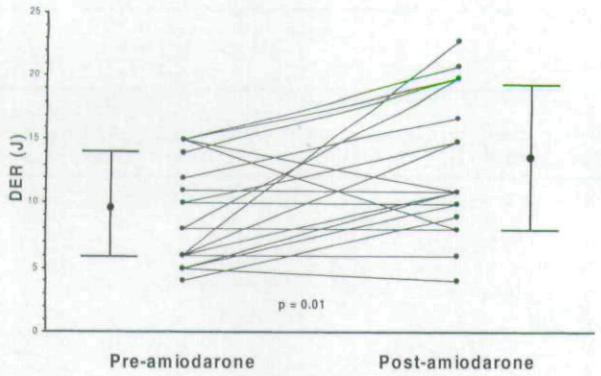

Figure 1. *Comparison of individual defibrillation energy requirements (DER) before and after chronic oral amiodarone therapy.*

Statistical Analysis

Continuous variables are expressed as mean ± 1 SD and were compared using a paired or unpaired *t*-test, as appropriate. Regression analysis was used to assess a relationship between two continuous variables. Stepwise regression analysis was used to test for independence between variables. A Chi-square or Fisher's exact test was used to compare nominal variables. $P < 0.05$ was considered statistically significant.

Results

The baseline defibrillation energy requirement was 9.4 ± 4.6 J and the defibrillation energy requirement after amiodarone therapy was 13.7 ± 5.6 J ($P = 0.01$; Fig. 1). The defibrillation energy requirement increased by 4.0 ± 5.3 J or 62% ± 74%. The shocking resistance before (47 ± 12 Ω) and after amiodarone therapy (46 ± 7 Ω) did not change significantly ($P = 0.8$).

The mean amiodarone, desethylamiodarone, and combined amiodarone-desethylamiodarone concentrations were 1.1 ± 0.56 mg/dL, 1.0 ± 0.44 mg/dL, and 2.1 ± 0.96 mg/dL, respectively. There was a linear relationship between the serum amiodarone concentration and the defibrillation energy requirement ($r = 0.6$, $P = 0.02$), the change in defibrillation energy requirement ($r = 0.8$, $P = 0.001$), and the percent change in defibrillation energy requirement ($r = 0.7$, $P = 0.004$; Fig. 2). The serum desethylamiodarone concentration also demonstrated a linear relationship with the defibrillation energy requirement ($r = 0.6$, $P = 0.02$), change in the defibrillation energy requirement ($r = 0.8$, $P = 0.002$), and percent change in the defibrillation energy requirement ($r = 0.7$, $P = 0.003$; Fig. 3). Additionally, a linear relationship was observed between the combined amiodarone-desethylamiodarone concentrations and the defibrillation energy requirement ($r = 0.6$, $P = 0.01$), change in the defibrillation energy requirement ($r = 0.7$, $P = 0.002$), and percent change in defibrillation energy requirement ($r = 0.7$, $P = 0.002$; Fig. 4). Stepwise regression analysis of amiodarone, desethylamiodarone, and combined amiodarone-desethylamiodarone concentrations demonstrated that only the combined concentrations of amiodarone and desethylamiodarone were independently associated with the defibrillation energy requirement.

There was no relationship between the defibrillation energy requirement and the daily amiodarone dose ($P = 0.6$), duration of amiodarone therapy ($P = 0.2$), total dose of amiodarone ($P = 0.1$), or interval between the defibrillation energy requirement determinations ($P = 0.4$). No clinical characteristics, including age, gender, ejection fraction, type of heart disease, or indication for implantable defibrillator therapy, correlated with the defibrillation energy requirement, change in defibrillation energy requirement, or percent change in the defibrillation energy requirement.

Discussion

Major Findings

The results of this prospective study demonstrate that chronic amiodarone therapy increases the defibrillation energy requirement by approximately 60%. Furthermore, the combined serum concentrations of amiodarone and desethylamiodarone independently correlate with the defibrillation energy requirement after initiation of amio-

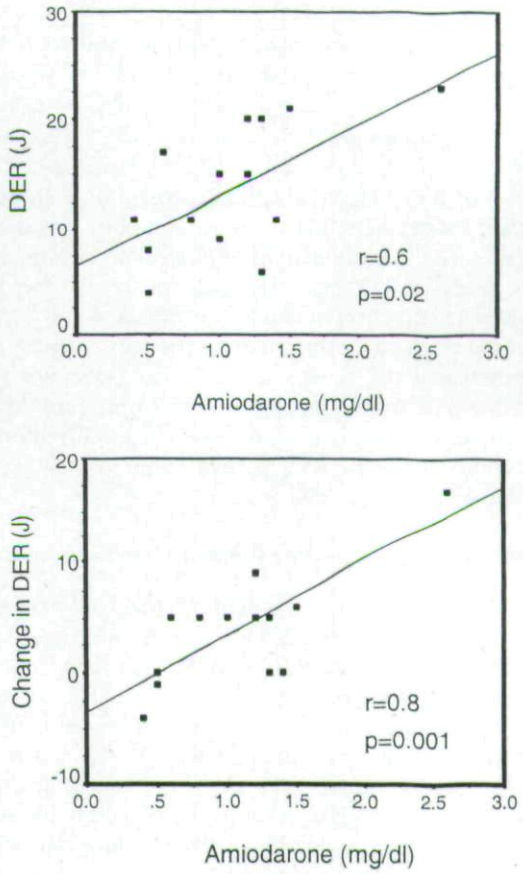

Figure 2. *Correlation of serum amiodarone concentrations with defibrillation energy requirement (DER; top panel) and change in defibrillation energy requirement (bottom panel).*

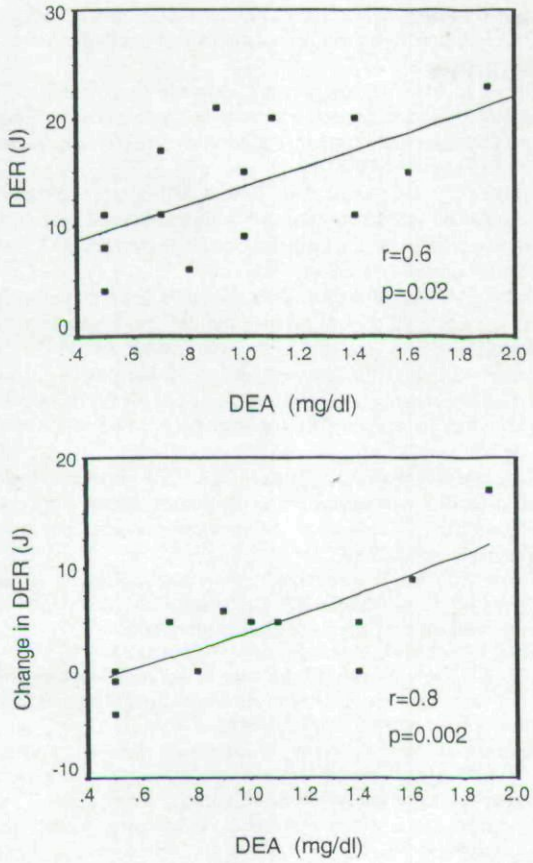

Figure 3. *Correlation of serum desethylamiodarone (DEA) concentration with defibrillation energy requirement (DER; top panel) and change in defibrillation energy requirement (bottom panel).*

darone therapy in patients with an implantable defibrillator.

Mechanism

The mechanism of amiodarone's effects on the defibrillation energy requirement is unclear, perhaps because the mechanism of successful defibrillation is controversial. Some investigators proposed that a defibrillation shock must be of sufficient energy to depolarize the myocardium in varying states of refractoriness.[9] This results in uniform ventricular refractoriness and termination of the fibrillation. Amiodarone and its metabolite desethylamiodarone increase action potential duration by blocking potassium channels.[10,11] Amiodarone's Class III effects may increase the volume of refractory myocardium, thereby necessitating a stronger shock for successful defibrillation.

Previous Studies

This is the first published study to compare the defibrillation energy requirement before and after the initiation of oral amiodarone therapy. The present study evaluated this relationship only with biphasic defibrillation. This is also the first published study to demonstrate that the amiodarone and desethylamiodarone concentrations correlate with the biphasic defibrillation energy requirement.

Only one previous study evaluated the relationship between amiodarone and desethylamiodarone concentrations and the defibrillation energy requirement.[8] In that study, amiodarone therapy correlated with an increased monophasic defibrillation energy requirement and a higher frequency of a subcutaneous defibrillation electrode use.[8] However, the drug concentration did not correlate with defibrillation efficacy.[8] The difference between that previous study and the present study may be due to different effects of amiodarone on biphasic and monophasic defibrillation.

Limitations

The major limitation of this study is the small sample size. Second, this study did not control for the effect of time on the defibrillation energy requirement. The mean time from defibrillator implantation to the study's baseline defibrillation requirement determination was 400 days. If biphasic defibrillation efficacy changes over time, it occurs within 2 months of implantation and then probably remains stable over at least 2 years.[12-14]

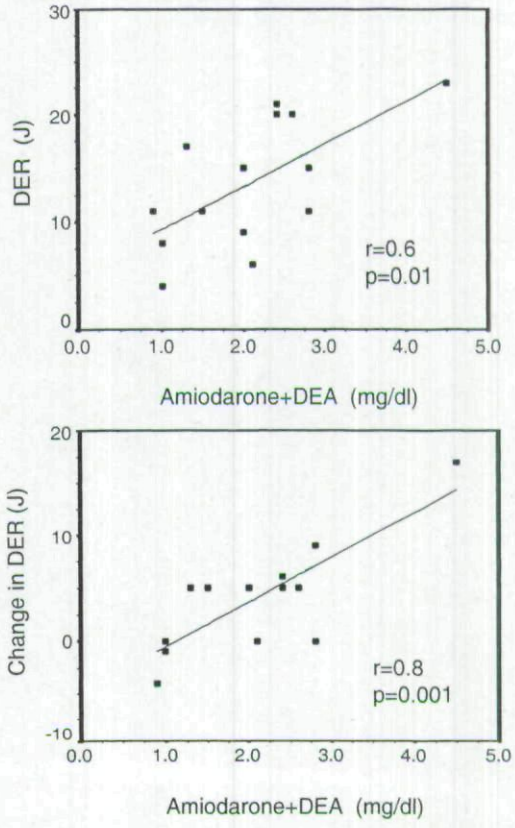

Figure 4. *Correlation of combined serum concentration of amiodarone and desethylamiodarone (amiodarone+DEA) with defibrillation energy requirement (DER; top panel) and change in defibrillation energy requirement (bottom panel).*

Clinical Implications

The results of this study suggest that the defibrillation energy requirement should be determined 2 to 3 months after amiodarone therapy is initiated in patients with an implantable defibrillator. This may be especially important for patients in whom increases in the defibrillation energy requirement may compromise the defibrillator safety margin.

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