Risk Factors for the Development of Specific Noncardiovascular Adverse Effects Associated With Amiodarone

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Noncardiovascular adverse effects associated with amiodarone result in substantial morbidity. Adverse effects involving the skin, liver, thyroid, and lungs have been reported in as many as 57%, 55%, 11%, and 13% of patients, respectively. Although risk factors for some amiodarone-induced adverse effects have been identified, risk factors for these specific side effects have not been systematically evaluated. Therefore, risk factors for development of amiodarone-induced dermatologic, hepatic, thyroid, or pulmonary adverse effects were identified using univariate analysis in 44 patients receiving the drug for supraventricular or ventricular arrhythmias (mean duration of therapy 99.5 ± 110.8 weeks). Dermatologic side effects occurred in 4 (9.1%) patients. Patients who experienced dermatologic side effects were younger than patients who did not (mean age, 48.3 ± 15.8 years versus 60.1 ± 9.5 years, respectively; P = .03). Patients younger than 60 years of age were more likely to develop photosensitivity or blue-gray skin discoloration than those aged 60 or older (P = .05). Hepatic adverse effects occurred in 3 (6.8%) patients. Left ventricular ejection fraction was lower in those who developed hepatic adverse effects than in those who did not (15.0 ± 4.0% versus 39.1 ± 13.9%, P = .005). Adverse thyroid effects occurred in 6 (13.6%) patients; and pulmonary fibrosis occurred in 2 (4.5%) patients. No specific risk factors for adverse thyroid effects or pulmonary fibrosis were revealed. In conclusion, age less than 60 may be a risk factor for amiodarone-induced dermatologic adverse effects, whereas severely depressed left ventricular ejection fraction may be a risk factor for hepatic side effects associated with amiodarone.

The adverse effect profile of the antiarrhythmic agent amiodarone has been well described.[1] The overall incidence of adverse effects attributable to amiodarone therapy ranges from 34 to 93%, and in 1 to 26% of patients receiving amiodarone therapy must be discontinued as a result of side effects.[1] Although amiodarone may produce cardiovascular adverse effects such as exacerbation of heart failure and proarrhythmia, these effects occur rarely. Noncardiovascular side effects associated with amiodarone—such as those involving the gastrointestinal tract, central nervous system, liver, thyroid, skin, and lungs—occur more commonly, and are more likely to limit use of the drug.[1] Although amiodarone is a highly effective agent, the noncardiovascular adverse effect profile has resulted in the recommendation that its use be limited to patients with arrhythmias refractory to therapy with other antiarrhythmic agents.[2,3]

Despite these recommendations, some authors have advocated study[4] or use[5] of amiodarone earlier in the course of certain arrhythmias, because of concerns about the safety of antiarrhythmic drugs from other Vaughan Williams classes.[6,7] In addition, preliminary data suggest that, unlike other antiarrhythmic agents such as encainide or flecainide,[8] amiodar-

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one may result in decreased mortality in patients with asymptomatic complex ventricular ectopic activity after acute myocardial infarction.[9–11] If these data are confirmed in continuing larger studies in this population and/or in patients with left ventricular dysfunction,[12] use of amiodarone is likely to become more widespread, and amiodarone may be given earlier in the course of arrhythmia therapy than is currently recommended. Thus, with the relatively high frequency of side effects associated with this agent, identification of risk factors for amiodarone-induced adverse effects is desirable, so that patients at risk may be monitored more closely, protective measures taken, and/or alternative therapy selected if necessary.

Risk factors for the development of certain adverse effects associated with amiodarone have been identified. Cumulative amiodarone dose and duration of therapy appear to be risk factors for many of the drug's adverse effects.[13,14] Pulmonary fibrosis,[15] some central nervous system effects,[13,16] and corneal microdeposits[17] appear to be associated with high daily amiodarone doses. Some adverse effects caused by the drug, such as those involving the central nervous system, are often associated with elevations in serum amiodarone/desethylamiodarone (DEA) concentrations.[18] Risk factors for other specific noncardiovascular adverse effects caused by amiodarone have not been systematically evaluated.

Dermatologic, hepatic, thyroid, and pulmonary adverse effects associated with amiodarone have been reported in as many as 57%, 55%, 11%, and 13% of patients, respectively.[19–22] However, despite high frequencies of these side effects, risk factors have not been well-studied. The purpose of this study is to determine risk factors for amiodarone-associated dermatologic, hepatic, thyroid, or pulmonary adverse effects.

METHODS

Patient Population

This study was a retrospective review of adverse effect data collected prospectively from a series of 44 consecutive patients referred to the Cardiac Electrophysiology Service at Henry Ford Hospital, who received amiodarone for the management of cardiac arrhythmias.

Data Collection

Specific noncardiovascular adverse effects evaluated were defined as follows: (1) dermatologic toxicity: blue-gray skin discoloration or photosensitivity; (2) hepatic abnormalities, including elevations in serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, τ-glutamyltransferase, or bilirubin greater than twice baseline, with or without symptomatic liver dysfunction; (3) thyroid toxicicty, including elevations or reductions in serum L-thyroxine (T_4), 3,5,3′-triiodo-L-thyronine (T_3), T_3 resin uptake, or thyroid stimulating hormone, with or without symptomatic hypo- or hyperthyroidism; and (4) pulmonary toxicicty, specifically pulmonary fibrosis or interstitial pneumonitis.

The following patient characteristics were evaluated as potential risk factors for these amiodarone-induced adverse effects: gender; age; race; left ventricular ejection fraction (EF), as determined by left ventriculography, 2-dimensional echocardiography, or radionuclide ventriculography; congestive heart failure, as determined by patient history and physical examination; coronary artery disease; serum amiodarone concentration at the time of each adverse effect, and combined serum amiodarone/DEA concentration at the time of each adverse effect.

Data Analysis

Risk factors for all categories of adverse effects were determined using univariate analysis. Nonparametric data were analyzed using chi-square analysis, unless expected cell frequencies were less than 5, in which case the Fisher exact test was used. Parametric data were analyzed using the Student unpaired t test, with the exception of cumulative amiodarone dose and duration of amiodarone therapy, which were not normally distributed, and therefore were analyzed using the Mann-Whitney test. For all analyses, $P < .05$ was considered suggestive,[23] and $P < .006$ (.05/9, adjusted for multiple comparisons) was considered significant.

RESULTS

Patient Characteristics

Characteristics of the 44 patients included in this study are presented in Table I. Twenty-one (47%) patients were older than 60 years of age. The majority of patients had coronary artery disease and/or congestive heart failure; 24 (55%) patients had EF of 40% or lower. Almost all patients were receiving amiodarone for the management of ventricular arrhythmias. Most patients had arrhythmias refractory to therapy with other agents; 38 (86%) patients had received prior therapy with 2 or more antiarrhythmic drugs or drug combinations, which were either ineffective or intolerable.

TABLE I

Patient Characteristics

Patients (n)	44
Male/female (n)	33/11
Whites/Blacks	38/6
Mean age (yr)	59 ± 11 (25–75)
Previous MI (n)	28
CAD (n)	30
CHF (n)	34
Mean EF (%)	37 ± 15 (15–70)
Presenting arrhythmia (n)	
Ventricular tachycardia	29
Sudden cardiac death	11
Ventricular premature beats	1
Atrial fibrillation	1
Syncope	2
Mean no. of antiarrhythmic drugs that failed	3.1 ± 1.5 (0–6)
Mean duration of amiodarone therapy (wk)	99.5 ± 110.8 (1.4–477.8)

CAD = coronary artery disease; CHF = congestive heart failure; EF = left ventricular ejection fraction; MI = myocardial infarction.
Values in parentheses are ranges.

TABLE II

Risk Factors for Adverse Dermatologic Effects

	Dermatol AE (n = 4)	No Dermatol AE (n = 40)	P
Male/female	4:0	29:11	0.56
Age (yr)	48.3 ± 15.8	60.1 ± 9.5	0.03
Whites/Blacks	4:0	34:6	1.00
Duration of therapy (wk)	74.0 ± 59.3	88.1 ± 108.9	0.58
Cumulative dose (g)	211.8 ± 188.6	194.5 ± 236.2	0.64
EF (%)	48.0 ± 18.1	36.7 ± 14.5	0.21
CHF	2 (50%)	32 (80%)	0.22
Serum A (μg/mL)	N/A*	1.8 ± 0.9	N/A
Serum A + DEA (μg/mL)	3.2 ± 0.7	2.2 ± 1.0	0.18

AE = adverse effects; A = amiodarone; N/A = not applicable; DEA = desethylamiodarone.
**Serum A concentrations reported only in combination with DEA in these patients.*

Dermatologic Adverse Effects

Dermatologic adverse effects occurred in 4 (9.1%) patients (Table II). One patient had blue-gray skin discoloration, and 3 patients experienced photosensitivity reactions. Patients with dermatologic reactions to amiodarone tended to be younger than those who did not experience these adverse effects; patients younger than 60 years were more likely to develop these side effects than those 60 years or older ($P = .05$).

Hepatic Adverse Effects

Adverse hepatic effects occurred in 3 (6.8%) patients (Table III). Two patients developed asymptomatic elevations in liver function tests: In one, serum τ-glutamyltransferase concentration became elevated more than 15 times baseline (to a maximum of 640 U/L), and total serum bilirubin concentration became elevated to approximately twice baseline (maximum of 1.9 mg/dL). The other patient developed elevation in serum alkaline phosphatase concentration of more than 5 times baseline (maximum of 613 U/L). The third patient developed clinical hepatic dysfunction manifested by abdominal tenderness, which responded to a decrease in amiodarone dosage. Left ventricular EF was significantly lower in patients who developed amiodarone-associated hepatic adverse effects than in those who did not.

Thyroid Adverse Effects

Adverse thyroid effects occurred in 6 (13.6%) patients (Table IV). Four patients developed asymptom-

TABLE III

Risk Factors for Hepatic Adverse Effects

	Hepatic AE (n = 3)	No Hepatic AE (n = 41)	P
Male/female	2:1	31:10	1.00
Age (yr)	68.3 ± 2.5	58.3 ± 10.6	0.11
Whites/Blacks	3:0	35:6	1.00
Duration of therapy (wk)	49.2 ± 35.8	97.2 ± 112.6	0.78
Cumulative dose (g)	138.2 ± 88.7	224.3 ± 271.9	1.00
EF (%)	15.0 ± 4.0	39.1 ± 13.9	0.005
CHF	3 (100%)	31 (76%)	1.00
Serum A (μg/mL)	N/A*	1.8 ± 0.9	N/A
Serum A + DEA (μg/mL)	2.4 ± 0.4	2.3 ± 1.0	0.89

Abbreviations are the same as in Table II.
**Serum A concentrations reported only in combination with DEA in these patients.*

TABLE IV

Risk Factors for Adverse Thyroid Effects

	Thyroid AE (n = 6)	No Thyroid AE (n = 38)	P
Male/female	5:1	28:10	1.00
Age (yr)	53.5 ± 16.2	59.8 ± 9.4	0.18
Whites/Blacks	6:0	32:6	0.57
Duration of therapy (wk)	153.9 ± 133.1	75.4 ± 89.1	0.13
Cumulative dose (g)	389.2 ± 419.8	172.8 ± 209.1	0.18
EF (%)	46.6 ± 22.6	36.2 ± 13.4	0.14
CHF	3 (50%)	31 (82%)	0.23
Serum A (μg/mL)	2.1 ± 0.5	1.8 ± 0.9	0.65
Serum A + DEA (μg/mL)	3.0 ± 0.4	2.2 ± 1.0	0.27

Abbreviations are the same as in Table II.

atic elevation of serum T_4 concentrations; 1 patient developed asymptomatic reduction in serum thyroid-stimulating hormone concentrations. One patient developed severe hyperthyroidism requiring therapy with propylthiouracil. None of the factors evaluated was significantly different in patients who experienced adverse thyroid effects compared with those who did not.

Pulmonary Adverse Effects

Two patients (4.5%) developed pulmonary fibrosis during therapy with amiodarone (Table V). None of the characteristics evaluated was revealed as a risk factor for amiodarone-associated pulmonary toxicity.

DISCUSSION

Amiodarone is effective for the management of a variety of cardiac arrhythmias, particularly for those refractory to therapy with other agents. For this reason, and because of concerns about the safety of class I antiarrhythmic agents, amiodarone use continues to increase. However, amiodarone administration results in a relatively high frequency of noncardiovascular adverse effects. Prediction of patients likely to experience specific adverse effects may be clinically useful, so that such patients may be monitored more closely, preventive measures taken, or alternative therapy selected if appropriate. In the present study, age less than 60 years was suggestive as a risk factor for dermatologic toxicity, whereas severely depressed left ventricular EF was a significant risk factor for development of adverse hepatic effects.

Dermatologic Adverse Effects

Age was suggestive as a risk factor for dermatologic adverse reactions associated with amiodarone. Patients who experienced these adverse reactions were younger than those who did not; patients younger than 60 years of age appeared to be at highest risk. Similarly, Hyatt and associates[24] noted a lower frequency of adverse dermatologic reactions associated with amiodarone in elderly patients than previously reported in younger patient populations.[19] This may be due to greater exposure to the sun in younger patients than in the elderly. In addition to this factor, it appears likely that duration of therapy and cumulative amiodarone dose are also risk factors for dermatologic adverse effects.[19] In this study, age-associated increases in the risk of dermatologic side effects were independent of duration of therapy and cumulative dose; these parameters were not significantly different in patients who experienced adverse dermatologic reactions compared with those who did not, likely because the mean duration of therapy in patients in this study was less than two years.[19]

Hepatic Adverse Effects

Mean left ventricular EF was significantly lower in patients who developed hepatic adverse effects com-

TABLE V

Risk Factors for Pulmonary Fibrosis

	Pulmonary Fibrosis (n = 2)	No Pulmonary Fibrosis (n = 42)	P
Male/female	1:1	32:10	0.44
Age (yr)	66.5 ± 0.7	58.6 ± 10.7	0.31
Whites/Blacks	2:0	36:6	1.00
Duration of therapy (wk)	57.2 ± 46.9	99.8 ± 112.6	0.98
Cumulative dose (g)	154.7 ± 113.8	231.2 ± 269.7	0.98
EF (%)	34.5 ± 21.9	37.6 ± 14.7	0.78
CHF	2 (100%)	32 (76%)	1.00
Serum A (μg/mL)	N/A*	1.8 ± 0.9	N/A
Serum A + DEA (μg/mL)	2.4 ± 0.3	2.3 ± 1.0	0.89

Abbreviations are the same as in Table II.
** Serum amiodarone concentrations reported only in combination with DEA in these patients.*

pared with those who did not. This may be due to underperfusion or congestion of the liver in patients with low cardiac outputs associated with extremely low left ventricular EFs. Harris and colleagues[19] found significant correlations between serum amiodarone and DEA concentrations and elevations in serum aspartate transaminase concentrations. In the present study, combined serum amiodarone/DEA concentrations were not different in those with hepatic dysfunction compared with those without.

Thyroid Adverse Effects

Risk factors for thyroid adverse effects associated with amiodarone were not revealed in this study. Although previous investigators have suggested that older patients might be at increased risk for amiodarone-induced thyroid disease,[19] our findings did not confirm this. Other investigators have also been unable to identify predictive factors for amiodarone-induced thyroid disease.[25] Baerman and associates[26] found no correlation between serum amiodarone or DEA concentrations and serum reverse T_3 concentrations. In the present study, serum amiodarone or DEA concentrations were not different in those with thyroid disease than in those without. Trip and Wiersinga[27] reported that the development of amiodarone-induced hypothyroidism was related to the presence of pretreatment microsomal and/or thyroglobulin antibodies. In the same study, predictive factors for the development of amiodarone-induced thyrotoxicity could not be identified.

Pulmonary Adverse Effects

Risk factors for the development of amiodarone-induced pulmonary fibrosis were not revealed in this study. However, the fact that only two patients developed pulmonary fibrosis may have precluded identification of risk factors. Previous investigators have suggested that patients with abnormal pretreatment lung function may be at risk for pulmonary toxicity associated with amiodarone.[28] In addition, the risk of pulmonary toxicity may be related to the duration of amiodarone therapy and/or cumulative amiodarone dose,[15] although studies have been inconsistently successful at correlating these factors with the development of amiodarone-induced pulmonary adverse effects.[18,29]

Limitations

Interpretation of the study results is limited by the retrospective nature of the data collection. However, all patients reported herein were observed prospectively for the development of adverse effects. In addition, because of the retrospective nature of the study, it was nonrandomized. Therefore, some treatment bias may exist; the electrophysiologist managing these patients may have avoided amiodarone or used lower doses in certain patients considered at higher risk for toxicity, such as the elderly or those with poor left ventricular function. The sample size was relatively small, and small numbers of patients developed specific amiodarone-induced noncardiovascular adverse events. Nevertheless, risk factors were identifiable for specific toxicities. It is possible that some existing risk factors for these adverse effects were not identified owing to small numbers of patients in certain side effect groups (type II error).

CONCLUSIONS

Amiodarone-induced dermatologic, hepatic, thyroid, or pulmonary adverse effects occur relatively frequently. However, risk factors have been identified that may help to predict the development of some specific noncardiovascular adverse effects. Age less than 60 years may be a risk factor for dermatologic adverse effects. Severely depressed left ventricular ejection fraction may be a risk factor for elevations in liver function tests and hepatic toxicity. Further study in larger patient populations is required to confirm these findings.

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