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Cardiovascular Adverse Drug Reactions during Initiation of Antiarrhythmic Therapy for Atrial Fibrillation

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ABSTRACT

Background: Patients with atrial fibrillation are often admitted to hospital for pharmacological cardioversion. However, it has been suggested that for patients without underlying heart disease, it might be safe to initiate antiarrhythmic drug therapy in the community setting.

Objective: To compare the frequency of cardiovascular adverse drug reactions during attempted pharmacological cardioversion of atrial fibrillation in patients with and without underlying heart disease.

Methods: A review of health records for patients admitted to hospital over a 1-year period for pharmacological cardioversion of atrial fibrillation or for whom atrial fibrillation was the primary diagnosis. Cardiovascular adverse reactions were defined as one or more of the following: bradycardia (heart rate less than 60 beats per minute), hypotension (systolic blood pressure less than 100 mm Hg), sinus pause (greater than 2 s), prolonged QT interval (longer than 0.55 s), or ventricular proarrhythmia (ventricular tachycardia, including *torsades de pointes*).

Results: During the study period, 106 patients received a total of 175 drug courses for conversion of atrial fibrillation. Of these drug courses, 81 (46%) resulted in at least one cardiovascular adverse drug reaction, and 21 (12%) resulted in discontinuation of the drug therapy. For drug courses given to patients with underlying heart disease, there was a significantly higher relative risk of cardiovascular adverse drug reactions (66% versus 36% of drug courses; relative risk 1.83, 95% confidence interval 1.33 to 2.51), and a nonsignificant trend toward increased risk of drug discontinuation because of these adverse reactions (19% versus 9%; relative risk 2.16, 95% confidence interval 0.99 to 4.72).

Conclusion: The risk of cardiovascular adverse drug reactions during initiation of antiarrhythmic therapy was higher for patients with underlying heart disease; however, even for patients without other heart disease, the risk of adverse drug reactions appeared high enough to warrant admission to hospital.

Key words: atrial fibrillation, antiarrhythmic agents, adverse drug reactions

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RÉSUMÉ

Historique : Les patients atteints de fibrillation auriculaire sont souvent admis à l'hôpital pour une cardioversion pharmacologique. Cependant, il existe des recommandations à l'effet que le traitement antiarythmique pouvait être amorcé de façon sûre dans les milieux communautaires chez les patients qui souffrent de fibrillation auriculaire en absence de cardiopathie.

Objectif : Comparer la fréquence des réactions cardiovasculaires indésirables secondaire à une cardioversion pharmacologique de la fibrillation auriculaire chez les patients qui avaient ou non une cardiopathie sous-jacente.

Méthodes : Les dossiers médicaux des patients admis à l'hôpital au cours d'une période d'une année pour une cardioversion pharmacologique d'une fibrillation auriculaire ou pour qui la fibrillation auriculaire était le diagnostic primaire ont été passés en revue. Les réactions cardiovasculaires indésirables ont été définies comme étant la bradycardie (fréquence cardiaque inférieure à 60 bpm), l'hypotension (tension systolique inférieure à 100 mm de Hg), l'arrêt (de plus de 2 s), l'intervalle Q-T allongé (supérieur à 0,55 s), ou encore la proarythmie ventriculaire (tachycardie ventriculaire, y compris torsades de pointes).

Résultats : Au cours de la période d'étude, 106 patients ont reçu un total de 175 cardioversions pharmacologiques pour leur fibrillation auriculaire. De ces traitements médicamenteux, 81 (46 %) ont provoqué au moins une réaction cardiovasculaire indésirable et 21 (12 %) ont entraîné l'arrêt du traitement. Chez les patients atteints d'une cardiopathie sous-jacente et qui ont reçu une cardioversion pharmacologique, le risque relatif de réaction cardiovasculaire indésirable était considérablement supérieur (66 % contre 36 %; risque relatif de 1,83; intervalle de confiance à 95 % : 1,33 à 2,51) et on a observé une tendance non significative de risque accru d'interruption du traitement à cause des réactions cardiovasculaires indésirables au médicament (19 % contre 9 %; risque relatif de 2,16; intervalle de confiance à 95 % : 0,99 à 4,72).

Conclusion : Le risque de réaction cardiovasculaire indésirable durant l'administration du traitement antiarythmique était plus élevé chez les patients qui souffraient de fibrillation auriculaire et de cardiopathie sous-jacente. En revanche, même chez les patients ne présentant aucune autre cardiopathie, le risque de réaction indésirable au médicament semblait être suffisant pour commander l'hospitalisation.

Mots clés : fibrillation auriculaire, antiarythmiques, réactions indésirables à un médicament

INTRODUCTION

Patients with atrial fibrillation are often admitted to hospital for pharmacological cardioversion or initiation of antiarrhythmic therapy for maintenance of sinus rhythm. Monitoring is generally recommended to screen for drug-related cardiovascular adverse events.[1] It has been postulated that for some patients with atrial fibrillation, antiarrhythmic drugs could be safely initiated in the community setting.[2] Identifying such a population would limit the number of hospital admissions required for this indication and would avoid considerable health-care costs.

The presence of underlying cardiac disease is associated with an increased incidence of adverse effects from antiarrhythmic drug therapy.[3–5] For example, it is well documented that proarrhythmia is more common in patients with diminished left ventricular function.[3,5] The objective of this study was to compare the frequency of cardiovascular adverse drug reactions during attempted pharmacological cardioversion of atrial fibrillation in patients with and without underlying heart disease. This investigation was carried out in an effort to identify a population in whom antiarrhythmic therapy for atrial fibrillation can be initiated safely in the community.

METHODS

This study consisted of a review of medical records at a 350-bed community hospital with 6 coronary care unit and 10 general cardiology beds. Inclusion criteria were as follows: patient admitted between July 1, 1995, and June 30, 1996; primary diagnosis of atrial fibrillation or admission for elective cardioversion of atrial fibrillation (according to physician's diagnosis in medical record discharge summary); and administration of at least one of the study drugs: quinidine, propafenone, procainamide, sotalol, or amiodarone.

The patients were grouped according to the presence or absence of heart disease, defined as ischemic heart disease, previous myocardial infarction, heart failure, valvular disease, previous ventricular arrhythmia, or a documented conduction abnormality. Adverse drug reactions were defined as follows: bradycardia (heart rate less than 60 beats/min), hypotension (systolic blood pressure less than 100 mm Hg), sinus pause (greater than 2 s), prolonged QT interval (greater than 0.55 s), or ventricular proarrhythmia (ventricular tachycardia, including *torsades de pointes*). These definitions were based on those reported in other studies of adverse drug reactions in patients with atrial fibrillation.[4,6,7] Uncorrected QT intervals were used in place of corrected QT intervals, because in some cases the corrected value was not available or could not be calculated from the information in the health record. The threshold of 0.55 s for the QT interval was based on the recommendations of McCollam and others.[8] All adverse drug reactions occurring in hospital during the treatment course for each target medication were recorded. Since it is often difficult to retrospectively assign causality to a medication, note was made of cases where drug courses were discontinued or altered specifically because of an adverse drug event.

The number and types of adverse drug reactions were summarized with descriptive statistics. The relative risk and 95% confidence intervals for adverse drug reactions occurring in patients with and without heart disease were calculated.[9] Because some patients received more than one drug course, all results were calculated according to the number of drug courses involved, as well as the number of patients experiencing each type of event.

RESULTS

During the study period, 106 patients received 175 drug courses for conversion of atrial fibrillation. Of these drug courses, 81 (46%) resulted in at least one cardiovascular adverse drug reaction, and in 21 cases (12% of the total) drug therapy was discontinued because of a cardiovascular adverse drug reaction. The mean time ± standard deviation from initiation of a drug course to the adverse event was 17.9 ± 15.4 h.

Patient characteristics are presented in Table 1. Patients experiencing an adverse drug reaction were slightly older and were more likely to have underlying heart disease. The types of heart disease identified included ischemic heart disease (18 patients), previous myocardial infarction (6 patients), heart failure (13 patients, including 1 patient with dilated cardiomyopathy), valvular disease (9 patients), previous ventricular arrhythmia (2 patients), and conduction abnormality (1 patient [sick-sinus syndrome]). Some patients presented with more than one cardiac abnormality.

As outlined in Table 2, bradycardia was the most common adverse drug reaction. Adverse drug reactions stratified by drug are presented in Table 3. Sotalol was associated with the highest rate of drug discontinuation because of an adverse reaction. There were 2 cases in which the antiarrhythmic drug was discontinued because of ventricular proarrhythmia, both in patients

Table 1. Characteristics and Treatment of Patients with and without Cardiovascular Adverse Drug Reactions

Characteristic	With Adverse Drug Reactions (*n* = 49)	Without Adverse Drug Reactions (*n* = 57)
Mean age ± SD (years)	72 ± 9	62 ± 18
Sex (no. and % male)	25 (51)	33 (58)
Concurrent agent for control of heart rate (no. and % of patients)	36 (73)	38 (67)
Heart disease (no. and % of patients)	21 (43)	17 (30)
Drug courses* (no. of courses)	81	94
Quinidine	20	38
Propafenone	22	27
Procainamide	9	24
Sotalol	23	3
Amiodarone	7	2

*Some patients received more than one drug course.

Table 2. Cardiovascular Adverse Drug Reactions in the Presence and Absence of Heart Disease

Adverse Drug Reaction	No. (and %) of Drug Courses	
	In Patients with Heart Disease (*n* = 36)	In Patients without Heart Disease (*n* = 70)
No. of drug courses	59 (100)	116 (100)
Type of adverse drug reaction		
Bradycardia (HR < 60 beats/min)	18 (31)	23 (20)
Hypotension (SBP < 100 mm Hg)	9 (15)	4 (3)
Sinus pauses (>2 s)	9 (15)	9 (8)
Prolonged QT interval (>0.55 s)	3 (5)	3 (3)
Ventricular proarrhythmia	0	3 (3)

HR = heart rate, SBP = systolic blood pressure.

Table 3. Types of Cardiovascular Adverse Drug Reactions (ADRs) Associated with Different Drugs

Drug	No. (and %) of Drug Courses*					
	Overall	Bradycardia	Hypotension	Sinus Pauses	Prolonged QT Interval	Ventricular Proarrhythmia
Quinidine	58 (100)					
ADRs	20 (34)	7 (12)	3 (5)	5 (9)	3 (5)	2 (3)
Drug discontinued	6 (10)	1 (2)	0	1 (2)	2 (3)	2 (3)
Propafenone	49 (100)					
ADRs	22 (45)	15 (31)	2 (4)	5 (10)	0	0
Drug discontinued	5 (10)	2 (4)	1 (2)	2 (4)	0	0
Procainamide	33 (100)					
ADRs	9 (27)	3 (9)	5 (15)	0	1 (3)	0
Drug discontinued	2 (6)	0	1 (3)	0	1 (3)	0
Sotalol	26 (100)					
ADRs	23 (88)	13 (50)	3 (12)	4 (15)	2 (8)	1 (4)
Drug discontinued	7 (27)	4 (15)	1 (4)	2 (8)	0	0
Amiodarone	9 (100)					
ADRs	7 (78)	3 (33)	0	4 (44)	0	0
Drug discontinued	1 (11)	0	0	1 (11)	0	0

*Total number of drug courses was 175.

without underlying heart disease who received quinidine.

There were trends toward patients with heart disease having a higher risk of experiencing an adverse drug reaction than those without underlying heart disease (58% versus 40% of patients; relative risk 1.46, 95% confidence interval 0.97 to 2.20) and of having their antiarrhythmic medication discontinued because of an adverse reaction (22% versus 13% of patients; relative risk 1.73, 95% confidence interval 0.73 to 4.10). In terms

of drug courses administered, cardiovascular adverse drug reactions were more common in patients with underlying heart disease (66% versus 36% of drug courses; relative risk 1.83, 95% confidence interval 1.33 to 2.51). There was also a trend toward higher risk of drug discontinuation because of cardiovascular adverse drug reactions for drug courses administered to patients with underlying heart disease (19% versus 9%; relative risk 2.16, 95% confidence interval 0.99 to 4.72).

DISCUSSION

These results suggest that patients with underlying heart disease are at greater risk of adverse drug reactions during initiation of antiarrhythmic therapy for atrial fibrillation. Nonetheless, the absolute risk was high even for patients without relevant cardiovascular conditions, and over 10% of such patients required discontinuation of therapy because of side effects.

Guidelines from the Canadian Cardiovascular Society[1] and the American Heart Association[3] for the treatment of atrial fibrillation imply that outpatient initiation of treatment may be reasonable for low-risk patients. However, neither statement clearly defines the patient characteristics associated with an acceptably low risk of drug-related adverse events. Therefore, it is difficult for clinicians to identify patients who may be candidates for initiation of antiarrhythmic therapy in the community setting. The proportion of patients with atrial fibrillation admitted to hospital for initiation of antiarrhythmic therapy and their individual characteristics appear to vary widely between physicians and institutions.[4]

The Canadian Cardiovascular Society[1] and American Heart Association[3] statements on atrial fibrillation illustrate the different opinions on initiation of antiarrhythmic therapy. The Canadian Cardiovascular Society generally recommends inpatient initiation: "Although many clinicians start antiarrhythmic drugs for this indication in out-patients, it is recommended that, in general, antiarrhythmic drug therapy be started in hospital with electrocardiographic monitoring." The American Heart Association recommendation is slightly different: "In patients without heart disease who have normal baseline QT interval, ventricular proarrhythmia is rare, and outpatient initiation of treatment is reasonable." The apparent discrepancy between these statements probably stems from the lack of objective research aimed at identifying a low-risk population.

The Stroke Prevention in Atrial Fibrillation (SPAF) study included 1330 patients, providing one of the largest databases of characteristics and outcomes of patients with atrial fibrillation.[10] Although this study was not designed to assess the risks associated with antiarrhythmic therapy, Flaker and others[5] analyzed the SPAF data using multivariate analysis to evaluate specific medications and other potential risk factors for cardiac death. In patients with a history of heart failure who had received antiarrhythmic drugs, the relative risk of arrhythmic death was 5.8 (p = 0.009, 95% confidence interval 1.5 to 21.7) compared with patients not taking antiarrhythmic drugs. It should be noted that for most patients, antiarrhythmic drugs had been initiated before study enrollment; therefore, an early proarrhythmic effect would not have been observed.

Maisel and others[4] reviewed medical records for 417 patients who underwent initiation of antiarrhythmic therapy for atrial fibrillation. Compared with the results presented here, they found similar rates of drug discontinuation because of adverse events (12% versus 13.4%) and a similar relative risk of drug discontinuation in patients with heart disease (2.16 versus 1.90). In that study, the risk of adverse events was greatest during the first 24 h of therapy.[4]

Chung and others[6] reviewed the charts of 120 patients with atrial arrhythmia who were admitted to hospital for initiation of sotalol therapy. The incidence of complications triggering therapy changes (17.5%) was similar to that observed by Maisel and others.[4] However, the presence of heart disease was not predictive of arrhythmic complications. Bradycardia was the most common adverse event encountered, which concurs with our results for the overall study population, as well as for those patients who received sotalol.

Zimetbaum and others[7] initiated antiarrhythmic therapy for atrial fibrillation in 172 outpatients and monitored them with a continuous-loop event recorder for 10 days. Patients were excluded from the study if they had QT interval prolongation, New York Heart Association class III or IV heart failure, or a pacemaker. In total, 6 adverse events were recorded, all in patients without structural heart disease. All events occurred at least 4 days after initiation of therapy, much later than in the cases reviewed here and beyond the usual time frame within which a patient would be monitored in hospital.

Most of the available data, including those from the present study, have been collected through reviews of medical records. There are inherent difficulties in obtaining accurate information from medical records. These problems are compounded by the fact that adverse events associated with antiarrhythmic therapy

may be difficult to distinguish from symptoms of the arrhythmia being treated. Our sample size was not large enough to conduct meaningful multivariate analysis to identify more specific independent risk factors for adverse events.[11] There may be a narrower set of patient characteristics associated with a particularly low risk of adverse drug reactions. In addition, the definition of adverse events varies considerably in the reported studies, and adjustment in the thresholds for defining adverse events can significantly influence the reported incidence.

Several published reports have recommended that outpatient initiation of antiarrhythmic therapy for atrial fibrillation is safe for patients without cardiac abnormalities.[2,3,12,13] However, the data reported here and the results of other studies suggest that adverse events may be common even in patients who do not have underlying heart disease. In this study, more than 1 in 10 patients without underlying heart disease required discontinuation of antiarrhythmic therapy because of adverse drug reactions. This degree of risk is probably too high for most physicians to justify initiation of therapy in the community. However, the decision may be based on the drug used, as well as the patient's cardiovascular history. For example, this study and others suggest that outpatient initiation of oral amiodarone may be relatively safe.[14,15]

On the basis of the available information, it is difficult to define a specific population for which antiarrhythmic therapy for atrial fibrillation can be initiated safely in the community. The results presented and reviewed here have prompted a large-scale prospective study (part of the Second Canadian Registry of Atrial Fibrillation[16]) aimed at identifying risk factors for adverse reactions to antiarrhythmic therapy in this population.

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