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Safety and efficacy of amiodarone in arrhythmias – a prospective study in the South Indian population

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Abstract

To study the cardiac and non-cardiac safety of amiodarone and measure the efficacy of amiodarone in restoring and maintaining sinus rhythm. 35 patients on amiodarone therapy were examined for its safety and efficacy during a period of 6-months. The dosing schedule of amiodarone in the study population was as follows: I.V. loading doses of 150-300 mg bolus over 30 minutes, followed by 1 mg per minute for 6 hours, followed by daily oral maintenance dose of 100-400 mg; I.V. + oral loading dose of 800-2320 mg per day, to a total dose of up to 10 gm, followed by daily oral maintenance dose of 100-400 mg; Oral loading dose of 200 mg T.D.S. for 5 days followed by 200 mg B.D. for 5 days and a daily oral maintenance dose of 100-200 mg O.D. Out of 35 patients, only 2 patients developed severe ADR (hypothyroidism) and discontinued amiodarone therapy. Amiodarone could restore rhythm in 15 (83.33%) out of 18 patients with Ventricular Tachyarrhythmias (VT) and in 10 (83.33%) patients out of 12 patients with Atrial Fibrillation (AF). In other types of arrhythmias (Supraventricular Tachycardia (SVT), Ventricular Tachycardia (VT), Ventricular Premature Complexes (VPCs) & Supraventricular Premature Complexes (SVPCs), amiodarone could restore rhythm in 5 (100%) out of 5 patients. Amiodarone was found to be safe and effective in treating all types of arrhythmias.

Key words**:** *amiodarone; arrhythmias; efficacy*

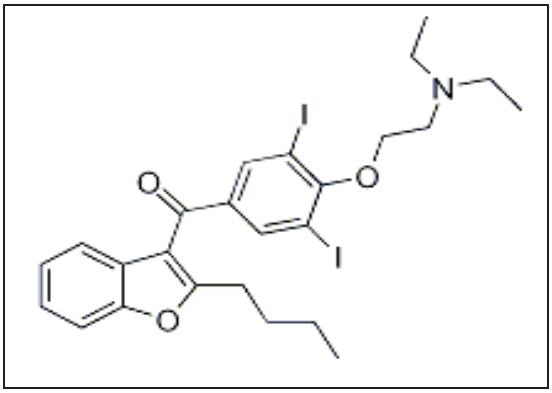
INTRODUCTION

An arrhythmia is any abnormality in rate, regularity, or site of origin or a disturbance in conduction that disrupts the normal sequence of activation in the atria or ventricles.[1] Arrhythmias may indicate an underlying abnormality of the heart muscle, valves or arteries. When the normal sequence of impulse initiation and propagation is perturbed, an arrhythmia occurs. Failure of impulse initiation may result in slow heart rates (bradyarrhythmias), whereas failure of impulses to propagate normally from atrium to ventricle results in dropped beats or "heart block" that usually reflects an abnormality in either the AV node or the His-Purkinje system. These abnormalities may be caused by drugs or by structural heart disease; in the latter case, permanent cardiac pacing may be required.[2] Arrhythmia may be classified by rate (normal, tachycardia, bradycardia), or mechanism (automaticity, reentry, fibrillation).[3] Lidocaine, procainamide, amiodarone, verapamil and isoproterenol are the various anti-arrhythmic agents used widely.[4] Among these, amiodarone has become the most widely prescribed anti-arrhythmic because of its wide spectrum of efficacy and relative safety in patients with structural heart disease.[5]

Indian Journal of Pharmacy Practice
Received on 01/12/2009
Accepted on 05/01/2010

Amiodarone

Structure



Systematic (IUPAC) name:

(2-butyl-1-benzofuran-3-yl)-[4-(2-diethylamino-ethoxy)-3,5-diiodophenyl]methanone.

Amiodarone is indicated for acute termination and maintenance of ventricular fibrillation, ventricular tachycardia (pulse less or with a pulse), atrial fibrillation and atrial flutter.[6] It is effective in the maintenance of direct current cardioversion in patients with atrial fibrillation and in the termination of reentrant

arrhythmias, including the WPW (Wolff-Parkinson-White) syndrome.[7] Intravenous amiodarone is also effective in suppressing ventricular arrhythmias, and oral amiodarone appears to decrease cardiac mortality after MI.[1z]

Amiodarone is a unique drug with a combination of pharmacological properties that are effective in treating a variety of arrhythmias.[8,9,10] This medication is a class III antiarrhythmic that blocks potassium channels and thus prolongs the action potential and refractory period in myocardial cells, thereby decreasing membrane excitability. Unlike other class III antiarrhythmic agents, amiodarone maintains this prolonged myocardial action potential despite faster heart rates, a characteristic that explains its effectiveness in treating tachycardias.[11] Amiodarone also acts as a weak sodium channel blocker, causing a decline in the rate of membrane depolarization and impulse conduction.[12] As a calcium channel blocker, Amiodarone can cause significant AV nodal block and bradycardia.[13,14] These properties cause smooth muscle relaxation as indicated by dilatation of coronary and peripheral arteries, thereby increasing coronary blood flow and reducing systemic blood pressure and afterload.[11,15]

Adverse effects are very common in patients using amiodarone.[16] Adverse reactions affecting the cardiovascular, central nervous, endocrine, gastrointestinal, hepatic, neuromuscular, skeletal and respiratory systems can occur with large doses (>400 mg/d).[17]

The aim of the study is to evaluate the safety and efficacy of amiodarone in various arrhythmias.

MATERIALS AND METHODS

This prospective study was conducted in the cardiology in-patient and out-patient departments of a tertiary care teaching hospital, with the approval of the Institutional ethics committee and informed consent of the patients. 35 patients prescribed with Amiodarone for a period of six months (September 2007 to March 2008) were included in the study.

Patients prescribed with a daily dose of not less than 200mg of amiodarone either orally and/or parenterally (I.V.) were included in the study. Children, pregnant and breast-feeding women and patients prescribed with amiodarone of a daily dose less than 200mg were excluded from the study.

The dosing schedule of amiodarone in the study population was as follows:

I.V. loading doses of 150-300 mg bolus over 30 minutes, followed by 1 mg per minute for 6 hours, followed by daily oral maintenance dose of 100-400 mg I.V. + oral loading dose of 800-2320 mg per day, to a total dose of up to 10 gm, followed by daily oral maintenance dose of 100-400 mg.

Oral loading dose of 200 mg T.D.S. for 5 days followed by 200 mg B.D. for 5 days and a daily oral maintenance dose of 100-200 mg O.D.

Patient data were collected in specially designed forms which included patient demographics (age and sex), History of present illness, past medical and medication history, social history, general and systemic examination, clinical and cardiac investigations, lab investigations, diagnosis, disease condition for which amiodarone was prescribed, dose, route, dosing interval and duration of therapy. diagnosis of these patients were made by the cardiologist based on clinical signs and symptoms, history of illness along with the results of cardiac investigations like E.C.G., echo and Holter monitoring if required.

The drug-charts were reviewed for prescribing patterns of amiodarone such as dose, route of administration and dosing intervals. Adverse drug reactions of amiodarone reported by the study group were also analyzed. The safety and effectiveness of amiodarone in the study group was determined by comparing dose and duration of amiodarone with the incidence of ADRs and outcome of the treatment. Statistical analysis was carried out using software Graph pad (Instat, Version 3.05).

RESULTS

A total of 35 patients who were diagnosed to have arrhythmias and prescribed with amiodarone not less than 200 mg daily dose were enrolled in the study.

Table 1 summarizes the patient demographics, duration of therapy, distribution of arrhythmias and severity of arrhythmias. Among 18 patients with Ventricular Tachycardia, the underlying cause was found to be Myocardial Infarction (MI) in 50% (n≥9) of the patients.

Of the 35 enrolled patients, loading dose was given for 91.43% (n≥32), of which, 46.88% (n≥15) were given I.V. + Oral loading dose (mean dose of 6670mg), 31.25% (n≥10) patients were given only oral loading dose (mean dose of 6180mg) and 21.87% (n≥7) were given only I.V. loading dose (mean dose of 1150mg). 3 patients were cases of Ventricular and Supra Ventricular Premature Complexes and they required only maintenance doses for regular rhythm. Oral maintenance dose of 100-200 mg O.D. were given for all the patients except two, as the drug was withdrawn for them due to adverse drug reactions (ADRs).

Table 1: Baseline characteristics

Characteristics	No. of patients (n=35)	%
Sex:		
Male	26	74.29
Female	9	25.71
Social History:		
Smoking	6	17.14
Both smoking & alcohol	2	5.71
Tobacco	1	2.86
Duration of Therapy:		
< 1 week	4	11.43
< 6 months	15	42.86
6 months – 1 year	9	25.71
> 1year	7	20
Severity of arrhythmias:		
Stable	10	28.57
Unstable	25	71.43
Distribution of arrhythmias:		
AF	12	34.29
VT	18	51.43
SVT	2	5.71
VPCs, SVPCs	3	8.57

Safety

Out of 35 patients enrolled for the study, 5 patients (14.29) developed mild ADR like hypotension (n≥3) and bradycardia (n≥2). Only 2 patients (5.71%) developed severe ADR (hypothyroidism) and discontinued amiodarone therapy. Hence the rest continued amiodarone therapy and ADRs did not affect treatment in 94.29% of the patients. The mild ADR was cardiac and severe ADR was non-cardiac. The distribution of ADR is summarized in **Table 2.**

Efficacy

Of the 35 patients enrolled, sinus rhythm was restored in all the 10 patients on oral therapy (n≥10), 14 patients with I.V + oral therapy (n≥15) and in 5 patients on I.V amiodarone therapy (n≥7). Amiodarone restored rhythm in 15 (83.33%) out of 18 patients with VT and in 10 (83.33%) patients out of 12 patients with AF. In other types of arrhythmias (SVT, VPCs & SVPCs), amiodarone restored rhythm in all 5 (100%) patients. **Table 3** summarizes the rate of 'P' wave in atrial fibrillation and QRS duration in Ventricular Tachycardia of ECG before and after administration of amiodarone.

Table 2: Distribution of ADRs

ADRs	No. of patietns (n=35)	
Mild (n≥5)	Hypotension (n≥3, 8.57%)	Bradycardia (n≥2, 5.71%)
Severe (n≥2)	Hypothyroidism (n≥2, 5.71%)	-

Table 3: paired "t"test for comparision of rate of "p" wave in atrial fibrillation and "qrs" duration in ventricular tachycardia before and after administration of amiodarone

Rate	n	Mean ± S.D	p value
Rate of P Wave:			
Before treatment	12	408.42 ± 6.11	
After treatment	12	124.33 ± 80.62	0. 0001
Rate of QRS Complex:			
Before treatment	18	134.47 ± 5.57	
After treatment	18	91.53 ± 14.5	0.0001

DISCUSSION

Amiodarone is indicated for acute termination & maintenance of stable (or) unstable Ventricular Tachycardia, Ventricular Fibrillation, Atrial Fibrillation and Atrial Flutter. It is effective in the maintenance of sinus rhythm in patients with Atrial Fibrillation and also in the termination of reentrant arrythmias.

The present study indicated suppression of Incessant VT or VF with amiodarone, in 70% of patients. In the other 20%, amiodarone was accompanied by Adenosine/ Lidocaine /DC shock for suppression. Overall amiodarone played a role in 90% of patients in the suppression of incessant VT or VF. The report of the present study is in accordance with the study conducted by Rosenbaum et al (1976) where total suppression of arrhythmias was observed in 72% of patients.[18]

In the present study, 100% of amiodarone patients were observed to have almost complete suppression of VPCs and non-sustained VT. This study report is similar to that of Canadian Amiodarone Myocardiac Infarction Arrhythmia trial (CAMIAT) pilot study in which almost complete suppression of asymptomatic VPCs were observed in 86% of the enrolled patients.[19]

Amiodarone exhibited excellent results in 15 of 18 patients (83.33%) with symptomatic VT or VF in the current study. These results are in accordance with the study done by Rosenbaum et al (1976) where they reported excellent results in 82% with symptomatic VT/VF.[18]

In the present study, amiodarone was given in 3 different doses of 960mg (group 1), 1050 mg (group 2) and 1200mg (group 3) over 24 hours for incessant VT or VF. There was no recurrence of VT/VF with in or after 24 hours in group 1 and 3 where as 50% recurrence was observed in group 2. The present report has no correlation with the study done by Scheinman MM et al where the reports were 32%, 45% and 53% of recurrence in low, medium and high dose groups respectively[20].

Conversion of sinus rhythm (SR) with I.V. amiodarone was achieved in 10 of 12 (83.33%) patients. This result was similar to that of the randomized controlled study conducted by Panos E.Vardas et al. They reported that conversion to SR with I.V. amiodarone was achieved in 80.05% of patients[21].

In the present study, loading and maintenance doses were found to have no significant effect on restoration and maintenance of SR in patients with AF. Maintenance of SR in patients with AF was achieved in 9 of 10 (90%) patients. The results were different from the reports of the study conducted by O'keefe et.al. where the maintenance of SR was 32.5% at 1 month.[22]

In the present study, the incidence of spontaneous marked QT prolongation resulted in polymorphic VT was observed in 2 of 35 patients (5.71%) in contrast to the reports of studies conducted by Greene HL et al where the incidence was found to be < 0.5%.[23]

Amiodarone induced torsade de pointes was absent in the present study.

A meta analysis of double blind study on amiodarone reported 1 year net risk of events as Pulmonary toxicity in 1%, hepato toxicity in 0.6%, peripheral neuropathy in 0.3% and hyper thyroidism was found in 0.7%.[24] None of the above toxicities were observed in the present study.

Amiodarone exhibited excellent results in the control of symptomatic VT/VF. It is effective in the suppression of incessant/ recurrent Ventricular Tachyarrhythmias and asymptomatic or symptomatic VPCs, SVPCs and non-sustained VT and SVT. It is effective in termination of AF, restoration and maintenance of SR in AF patients. Amiodarone exhibits good safety for other cardiac and non-cardiac ADRs in the treatment of various arrhythmias.

Hence it was observed that effective restoration and maintenance of sinus rhythm was achieved in patients after treatment with amiodarone. The improvement in cardiac condition was found to be higher. Only 2 ADRs were severe requiring discontinuation of the drug. The others were not serious and did not lead to any compromise in normal life-style.

Limitations of the Study

The time period was very less and hence the number of subjects was minimal. The same study can be carried out in a larger population.

ACKNOWLEDGEMENT

We sincerely thank Dr.Ramesh, Professor, Department of Cardiology, Sri Ramachandra University, Chennai, for his valuable guidance and encouragement throughout the study.

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