

Safety of Amiodarone in Ventricular Arrhythmia in Patients Admitted in Bangabandhu Sheikh Mujib Medical University

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Abstract

Background: Amiodarone is the most effective antiarrhythmic medications available today for the treatment of both atrial and ventricular arrhythmias. It is an iodinated benzofuran derivative with demonstrated efficacy against a range of cardiac arrhythmias, including atrial fibrillation, paroxysmal supraventricular tachycardias, and life-threatening ventricular arrhythmias.

Objective: To evaluate the status of amiodarone with therapeutic dose in Bangladeshi population.

Materials and Methods: The quasi experimental study was conducted in the Department of Cardiology in Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka during April, 2019 to March, 2020 Patients got admitted in the Department of Cardiology, BSMMU, consecutive patients who had been treated with amiodarone for arrhythmia were included in this study. Patients without an amiodarone prescription were assumed and patients who will not give informed written consent were excluded in this study.

Results: The most common adverse event was bradycardia or conduction disturbance (9.0%) followed by 4(2.2%) thyroid toxicity, 3(1.7%) hepatic toxicity, 2(1.1%) eye toxicity and 1(0.6%) pulmonary toxicity. In multi variable logistic regression, bradycardia or conduction disturbance, amiodarone daily dose (≥ 300 mg) and duration of amiodarone (>4 month) was found to be significantly ($p < 0.05$) associated with adverse effects of amiodarone.

Conclusion: The most common adverse event was bradycardia or conduction disturbance followed by thyroid toxicity, hepatic toxicity, eye toxicity and pulmonary toxicity. Bradycardia or conduction disturbance, amiodarone daily dose (≥ 300 mg) and duration of amiodarone (>4 month) was found to be significantly associated with adverse effects of amiodarone.

University Heart Journal 2021; 17(2): 118- 121

Introduction:

Amiodarone is the most effective antiarrhythmic medications available today for the treatment of both atrial and ventricular arrhythmias. Its efficacy is likely related to diverse effects on a number of cardiac receptors.¹

Amiodarone is commonly utilized for treating both supraventricular and ventricular arrhythmias. While this drug is a very effective antiarrhythmic agent, it also leads to many well-known side effects involving a variety of organs such as the thyroid, liver, lungs, and eyes including many that are dose- and duration-dependent.² The use of amiodarone must be balanced between the drug's potentially serious adverse effects and its antiarrhythmic effects. However, current guidelines still recommend that amiodarone be chosen as the first-line therapy in some patient groups.³

Amiodarone, a potent antiarrhythmic drug that is useful for both atrial and ventricular arrhythmia, has a combination of

β -blockade, calcium channel blockade, and class III antiarrhythmic effects. In patients with acute-onset AF and also with impaired left ventricular function, amiodarone or digoxin has been recommended because of a minimal negative inotropic effect.⁴ In patients with persistent AF, amiodarone has been shown to be effective in achieving and maintaining sinus rhythm (50%-70%) in some studies.⁵⁻⁷ However, amiodarone has serious systemic adverse effects; furthermore, amiodarone has been suggested to be associated with an increase in mortality in patients with severe acute or chronic heart failure.

Amiodarone is an iodinated benzofuran derivative with demonstrated efficacy against a range of cardiac arrhythmias, including atrial fibrillation, paroxysmal supraventricular tachycardias, and life-threatening ventricular arrhythmias. Despite its many side effects, some of which may be serious, orally administered amiodarone

has been widely used as a highly effective alternative to more conventional antiarrhythmic therapies in patients with refractory, ventricular arrhythmias.

Materials and Methods:

The quasi experimental study was conducted in the Department of Cardiology in Bangabandhu Sheikh Mujib Medical University, Shahbagh, Dhaka during April, 2019 to March, 2020 Patients got admitted in the Department of Cardiology, BSMMU, consecutive patients who had been treated with amiodarone for arrhythmia were included in this study. Patients without an amiodarone prescription were assumed and patients who will not give informed written consent were excluded in this study. All patients get guideline directed therapy including revascularization. Loading dose followed by maintenance dose of amiodarone was given and recorded. Baseline demographic, ECG (significant number of PVC, multifocal in origin, R on T phenomenon, couplets, triplets, short run), Echo, 24H Holter ECG (significant number of PVC, multifocal in origin, R on T phenomenon, couplets, triplets, short run, non sustained VT) or cardiac monitoring record, electrolyte, creatinine, thyroid profile, eye condition was kept. Patients were followed up at end of first, third & sixth month. Occurrence of symptoms of arrhythmia, hospitalization form arrhythmia and cardiac death were noted. Focused clinical examination

of eye, skin, nervous system, thyroid status, cardiovascular, respiratory system was done and 12 lead ECG was taken in each visit. If any adverse effects of amiodarone arises, then the patient was treated according to standard guideline and amiodarone was discontinued in relevant case. 24H Holter ECG to look for correction of index arrhythmia or appearance of newer arrhythmia, thyroid function test, X-ray of chest, liver function test was done after 6 months in asymptomatic cases, and early in clinically relevant cases. Data was recorded in preformed data sheet. Treatment outcome and complications was analyzed. Statistical analyses were carried out by using the Statistical Package for Social Sciences (SPSS) version 23.0 for Windows Software. Continuous data were expressed as mean \pm standard deviation (SD) and categorical data were expressed as frequency and percentages. Mean and standard deviation were computed for quantitative variables and was analyzed by paired t-test. Chi square test was used for categorical variables. P values <0.05 was considered as statistically significant.

Result:

Smoker, amiodarone daily dose and duration of amiodarone treatment higher in side effects group than without side effects group. The difference were not statistically significant ($p>0.05$) between two group (Table-1). The most common adverse event was bradycardia or conduction

Table-I
Baseline clinical characteristics of the study patients (n=178)

	Side effects (n=26)		Without side effects (n=152)		p value
	n	%	n	%	
Demographic variable					
Male	15	57.7	89	58.6	0.934
Mean age (years)	65.7	± 10.8	64.5	± 11.9	0.631
Mean BMI (kg/m ²)	22.9	± 4.0	22.3	± 3.7	0.451
Co-morbidities					
Diabetes	6	23.1	28	18.4	0.372
Hypertension	7	26.9	25	16.4	0.155
Dyslipidemia	7	26.9	32	21.1	0.503
Coronary artery disease	13	50.0	54	35.5	0.159
Congestive heart failure	4	15.4	18	11.8	0.405
Stroke	3	11.5	12	7.9	0.379
Smoker	9	34.6	28	18.4	0.060
Cardiac status					
Ischemic heart disease	1	3.8	2	1.3	0.379
Acute decompensate chronic heart failure	2	7.7	3	2.0	0.155
Cardiac arrest	3	11.5	9	5.9	0.247
Cause of amiodarone use					
Atrial fibrillation	19	73.1	113	74.3	
Ventricular premature beat	2	7.7	10	6.6	0.977
Ventricular tachycardia	5	19.2	29	19.1	
Mean amiodarone daily dose (mg)	299.4	± 86.7	264.8	± 91.3	0.074
Mean duration of amiodarone (month)	4.9	± 1.8	4.1	± 2.2	0.081

disturbance (9.0%) followed by 4(2.2%) thyroid toxicity, 3(1.7%) hepatic toxicity, 2(1.1%) eye toxicity and 1(0.6%) pulmonary toxicity (Table-2). In multi variable logistic regression, bradycardia or conduction disturbance, amiodarone daily dose (≥ 300 mg) and duration of amiodarone (>4 month) was found to be significantly ($p < 0.05$) associated with adverse effects of amiodarone (Table-3).

Table-II*Reasons for discontinuation of therapy*

Adverse effect	Frequency	Percentage
Bradycardia or conduction disturbance	16	9.0
Thyroid toxicity	4	2.2
Hepatic toxicity	3	1.7
Eye toxicity	2	1.1
Pulmonary toxicity	1	0.6

Table-III*Multivariate analysis predictors for adverse effects of amiodarone*

Variable	OR (95% CI)	p value
Age (≥ 65 years)	0.79 (0.04–14.83)	0.875
BMI (≥ 25 kg/m ²)	0.82 (0.19–3.99)	0.809
Coronary artery disease	1.08 (0.43–2.73)	0.864
Bradycardia or conduction disturbance	3.05 (1.06–8.82)	0.039
Pulmonary disease	0.95 (0.52–1.14)	0.169
Thyroid dysfunction	1.23 (0.41–12.83)	0.876
Liver disease	3.26 (0.51–20.86)	0.212
Amiodarone daily dose (≥ 300 mg)	3.16 (1.18–8.47)	0.022
Duration of amiodarone (>4 month)	3.63 (1.26–10.44)	0.017

Discussion:

In current study observed that smoker, amiodarone daily dose and duration of amiodarone treatment higher in side effects group than without side effects group. The difference were not statistically significant ($p > 0.05$) between two group. Kim et al.⁸ study observed there were no significant differences between the two groups, except for the mean dose and total duration of amiodarone treatment. The mean daily dose of amiodarone was higher in patients with adverse events than in those without adverse events (231 ± 130 mg vs. 208 ± 102 mg, $p = 0.039$). The duration of amiodarone treatment was longer in patients with side effects than in those without ($813 \pm$

$1,086$ days vs. 425 ± 730 days, $p < 0.001$). In a randomized controlled trial by Roy et al.⁶, 18% of patients who had received 200 mg/day amiodarone for the maintenance of sinus rhythm discontinued taking the drug because of adverse events during a 16-month follow-up. In another trial with a similar study design, the incidence of adverse effects requiring discontinuation was 12.3% during the first year.⁹

The guidelines published by the North American Society of Pacing and Electrophysiology in 2000 estimated that the incidence of adverse effects of amiodarone was 15% during the first year and as high as 50% with long-term therapy.¹⁰

Julian et al.¹¹ demonstrated that 38.5% of patients in the amiodarone group (200 mg/day) discontinued medication, compared with 21.4% of those in the placebo group, during the 21-month study period. Bardy et al.¹² demonstrated study drug discontinuation rates of 32% in the amiodarone group and 22% in the placebo group among patients with congestive heart failure. Their study used a median dose of 300-mg/day amiodarone and a median study follow-up period of 45.5 months.¹²

In present study showed that the most common adverse event was bradycardia or conduction disturbance (9.0%) followed by 4(2.2%) thyroid toxicity, 3(1.7%) hepatic toxicity, 2(1.1%) eye toxicity and 1(0.6%) pulmonary toxicity. Kim et al.⁸ reported the most frequent adverse effect was bradycardia or conduction disturbance, which occurred in 88 patients (9.5%). Thyroid and hepatic toxicities occurred in 23 patients (2.5%) and 20 patients (2.2%), respectively. The chronic use of low dose amiodarone was associated with an increased risk of bradycardia compared with placebo (3.3% vs. 1.4%) in a previous meta-analysis.¹³ An additional study reported that the overall incidence of bradycardia was 5%.¹⁰ This high iodine content and the direct toxic effects of amiodarone on the thyroid parenchyma alter thyroid function,¹⁴ and the incidence of amiodarone-induced thyroid dysfunction in previous studies was 14% to 18%.¹⁵ Hepatotoxicity due to amiodarone was 1.7% in the current study, which is considerably lower than the previously reported incidences of 14% to 82%,¹⁶ among which 20% to 40% of patients required drug discontinuation because of hepatotoxicity.¹⁷ Pulmonary toxicity due to amiodarone was found 0.6% in this study. Recent studies reported that the incidence of amiodarone-induced pulmonary toxicity (AIPT) was 5% to 13%.¹⁸

In this study observed that in multi variable logistic regression, bradycardia or conduction disturbance, amiodarone daily dose (≥ 300 mg) and duration of amiodarone (>4 month) was found to be significantly ($p < 0.05$) associated with adverse effects of amiodarone. Kim et al.⁸

observed the independent risk factors for amiodarone related adverse effects, multiple logistic regression analyses were performed. After controlling for confounders, the duration of amiodarone treatment was the only independent risk factor for adverse events (odds ratio, 1.21; 95% confidence interval, 1.03 to 1.41; $p = 0.016$, per year). Previous studies showing that the cumulative administered dose of amiodarone was a major risk factor for amiodarone-induced organ toxicity.^{10,19,20} Age, gender, and underlying disease have also been suggested to be predictors of specific organ toxicities,²¹⁻²³ however, these factors were not associated with the overall adverse effects of amiodarone in the current study. We also performed multivariate analyses to identify independent predictors for specific organ toxicities, but the data were limited because of the small number of adverse events. Doyle and Ho²⁴ study showed cessation of amiodarone therapy because of intolerable adverse effects was more common compared with a placebo or rate control drug (10.7 vs 1.9 per 100 patient-years; RR, 3.0; 95% CI, 1.4-6.2; $P < 0.001$), but amiodarone was not associated with an increased incidence of hospitalizations (RR, 1.1; 95% CI, 0.6-2.1; $P = 0.77$).

Conclusion:

The most common adverse event was bradycardia or conduction disturbance followed by thyroid toxicity, hepatic toxicity, eye toxicity and pulmonary toxicity. Bradycardia or conduction disturbance, amiodarone daily dose (≥ 300 mg) and duration of amiodarone (> 4 month) was found to be significantly associated with adverse effects of amiodarone.

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