Title: A Cross-sectional study to find the prevalence of amiodarone related adverse effects in patients with various cardiovascular disorders in a teaching hospital in Western Area of Saudi Arabia

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Type: Orginal article

Authors:
Ahmed S. Ali¹, Mazen M. Humayran², Ashraf Albukhari², Abdulaziz Alshamrani², Maan Samkari², Abdulrahman Batarfi², Abdullah Duwaidi²

Affiliation:
¹ Department of Pharmacology, King Abdulaziz University, Jeddah, Saudi Arabia
² Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Corresponding author:
Name: Ashraf Albukhari
Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
E-mail: ashraf.albukhari97@gmail.com
Abstract

Background: Amiodarone has been increasingly used to treat acute arrhythmic episodes in patients with cardiovascular disorders. However, adverse effects of this drug caused by poor clinical follow-up and careless administration have been reported; hence, further attention to and research on this topic is warranted. This study aimed to identify amiodarone use and adverse effects among patients at King Abdulaziz University Hospital and explore any correlations between adverse effects and risk factors.

Methods: This study retrospectively analyzed data from the electronic health records of 142 patients with arrhythmia receiving amiodarone treatment at King Abdulaziz University Hospital from January 2016 to December 2018, regardless of indication, age, duration, and dose. We excluded patients with: (1) insufficient data regarding the amiodarone dose and duration, (2) no clinical follow-up, and (3) lack of baseline clinical parameters. The Research Ethics Committee granted ethical approval via reference number: 582-19 dated: 18/01/2021.

Results: We found that 20.4% of patients experienced adverse effects after amiodarone treatment. Patients with underlying comorbidities, such as hypertension, diabetes, and thyroid dysfunction, were more likely to experience amiodarone adverse effects. Further, adverse effects were observed more frequently in women, older adults, patients with low body mass index, and patients administered high doses of amiodarone.

Conclusion: Our findings suggest that amiodarone treatment should accompany meticulous clinical follow-up. This may direct the clinician to either decrease dosage, discontinue amiodarone treatment, or seek alternative drugs once adverse effects appear.

Keywords: Amiodarone, arrhythmia, comorbidity, adverse effects, cardiovascular disorder.
Introduction

Amiodarone (AMI) is a class III antiarrhythmic drug that works at potassium and voltage-gated sodium channels by markedly prolonging the action potential and repolarization phases while reducing atrioventricular conduction and sinus node function [1]. AMI effectively manages refractory ventricular arrhythmias, including those associated with ischemic heart disease and cardiomyopathies [2]. It is mainly used to treat chronic atrial arrhythmias refractory to conventional drugs, with an impressive conversion rate of chronic atrial fibrillation to sinus rhythm [3]. Paroxysmal atrial arrhythmias, including those associated with Wolff–Parkinson-white syndrome, can cause sudden death by rapid atrial fibrillation, although they are effectively suppressed or modified by AMI [4]. Some side effects associated with increased AMI doses have been recorded. In most patients, these side effects are acceptable or tolerable without necessitating drug discontinuation; however, some patients require dose reduction. Only a few patients experience complications, such as pulmonary toxicity [5], hypothyroidism, and hyperthyroidism [6].

In 2007, a published practical guide reported an incidence of 15% for AMI adverse effects in the first year of its use which increases up to 50% with long-term use. The incidence of pulmonary toxicity may present at any time during therapy. Laboratory investigations recommended in patients receiving AMI include baseline liver, thyroid, and pulmonary function tests every six months; yearly chest X-rays; computed tomography scans and electrocardiogram for unexplained cough or dyspnea, especially in patients with underlying lung diseases; and an ophthalmologic evaluation at baseline if visual impairment or symptoms occur [7]. A study in Korea that involved 930 patients reported an incidence of 16.6% for AMI adverse effects, due to which 15.1% of patients had to discontinue the drug. Moreover, the incidence of AMI adverse effects
increased up to 70% during the 5-year follow-up [8]. Unfortunately, the number of such studies in Saudi Arabia is insufficient. Therefore, this study focuses on the adverse effects of AMI in patients who attended a center in the Western area of Saudi Arabia. Patient comorbidities, dose duration, and cumulative AMI dosage were observed. Through this study, we sought to identify the risk factors for adverse effects of AMI and the prevalence of these adverse effects among patients involved in the study.

**Subjects and methods**

Patient data were collected from King Abdulaziz University Hospital (KAUH) from January 2016 to December 2018. Patients’ medical record numbers were used to determine the indications for prescription of AMI, dose, duration, comorbidities, and demographic factors from patient electronic files. Patients who met the inclusion criteria were included in the study. The study excluded patients with the following: 1) insufficient data regarding AMI dosage and duration, 2) no clinical follow-up, and 3) lack of baseline clinical parameters. The Research Ethics Committee granted ethical approval via reference number: 582-19 dated: 18/01/2021. The data collected were analyzed using Microsoft Excel, 2019 (Microsoft Corporation, Redmond, WA, USA) and Minitab Statistical software, version 20 (Minitab, LLC, USA). All descriptive statistics were analyzed using Minitab software, and the grouping of data was performed using Microsoft Excel. To identify the correlation between AMI adverse effects and risk factors and to determine the prevalence of AMI-related adverse effects among patients administered AMI, we interpreted the statistical results based on Bradford Hill’s (1965) nine viewpoints for causation [9]; however, we will only use viewpoints that apply to this study, which are as follows:
i. Strength: Very strong associations will be given closer attention than weaker ones.

ii. Specificity: If the observed association is highly specific, it is more likely to be causal.

iii. Temporality: Exposure-disease relationship to be causal exposure must precede the onset of disease.

iv. Biological gradient: Continuous exposure to a particular biological hazard worsens the disease.

v. Plausibility: If any known explanation can be derived from the observed causal relationship, it has more merit than the relationship with no explanation within the current scope of knowledge.

vi. Coherence: If the causal relationship observed is consistent with the current knowledge of the variables involved.

**Results**

Of the 142 patients involved in this study, only 29 manifested AMI-linked adverse side effects, 21 of whom were statistically significant. Table 1 shows the patients’ age and body mass index (BMI) summary according to their sex. 75 (53.6%) patients were male, and 65 (46.4%) were female. Figure 1 shows the distribution of males and females by age and BMI, it can be observed that this study had male patients with an average age of about 61.8 years and an average BMI of 24.02 kg/m², while female patients were older, with an average age of 63.34 years and a comparably higher BMI of 24.74 kg/m².
Figure 1: Descriptive statistics: Patients’ age and body mass indices (Panel variable: Patient’s sex)

The average age of our sample cohort (see Table 1) was 63 years, and the average BMI was 24.35 kg/m², indicating that the sample population’s average BMI was within the healthy range. Statistical analysis shows a presence of outliers in age and BMI. In women, there were four outliers by age, while males had six outliers. Approximately 75% of women were aged between 25–78 years, while 75% of men were aged between 30–75 years. Since the sample population's mean age was 63 years, men's outliers were mostly below the average sample age, therefore pulling down the average age of men in the sample population as shown in Table 1. The outliers in the women population were few, keeping the average age of women in the sample slightly above the mean age of the entire sample population.

There were also outliers in BMI, three female, and two male outliers. Male BMIs were more distributed in the mean region. About 35% of the men had a BMI < 20, while only 25% of women had a BMI < 20. In addition, from statistical analysis results, although women have a higher BMI by average, it was seen that 25% of men had a very high BMI. Although women had
several outliers below the average BMI, the number was counteracted by most women who had slightly higher BMI values above average.

Figure 2: A pie chart showing patient comorbidities

Figure 2 shows that the most common comorbidities in patients who arrived at KAUH with cardiovascular disorders were diabetes, hypertension, hyperlipidemia, heart failure, and a combination of these comorbidities.

These comorbidities have statistical relevance; therefore, we studied them as the main comorbidities in cardiovascular disorder patients. Patients with no comorbidities were also seen to be of statistical relevance to be included in the statistical analysis in determining the correlation between patients’ comorbidities and adverse effects.

From the statistical results, 72.5% of patients had atrial fibrillation, 23.9% ventricular fibrillation, 1.4% had atrial fibrillation and flutter, and the remaining 2.1% had other types of arrhythmia. Therefore, it is seen that the most prevalent arrhythmia among patients is atrial and ventricular fibrillation.
<table>
<thead>
<tr>
<th>S/N</th>
<th>Type of Arrhythmia</th>
<th>Mean age (years)</th>
<th>Mean BMI (Kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atrial Fibrillation</td>
<td>66.37</td>
<td>26.1</td>
</tr>
<tr>
<td>2</td>
<td>Ventricular Fibrillation</td>
<td>50.97</td>
<td>18.91</td>
</tr>
<tr>
<td>3</td>
<td>AF and Flutter</td>
<td>65.5</td>
<td>27.98</td>
</tr>
<tr>
<td>4</td>
<td>Atrial Flutter</td>
<td>50</td>
<td>27.18</td>
</tr>
</tbody>
</table>

**Table 1:** Patients statistical distribution summary based on age and body mass index

**Table 2:** Patient’s mean age and BMI for each type of arrhythmia
<table>
<thead>
<tr>
<th></th>
<th>Pulseless v-tach</th>
<th>58</th>
<th>25.71</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>SVT</td>
<td>68</td>
<td>17.78</td>
</tr>
</tbody>
</table>

BMI, body mass index; S/N, Serial Number; AF, atrial fibrillation; SVT, supraventricular tachycardia

As seen in Table 2, the average age of a patient with atrial fibrillation was 66.4 years, with an average BMI of 26.1 kg/m², and the average age of a patient with ventricular fibrillation was 60 years, with an average BMI of 18.91 kg/m². In our study, patients with atrial fibrillation were heavier than patients with ventricular fibrillation.

The total AMI administered to each patient was calculated from the data collected at KAUH by considering the AMI dose, treatment duration, and treatment frequency.

Figure 3 shows the distribution of the total AMI dosage. The average total AMI dosage was 3851.7 mg. As seen in Figure 3, the distribution is not normal, i.e., the amount of AMI administered to patients is not evenly distributed about its mean value.

**Figure 3:** Distribution of total AMI dosage administered to patients
A significant variation in the total AMI administered was observed with many outliers from 4,600 to 73,000 mg. Moreover, 75% of patients were administered $\geq 150$ mg, 50% of patients had $\geq 300$ mg, and only 25% received $\geq 1840$ mg of cumulative AMI, meaning that only a few patients received extreme amounts of AMI. Table 3 demonstrates that many patients showed no adverse effects, and these patients were administered with an average total AMI of approximately 3,163.7 mg, which was below the average amount of AMI administered to the entire sample of patients.

However, there is still a significant variation in the amount of total AMI administered to patients who showed no adverse side effects. It is worth noting that only 25% of the patients were administered a total AMI dose of $\geq 1,275$ mg.

Seven patients had hypotension. The total amount of AMI administered to this group was, on average, 1,864.3 mg, which is also below the average amount of AMI administered to the entire population sample. The variation in the amount of AMI is still significantly large in this group, and only 25% of patients who had hypotension as an adverse effect were administered with $\geq 6,000$ mg of total AMI, while 75% received $\geq 150$ mg.

Furthermore, in this study, only three patients had abdominal pain as a side effect after AMI, and the average amount of total AMI administered to this group was 1,864.3 mg. The small number of patients in this category makes the statistical analysis insignificant.

Three patients had vomiting as an adverse effect associated with AMI therapy. An average of 216.67 mg of AMI was administered to this group, lower than that in any other group that showed any adverse side effects.
The duration of treatment is shown in Table 3. Patients who had hypothyroidism received AMI therapy for a longer duration on average, followed by those with abnormal liver function tests as an adverse effect.
**Table 3:** Correlation of amiodarone side effects with age, BMI, dosage, sex, comorbidities, and arrhythmias

<table>
<thead>
<tr>
<th>S/N</th>
<th>Adverse Effect</th>
<th>N</th>
<th>Mean Age (year)</th>
<th>Mean BMI (kg/m)</th>
<th>BMI Description</th>
<th>Mean Dosage (mg)</th>
<th>Standard deviation</th>
<th>Common arrhythmia</th>
<th>Common Comorbidity</th>
<th>Common Comorbidity</th>
<th>*MDOT (days)/ Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypotension</td>
<td>7</td>
<td>69</td>
<td>16.59</td>
<td>Underweight</td>
<td>1864</td>
<td>2826</td>
<td>AF</td>
<td>HT,DM</td>
<td></td>
<td>9.29/Amp</td>
</tr>
<tr>
<td>2</td>
<td>Abdominal pain</td>
<td>3</td>
<td>71</td>
<td>21.72</td>
<td>Healthy</td>
<td>2300</td>
<td>3208</td>
<td>AF</td>
<td>HT</td>
<td></td>
<td>11.33/Amp</td>
</tr>
<tr>
<td>3</td>
<td>High-LFTs</td>
<td>2</td>
<td>36</td>
<td>13.63</td>
<td>Underweight</td>
<td>31575</td>
<td>44442</td>
<td>-</td>
<td>TGA, Fontan</td>
<td></td>
<td>90.5/Amp</td>
</tr>
<tr>
<td>4</td>
<td>Vomiting</td>
<td>3</td>
<td>62</td>
<td>21.08</td>
<td>Healthy</td>
<td>216.7</td>
<td>115.5</td>
<td>AF</td>
<td>HT</td>
<td></td>
<td>1/Amp</td>
</tr>
<tr>
<td>5</td>
<td>Vomiting, abdominal pain</td>
<td>2</td>
<td>70</td>
<td>30.08</td>
<td>Obese</td>
<td>5625</td>
<td>6894</td>
<td>AF</td>
<td>DM</td>
<td></td>
<td>17.5/Amp</td>
</tr>
<tr>
<td>6</td>
<td>Pulmonary toxicity</td>
<td>2</td>
<td>23</td>
<td>9.05</td>
<td>Underweight</td>
<td>300</td>
<td>212</td>
<td>-</td>
<td>-</td>
<td></td>
<td>2/Amp</td>
</tr>
<tr>
<td>7</td>
<td>Hypothyroidism</td>
<td>2</td>
<td>65</td>
<td>22.66</td>
<td>Healthy</td>
<td>25350</td>
<td>35638</td>
<td>AF</td>
<td>HT, HPT</td>
<td></td>
<td>172/Amp</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>113</td>
<td>62</td>
<td>25.03</td>
<td>Overweight</td>
<td>3164</td>
<td>10302</td>
<td>AF</td>
<td>None,DM, HT</td>
<td></td>
<td>14.21/Amp</td>
</tr>
</tbody>
</table>

DM: Diabetes Mellitus  *MDOT: Mean duration of treatment  HPT: Hyperparathyroidism

HT: Hypertension
Discussion

This study aimed to identify the prevalence of AMI-related adverse effects and elucidate their correlation with various risk factors. Our results for patients who showed AMI-related adverse effects are similar to the results obtained in previous studies. According to Park and Kim [10], 16.6% of the patients had AMI adverse effects during the first year of treatment. Similarly, 20.42% of patients in our study had AMI-related side effects. Furthermore, more female patients experienced adverse effects than male patients, and women in this study were older than men.

A study by Essebag et al. [11] showed a relationship between AMI side effects, gender, and age of patients. According to Essebag et al. [11], AMI dose should be reduced when used in female patients and those with lower body weights. The latter is consistent with our study, wherein 12 out of 29 patients were underweight, and those categorized as obese showed no adverse effects at all (n=113). This suggests that patients with higher BMIs may have had an advantage that prevented them from experiencing adverse effects of AMI.

Table 3 shows that none of the patients who experienced adverse effects had any comorbidities. This may suggest that there must exist a correlation between patients’ comorbidities and adverse effects of AMI; however, this correlation is not a direct one, as it was observed that among the 113 patients who showed no adverse effects, 93 had one or more comorbidities but did not manifest any adverse effects. The frequency of hypertension as comorbidity among the affected patients indicates that arrhythmic patients with hypertension complications are more likely to manifest adverse effects under AMI therapy.

It was found that the average amount of AMI administered to patients without adverse effects was higher than in those with hypotension. Although this result seems confusing, a closer observation of the box plots in the histograms below for both patients without side effects and
those with hypotension (Figures 4 and 5) reveals that those who showed no adverse effects have a large number of outliers while those with hypotension have no outliers.

**Figure 4:** Histogram showing total amiodarone dosage for patients who had hypotension

**Anderson-Darling Normality Test**

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-Squared</td>
<td>1.35</td>
</tr>
<tr>
<td>P-Value</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Mean</td>
<td>1864.3</td>
</tr>
<tr>
<td>StDev</td>
<td>2826.0</td>
</tr>
<tr>
<td>Variance</td>
<td>7986428.6</td>
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<tr>
<td>Skewness</td>
<td>1.22722</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>-0.84193</td>
</tr>
<tr>
<td>N</td>
<td>7</td>
</tr>
<tr>
<td>Minimum</td>
<td>150.0</td>
</tr>
<tr>
<td>1st Quartile</td>
<td>150.0</td>
</tr>
<tr>
<td>Median</td>
<td>300.0</td>
</tr>
<tr>
<td>3rd Quartile</td>
<td>6000.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>6000.0</td>
</tr>
</tbody>
</table>

**95% Confidence Interval for Mean**

-749.4 to 4477.9

**95% Confidence Interval for Median**

150.0 to 6000.0

**95% Confidence Interval for StDev**

1821.1 to 6223.1

**Figure 5:** Histogram showing total AMI dosage for patients who showed no side effects

Outliers have affected the mean of patients with “no adverse effects” substantially. This is confirmed by the fact that the third quartile for the group with no adverse effects is lower than
their mean, and the adjusted average total AMI dosage for those who showed no adverse effects (after ignoring the three outliers) is 1,604.5 mg, substantiating that the said outliers greatly affected the mean.

If we observe the total population without considering the mean values (as they are greatly affected by outliers), the outliers may impair our observation of patients. It was found that 25% of patients who had hypotension and abdominal pain were administered an AMI dose of > 6,000 mg, while 25% of those with no adverse effects were administered > 1,275 mg of AMI. A higher third quartile among hypotension and abdominal pain patients shows that the rest of the 75% were administered with comparably higher doses of AMI too. Greene et al. [12] suggested that the lowest possible dose should help limit side effects, but on the other hand, the dose should be kept high enough for optimal antiarrhythmic control.

Patients who had AMI-induced hypothyroidism (AIH) were treated for a longer time (an average of 172 days) than any other group of patients. According to Hamilton et al. [13], AIH is expected to resolve 2–4 months after drug cessation, which corresponds to the half-life of AMI, which is 50–60 days. Therefore, a patient treated for a long time is at risk of accumulating substantially high amounts of AMI in the body, given that the half-life of AMI is prolonged. Hamilton et al. [13] suggested that the accumulation of AMI releases a high amount of iodine in the body, which inhibits thyroid hormone synthesis; hence, a large percentage of patients with AIH have associated autoimmune thyroid diseases [14], which is similar to our study wherein both patients who had AIH also had hyperparathyroidism as comorbidity. This suggests that AIH was caused by underlying thyroid comorbidities and the long duration of AMI treatment.

The average age of patients who had adverse effects in this study, except for those with pulmonary toxicity and abnormal liver function tests, was higher than those who showed no side
effects, constituting about 70% of those with adverse effects. We speculate that there might be an explicable relationship between age and side effects caused by AMI therapy, i.e., the older the patient, the more likely AMI therapy will cause side effects. Corsonello et al. [15] reported that changes in pharmacokinetics and pharmacodynamics are associated with aging. In older patients, drug elimination is prolonged due to the decline of various body functions responsible for drug pharmacodynamics. Further, in their study, Corsonello et al. [15] showed that aging and associated comorbidities could expose the patient to severe adverse effects of AMI.

Pulmonary toxicity mainly affects younger patients, especially those with lower BMIs. It was previously suggested that AMI dosage should be reduced in patients with lower body weights to prevent drug toxicity and the need for pacemaker injection [11]. In this study, pulmonary toxicity occurred in 1.4% of patients, which is within the 1–2% range of AMI patients, according to Singh et al. [16]. A patient who experienced pulmonary toxicity in our study had heart failure complications. According to Papiris et al. [17], this might be the direct reason for pulmonary toxicity because AMI's risk of adverse effects increases due to the patient’s underlying health complications.

According to Hamilton et al. [13], vomiting after using AMI is a common intolerance. Patients who experienced vomiting in this study were administered with an average of 216 mg of AMI, which is small compared to the amount of AMI that caused other side effects, suggesting that vomiting is indeed just a common intolerance. Hamilton et al. [13] further suggested that vomiting can be minimized by dividing the dose twice a day.
This study had some limitations, mainly its relatively small sample size and data from a single center. Furthermore, many patients lacked data regarding previous laboratory values and radiographic images and were excluded.

**Conclusion**

Despite the usefulness of AMI as an effective antiarrhythmic agent, the associated side effects and toxicity calls for further attention and research. Moreover, caution must be applied when providing AMI treatment considering the side effects. Previous or underlying medical conditions should be determined in arrhythmic patients, and during drug administration, meticulous clinical follow-up must be conducted to observe the surfacing of any AMI-induced adverse effect. Any such adverse effects must prompt dose reduction, drug discontinuation, or consideration of an alternative treatment to AMI, depending on the severity of the adverse effects. The findings in this study regarding the risk factors for adverse effects can lead to improved outcomes for patients. Our insights may be further used to design prospective studies to evaluate the ideal dosage.

**List of Abbreviations:**

AMI Amiodarone  
KAUH King Abdulaziz University Hospital

**Conflict of interest:**
The authors declare that there is no conflict of interest regarding the publication of this article.

**Funding:**
None.

**Consent to participate:**
Written informed consent was obtained from all the participants.

**Ethical Approval:**
Ethical approval for the present study was granted by the Research Ethics Committee, KAUH via
References


