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Original Research

Overview of the use of antiarrhythmic drugs at a tertiary hospital in Oman

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Abstract

Background: Antiarrhythmic drugs are commonly used to treat arrhythmia. However, data on the usage pattern of antiarrhythmic drugs, associated side effects, and the role of clinical pharmacist interventions in the Middle East are scarce. **Objective:** The purpose of this study was to describe the usage pattern, side effects, and clinical pharmacist interventions of antiarrhythmic drugs at the Sultan Qaboos University Hospital (SQUH), a tertiary care hospital in Oman. **Methods:** This retrospective observational study included adult patients (≥18 years) who received at least one dose of antiarrhythmic drugs at SQUH between January 2020 and December 2021. Ethical approval was obtained prior to conducting the study. **Results:** In total, 400 patients were enrolled in this study. Their mean age was 62.5 ± 16.6 years (range:19-96), and 55.3% (221/400) were male. Atrial arrhythmias were the most commonly observed (344/400, 86.0%). Beta-blockers (337/500, 67.4%) were the most prescribed class of drugs. The most commonly prescribed drugs were bisoprolol (263/400, 65.8%), carvedilol (65/400, 16.3%), and amiodarone (59/400, 14.8%). The majority of patients (300/400, 75.0%) received monotherapy, whereas 25% (100/400) received combination therapy. A total of 109 side effects were reported in 45 patients, resulting in an incidence rate of 11.3 %, with cardiovascular side effects accounting for the majority (41/109, 37.6%) of these. Amiodarone had the highest prevalence of adverse effects (33/109, 30.3%). A total of 122 clinical pharmacist interventions were observed in 13.0 % (52/400) of patients. Beta-blockers were associated with more than half of the interventions (61/122, 50.0%). Age (61.84 years vs. 66.75 years; p=0.047), comorbidities (83.6% vs. 96.2%; p=0.019), renal impairment (19.6% vs. 40.4%; p=0.001, heart failure (11.8% vs. 28.9%; p=0.002), concomitant medications (84.5% vs. 98.1%; p=0.004), polypharmacy (51.1% vs. 69.2%; p=0.022) and duration of therapy of less than one year (9.3% vs. 27.3%; p<0.001) was significantly associated with the need for intervention. **Conclusion:** Beta-blockers were the most commonly prescribed antiarrhythmic drugs in SQUH. Amiodarone was associated with the highest prevalence of side effects. Clinical pharmacy intervention at the SQUH was mainly related to antiarrhythmic drug selection and dose optimization.

Keywords: arrhythmia; antiarrhythmic drugs; beta-blockers; amiodarone; clinical pharmacy

INTRODUCTION

Cardiac arrhythmias are irregular heartbeats caused by structural or electrical abnormalities in the cardiac conduction system. They are a significant cause of morbidity and mortality.[1] Their complications, depending on the type of arrhythmia, may include an increased risk of thromboembolic events, stroke, heart failure, and sudden death.[2,3] They are also associated with a decrease in quality of life.[4]

Pharmacological and nonpharmacological modalities such as pacemakers, cardioversion, catheter ablation, and surgery are among the available therapeutic options for arrhythmias.[5,6] Pharmacological treatment is widely used to suppress ectopic automaticity and modify impulse conduction, thus preventing the occurrence of arrhythmias and reducing their associated symptoms and complications.[7,8] Nonetheless, their use is particularly limited by their ability to precipitate fatal proarrhythmias and their effects on various other organ systems.[5] Therefore, it is clinically imperative to ensure that their expected benefits outweigh their adverse effects and that their use is optimally utilized.

There have been several reports on the utilization patterns and adverse effects of antiarrhythmic drugs. For example, Markman et al. found that the rate of antiarrhythmic prescriptions in the United States nearly tripled between 2004 and 2016, with the most notable substantial increases for amiodarone, sotalol, flecainide, and dofetilide.[9] A similar study in Denmark reported an increase in flecainide and amiodarone use from 1999 to 2017.[10]

Tardos et al., reported a significant gap between clinical practice and guideline recommendations for the first-line management of patients with atrial fibrillation.[11] A similar finding was also reported by Chiang et al., and Allen LaPointe et al., regarding the inconsistent use of amiodarone and guideline recommendations.[12,13]

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Similar to other drug classes, clinical pharmacist interventions can improve the use of antiarrhythmic drugs. Snider et al., reported that monitoring outpatient antiarrhythmic drugs by clinical pharmacists improved patient adherence to recommended and approved protocols, and helped identify adverse effects and clinically significant drug interactions.[14] For example, Freeland et al., found that the involvement of clinical pharmacists in the initiation and monitoring of dofetilide and sotalol helped prevent potential life-threatening ventricular arrhythmias due to inappropriate or miscalculated dosing of these agents.[15] In addition, Long III et al., concluded in their study that clinical pharmacist interventions efficiently attain and maintain the desired serum potassium levels in patients taking antiarrhythmic drugs.[16]

In Oman, a clinical audit of pharmaceutical care in cardiology and infectious disease wards at the Royal Hospital revealed that cardiovascular drugs are associated with the highest rate of pharmaceutical care issues that clinical pharmacists successfully resolve.[17] However, the clinical significance of these interventions has not been evaluated.

Studies on drug utilization in the Middle East are scarce. We were unable to trace any studies related to the use of antiarrhythmic agents and their associated adverse effects in this region. Therefore, this study aimed to describe the utilization pattern and side effects of antiarrhythmic agents in a tertiary care hospital that represents a snapshot of their use in Oman. It also aimed to describe clinical pharmacist intervention in the use of antiarrhythmic drugs.

METHODS

Setting and design

This retrospective observational study was conducted in 2021 at Sultan Qaboos University Hospital (SQUH), a tertiary care academic institution. Patients aged ≥18 years who were prescribed at least one of the available antiarrhythmic drugs between January 2020 and December 2021 were included in the study. Ethical approval was obtained from the Medical Research Ethics Committee of Sultan Qaboos University, Muscat, Oman (approval number: SQU-EC/338/2021)

Data collection

Data were collected from Electronic Patient Records (EPR), which is the information system used by the SQUH to store patient data. Data on demographics and clinical characteristics, such as age, sex, height, weight, indication and duration of antiarrhythmic agent therapy, comorbidities, and concomitant medications, were collected. The incidence of side effects was determined based on the physician's identification and documentation of the EPR. If a patient was identified as having more than one prescription, the latest prescription was considered.

Antiarrhythmic agents

The available antiarrhythmic drugs at SQUH include procainamide, lidocaine, flecainide, atenolol, bisoprolol, carvedilol, esmolol, propranolol, amiodarone, sotalol, diltiazem, verapamil, adenosine, digoxin, and magnesium sulfate. These drugs were classified using the Vaughan-Williams classification system.

The assessment of the indications for antiarrhythmic drugs was based on the guidelines of the European Society of Cardiology, the American Heart Association and American College of Cardiology guidelines.[18,19]

Clinical pharmacist intervention

Data on clinical pharmacist interventions for hospitalized patients who received at least one dose of available antiarrhythmic drugs were extracted from electronically stored forms. They were then analyzed to determine the rate of clinical pharmacist intervention, type of intervention, physician acceptance rate, and clinical significance.

Statistical analysis

Descriptive statistics were used to describe the data. Categorical variables are reported as frequencies and percentages. For continuous variables, mean and standard deviation were used to summarize the data. All statistical analyses were performed using STATA version 14.1 (STATA Corporation, College Station, TX, USA).

RESULTS

A total of 400 patients were enrolled in this study, of whom 55.3% (n=221) were men. The mean age of the study cohort was 62.5 ± 16.6 years (range:19–96 years), and the mean weight and height were 73.1 ± 18.3 kg and 159.3 ± 11.4 cm, respectively. The age group of 61-80 years (49.0%, n=196) was the most common in our study. Table 1 summarizes the demographic and clinical characteristics of the study population.

Table 1. Demographic and clinical characteristics of the studied population (N = 400)

Variable		**N (%)**
Age, mean ± SD, years	62.5 ± 16.6	
Age groups		
	18-40	50 (12.5)
	41-60	104 (26.0)
	61-80	196 (49.0)
	>80	50 (12.5)
Sex		
	Male	221 (55.3)
	Female	179 (44.7)
Type of arrhythmia		
	Atrial	344 (86.0)
	Ventricular	56 (14.0)
Number of comorbidities		
	0	59 (14.8)

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	1-3	186 (46.5)
	≥ 4	155 (38.8)
Comorbidities (by organ system)		
	Cardiovascular	312 (78.0)
	Endocrinology	167 (41.8)
	Renal	90 (22.5)
	Neurologic	58 (14.5)
	Others	226 (60.4)
Concomitant medications		
Number	0	60 (15.0)
	1	27 (6.75)
	2-5	168 (42.0)
	≥ 6	145 (36.3)
Pharmacologic class		
	Anticoagulants/ antiplatelets	295 (73.8)
	Antihypertensives	276 (69.0)
	Lipid lowering agents	192 (48.0)
	Proton pump inhibitors	158 (39.5)
	Antidiabetics	121 (30.3)
	Others	354 (88.5)
Duration of therapy		
	< 1 year	51 (12.8)
	1-5 years	233 (58.3)
	6-10 years	92 (23.0)
	≥ 11 years	24 (6.0)

Clinical characteristics

Atrial arrhythmias (86.0%, n = 344) were the most frequently occurring type of arrhythmia, followed by ventricular arrhythmias in 56 patients (14.0 %). The majority of patients (85.3%, n = 341) had at least one comorbidity with cardiovascular (78.0%, n = 312) being the most commonly affected system, followed by endocrine (41.8%, n = 167) and renal (22.5%, n = 90) systems. More than half of the patients (58.3%, n = 233) were on antiarrhythmic drugs for 1–5 years, followed by 6–10 years and less than one year in 92 (23.0%) and 51 (12.8%) patients, respectively. Most patients (42.0%, n=168) were on 2–5 concomitant medications, followed by 6 or more concomitant medications and no concomitant medications in 145 (36.3%) and 60 (15.0%) patients, respectively.

Anticoagulants and antiplatelet agents were the most commonly prescribed concomitant drugs (73.8%, 295), followed by antihypertensives (69.0%, n = 276) and lipid-lowering agents (48.0%, n = 192).

Antiarrhythmic agents

Table 2 summarizes the use of antiarrhythmic drugs in the study population. Monotherapy was prescribed for 300 patients (75%) and combination therapy was prescribed for 100 patients (25%). The most common monotherapy agent was bisoprolol (n=184), followed by carvedilol (n=51), and amiodarone (n=17). The most common combination therapy was bisoprolol and amiodarone (n=31), followed by flecainide and bisoprolol (n=28) and bisoprolol and digoxin (n=16).

Table 2. List of antiarrhythmic drugs utilized at Sultan Qaboos University hospital

Type of Therapy	**Drug**	**N**		
		Total	**AT**	**VA**
Monotherapy		300	262	38
	Bisoprolol	184	160	24
	Carvedilol	51	49	2
	Amiodarone	17	12	5
	Digoxin	12	12	
	Flecainide	10	3	7
	Adenosine	9	9	
	Verapamil	6	6	
	Diltiazem	6	6	
	Others	5	5	
Combination		100	81	19
	Bisoprolol + Amiodarone	31	25	6
	Flecainide + Bisoprolol	28	19	9
	Bisoprolol + Digoxin	16	16	
	Carvedilol + amiodarone	7	3	4
	Carvedilol + Digoxin	7	7	
	Bisoprolol + Diltiazem	3	3	
	Amiodarone + Verapamil	2	2	
	Atenolol + Digoxin	2	2	
	Bisoprolol + Sotalol	1	1	
	Amiodarone + Diltiazem	1	1	
	Amiodarone + Magnesium sulphate	1	1	
	Digoxin + Magnesium sulphate	1	1	

AA: atrial arrhythmia; VA: ventricular arrhythmia

Side effects of antiarrhythmic agents

Table 3 shows the documented side effects associated with the use of antiarrhythmic drugs. A total of 109 side effects were reported for 86 prescriptions in 82 patients (20.5 %). Amiodarone was responsible for the highest reported side effects (30.3%, n=33), followed by bisoprolol (27.6%, n =30), and carvedilol (17.4%, n=19). Bradycardia was the most commonly reported side effect (24.8%, n=27), followed by dizziness and fatigue in 17 (15.6%) and 7 (6.4%) patients, respectively.

The side effects associated with the use of antiarrhythmic drugs led to the discontinuation or change of the drug in 41 (10.5%) prescriptions. Amiodarone was associated with the highest rate of discontinuation (4%, n=16).

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Table 3. List of reported side effects to antiarrhythmic drugs (N = 109)*

Drug	Side effects		Action		
	N (%)	Type (n)	Discontinued	Switched	Continued
Amiodarone	33 (30.3)		16		9
		Hepatic dysfunction (7)			
		Thyroid dysfunction (6)			
		Bradycardia (5)			
		Others (15)			
Bisoprolol	30 (27.6)		3	5	16
		Bradycardia (10)			
		Dizziness (9)			
		Fatigue (3)			
		Others (8)			
Carvedilol	19 (17.4)			3	9
		Bradycardia (5)			
		Dizziness (3)			
		Dyspnea (3)			
		Others (8)			
Digoxin	10 (9.2)		4	1	5
		Bradycardia (5)			
		Dizziness (1)			
		Heart block (1)			
		Others (3)			
Atenolol	6 (5.5)		1		
		Bradycardia (2)			
		Sexual dysfunction (2)			
		Heart block (1)			
		Others (10)			
Flecainide	5 (4.6)				3
		Dizziness (2)			
		Fatigue (1)			
		Sexual dysfunction (1)			
		Others (1)			
Adenosine	3 (2.8)				2
		Chest pain (2)			
		Chest pressure (1)			
Sotalol	2 (1.8)		1	1	
		Dyspnea (1)			
		Postural hypotension (1)			
Diltiazem	1 (1.1)				1
		Hypotension (1)			

Reported in 82 patients

Clinical Pharmacist Interventions

The clinical pharmacist intervention data are summarized in Table 4. A total of 122 interventions were performed in 52 patients (13.0 %). Class II agents required the highest number of interventions (61, 50.0%), with bisoprolol and carvedilol being responsible for 28 prescriptions each. The most common

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Table 4. Types of clinical pharmacist intervention towards different antiarrhythmic drugs use (N = 122)

			N (%)
Class I			2 (1.6)
	Flecainide		1 (0.8)
	Lidocaine		1 (0.8)
Class II			61 (50.0)
	Bisoprolol		28 (23.0)
	Carvedilol		28 (23.0)
	Atenolol		3 (2.4)
	Labetalol		2 (1.6)
Class III			24 (19.7)
	Amiodarone		24 919.7)
Class IV			19 (15.6)
	Diltiazem		18 (14.8)
	Verapamil		1 (0.8)
Miscellaneous			16 (13.1)
	Digoxin		15 (12.3)
	Magnesium sulphate		1 (0.8)
Types			
	Choice		45 (36.9)
		availability	2 (1.6)
		addition	20 (16.4)
		deletion	16 (13.1)
		contraindication	1 (0.8)
		selection	1 (0.8)
		restart	3 (2.5)
		stop	1 (1.6)
	Dosing regimen		49 (40.2)
		dose	36 (29.5)
		frequency	10 (8.2)
		duration	1 (0.8)
		combination	1 (0.8)
		administration	1 (0.8)
		interaction	1 (0.8)
	Information		13 (10.7)
		nurse	1 (0.8)
		physician	12 (3.3)
	Prescribing issues		11 (9.0)
		omission	4 (3.3)
		order expiry	7 (5.3)

type of intervention was related to dosing regimen (49, 40.2%), followed by drug choice (45, 36.9%). For the dosage regimen, the dose (36, 29.5%) was the most common intervention, followed by frequency (10, 8.2%), while for therapeutic choice, it was related to the addition of the drug (20, 16.4%), followed by deletion of the drug (16, 13.1%).

Intervention outcomes were accepted in 114 (96.6%) prescriptions. The potential clinical significance of the intervention was recorded for 115 interventions. Of these, 82 (71.3%) led to possible efficacy improvement, 23 (20.0%) led to a potential reduction in toxicity risk, 7 (6.1%) prevented unnecessary exposure, and 3 (2.6%) were undocumented.

Table 5 compares patients who underwent an intervention with those who did not. Intervention was more in patients with older age (66.75 vs. 61.84, p = 0.047), heart failure (28.9% vs. 11.8%, p = 0.02), renal impairment (40.4% vs. 19.6%, p = 0.001), polypharmacy (69.2% vs. 51.1%, p = 0.022), and a duration of less than a year of therapy (27.3% vs. 9.3%, p = 0.001).

DISCUSSION

Antiarrhythmic drugs are commonly used to treat cardiac arrhythmia. However, their utilization in the Middle East has yet to be explored. In this study, we examined the usage patterns of these agents in a tertiary hospital in Oman, and described their side effects and related clinical pharmacist interventions.

The mean age of this study population was 62.5 years, which is older than that reported in the Gulf SAFE study (59.1 years) but closer to that of a Canadian study (64.0 years).[20,21] The reasons for this difference are unclear, but may be attributed to the larger sample size and the different centers included in the Gulf SAFE study.

Atrial arrhythmias were the most common type (86.0%) of arrhythmia in our study. This finding is in agreement with those of previous studies.[9,22]

Most subjects (46.5%) had more than one comorbidity. Cardiovascular disease (78.0%), mainly hypertension, accounted for most of these cases. These findings are consistent with those of previous studies in this region and others.[20,23]

The high concomitant use of anticoagulant and antiplatelet agents followed by antihypertensive and lipid-lowering agents in this study and others is explained by the use of these agents for primary or secondary prevention of cardiovascular events or to treat the associated comorbidities in this population.[24,25]

Beta-blockers were the most commonly prescribed antiarrhythmic drugs. Similar findings have been reported previously.[26] The preference for using beta-blockers could be due to there being more favorable evidence of patient safety and high efficacy in suppressing arrhythmias for this category. Such a tendency for a rate-control strategy among physicians at SQUH has also been observed by Zubaid et al., and others.[22,27,28] Although clinical trials that compare the efficacy of different beta-blockers at controlling rates or symptoms in atrial fibrillation are lacking, guideline recommendations largely support the use of metoprolol or bisoprolol to manage arrhythmias.[29,30] Metoprolol is not available at SQUH; therefore, bisoprolol was the most commonly prescribed beta-blocker in our study.

In this study, hundred patients (25.0%) used a combination of antiarrhythmic drugs, which was lower than that reported

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Table 5. Factors associated with the requirement for clinical pharmacist intervention

Characteristic		**Without interventions (n=348, 87%), n (%)**	**With interventions (n=52, 13%) n (%)**	**p**
Age, mean ± SD, years		61.84 ± 16.77	66.75 ± 15.3	0.047
Gender				0.883
	Male	153 (44)	24 (46.1)	
	Female	195 (56)	28 (53.9)	
Indication (type)				0.201
	Atrial/supraventricular	296 (85.1)	48 (92.3)	
	Ventricular	52 (15)	4 (7.7)	
Comorbidities		291 (83.6)	50 (96.2)	0.019
	Coronary artery disease	73 (21)	12 (23)	0.870
	Diabetes mellitus	126 (36.2)	25 (48)	0.135
	Dyslipidemia	80 (23)	13 (25)	0.885
	Heart failure	41 (11.8)	15 (28.9)	0.002
	Hypertension	197 (56.6)	37 (71.2)	0.067
	Renal impairment	68 (19.6)	21 (40.4)	0.001
Concomitant medications		294 (84.5)	51 (98.1)	0.004
	Polypharmacy (≥ 5)	178 (51.1)	36 (69.2)	0.022
Therapy type				0.994
	Monotherapy	265 (76.1)	39 (75)	
	Dual therapy	83 (23.9)	13 (25)	
Duration of therapy				
	<1 year	48 (9.3)	14 (27.3)	<0.001
	1-5 years	185 (53.2)	26 (50)	0.718
	6-10 years	91 (21.2)	10 (18.2)	0.694
	>10 years	24 (5.6)	2 (3)	0.557

in other studies. For example, a Canadian study showed that over 50% of the subjects received combination therapy.[22] In the present study, it was also observed that the most commonly prescribed combinations were beta blockers with other agents. Beta-blockers have emerged as the drugs of choice for rate control over digoxin and calcium channel blockers.[28] Also, the addition of low-dose digoxin (≤ 125 mcg/day) to beta-blockers has been shown to achieve better control of resting heart rate and improve the quality of life of patients with atrial fibrillation.[31]

The overall documented side effects due to antiarrhythmic drugs in this study were 109 recorded in 82 patients (20.5%), which is higher than that reported in previous studies (4.9%).[32] Most of these side effects were cardiovascular, which corroborates earlier findings that antiarrhythmic-induced bradycardia, primarily due to beta-blockers, is expected during therapy.[33] Among the various drugs, amiodarone was associated with the highest incidence of side effects (15.5%) and led to the highest rate of drug discontinuation (16/24). This is in agreement with a study conducted in Spain, in which amiodarone was associated with a significant risk of side effects.[32] However, this study reported no amiodarone-induced pulmonary toxicity, which may be attributed to the use of a lower dose of amiodarone in our subjects than in previous studies.[34]

The current study reiterates the vital role of clinical pharmacists in the use of antiarrhythmic drugs. Dosing regimens (40.2%) and drug choices (36.9%) constituted the majority of the recorded interventions. Beta-blockers recorded the highest clinical pharmacist intervention, which was expected owing to their high utilization. This is consistent with the findings of a previous study, which suggested that beta-blockers are among the primary drug classes associated with drug therapy issues in cardiology clinics.[35]

The presence of comorbidities among older patients, mainly heart failure and renal impairment, increases the likelihood of the need for intervention. Renal impairment and heart failure affect the pharmacokinetics of several antiarrhythmic agents, necessitating dose adjustments.[36,37] Polypharmacy is well documented to be associated with interactions and the need for interventions.[38]

Since clinical pharmacists administer interventions mainly to hospitalized patients, a duration of less than one year was significantly associated with a higher number of interventions, a finding reported previously in another study (Alderman and Farmer, 2001).[39] It is also common to note that dose and

regimen adjustments to reach the maintenance dose occur during the first year of therapy.

Our study has some limitations. First, as with any retrospective study, our results might have been affected by missing data due to inadequate documentation related to side effects and interventions. Second, the existence of cardiovascular comorbidities, along with arrhythmia, made it challenging to determine the primary indication for beta-blockers, whether arrhythmia or comorbidity. Third, the clinical pharmacist's intervention was not followed up to ascertain the clinical outcomes. Fourth, the data were gathered from a single tertiary hospital.

CONCLUSION

Antiarrhythmic drugs from all classes were used to treat arrhythmias at the SQUH. Beta blockers were the most prescribed agents, with bisoprolol being the most prescribed agent. Most reported side effects are cardiovascular in nature, with bradycardia being the most common side effect. Amiodarone was associated with the highest incidence of side effects. Clinical pharmacists helped safely and effectively use antiarrhythmic drugs in our setting. Their intervention was mainly related to the selection and dose optimization of antiarrhythmic agents. However, further prospective studies are needed to properly evaluate the outcomes of this intervention.

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None

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS (CRediT)

Conceptualization: RC, AA; Data curation: RC; Formal analysis: RC; Methodology: RC, KA, MZ, AA; Supervision: AA; Writing – original draft: RC, MZ; Writing –review & editing: MZ, AA, KA

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