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Case Series

Unravelling Drug-Induced Arrhythmias: A Case Series Analysis

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Abstract

Background: Drug-induced arrhythmias pose a significant clinical challenge, with potential life-threatening complications such as cardiac arrest and sudden cardiac death. Understanding the epidemiology, implicated drugs, and clinical characteristics of drug-induced arrhythmias is crucial for optimizing patient care and improving outcomes.

Methods: A retrospective cohort study involving 500 arrhythmia-diagnosed patients was conducted. Drug-induced cases were identified through meticulous medication histories. Various demographic and clinical variables were collected, and statistical analyses, including logistic regression, explored the association between drug exposure and arrhythmia development.

Results: Among the 500 patients diagnosed with arrhythmias, 115 cases (23%) were attributed to pharmacological agents. Notably, amiodarone was significantly associated with arrhythmia development ($p<0.001$, OR=2.5, 95% CI 1.8–3.4), as were ciprofloxacin ($p=0.006$, OR=1.8, 95% CI 1.2–2.7), sertraline ($p=0.014$, OR=1.6, 95% CI 1.1–2.3), and amitriptyline ($p<0.05$, OR=1.6, 95% CI 1.1–2.3). Advanced age (>65 years) was significantly associated with a higher risk of drug-induced arrhythmias (OR=2.5, $p<0.001$), similar to a history of cardiovascular disease (OR=3.1, $p<0.001$). Polypharmacy (OR=2.8, $p=0.002$) also emerged as an independent risk factor.

Conclusion: Understanding the complexity of drug-induced arrhythmias is crucial for patient care. Tailored risk assessment and management strategies are imperative to mitigate adverse outcomes associated with these arrhythmias, especially in high-risk patient populations. Incorporating personalized approaches into clinical practice can enhance patient safety and improve outcomes in individuals prone to drug-induced arrhythmias.

Keywords: Amiodarone, Amitriptyline, Arrhythmias, Cardiac, Cardiovascular Diseases, Logistic Models, Patient Safety, Polypharmacy, Retrospective Studies, Sertraline

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Introduction

Drug-induced arrhythmias represent a complex and challenging aspect of clinical cardiology. While arrhythmias can arise from various etiologies, medications have been implicated as significant triggers or exacerbators of cardiac rhythm disturbances (1). Understanding the epidemiology, implicated drugs, and clinical characteristics of drug-induced arrhythmias is crucial for optimizing patient care and improving outcomes. This study aims to delve into the landscape of drug-induced arrhythmias, drawing insights from a retrospective cohort study and relevant literature (2,3).

Drug-induced arrhythmias encompass a diverse array of rhythm disturbances, ranging from mild palpitations to life-threatening ventricular tachyarrhythmias. The prevalence and incidence of drug-induced arrhythmias vary depending on multiple factors, including patient demographics, comorbidities, and medication profiles (4). Advanced age, a history of cardiovascular disease, and polypharmacy emerged as independent risk factors for drug-induced arrhythmias (5,6). These findings underscore the multifactorial nature of arrhythmia pathogenesis, necessitating tailored risk assessment strategies (7,8,9).

A wide range of medications has been associated with drug-induced arrhythmias, including antiarrhythmic agents, antibiotics, psychotropic medications, *etc*. (10,11). Among these, antiarrhythmic agents constitute a significant proportion, with drugs like amiodarone exhibiting pronounced arrhythmogenic potential (3,9). Mechanistically, drug-induced arrhythmias can result from various electrophysiological effects, including QT interval prolongation, sodium channel blockade, and alterations in potassium currents (3,12). For instance, certain antidepressants and antipsychotics have been implicated in QT interval prolongation, predisposing patients to torsade de pointes and sudden cardiac death (13,11). Additionally, drug interactions and genetic predispositions can further modulate individual susceptibility to drug-induced arrhythmias (14,15).

Drug-induced arrhythmias manifest with diverse clinical presentations, ranging from asymptomatic electrocardiographic abnormalities to life-threatening arrhythmic events (11). The identification and management of drug-induced arrhythmias require a comprehensive approach, including thorough medication reconciliation, risk stratification, and close monitoring of cardiac function (16). Clinicians should remain vigilant for potential drug-drug interactions and adverse effects, particularly in patients with pre-existing cardiovascular conditions (17). Furthermore, individualized management strategies, such as dose adjustments and drug substitutions, may be necessary to minimize the risk of arrhythmic complications (18).

Materials and Methods

The methodology employed in this retrospective cohort study aimed to provide a comprehensive analysis of the epidemiology, implicated drugs, and clinical characteristics of drug-induced arrhythmias. Over the course of the study period from January 1, 2021, to December 31, 2023, a cohort comprising 500 patients diagnosed with arrhythmias was retrospectively analyzed. Prior to data collection, institutional review board approval was obtained. Detailed demographic information, including age, sex, and comorbidities, was extracted from electronic medical records. Extensive medication histories, encompassing current prescriptions and recent changes, were meticulously documented. The type and dosage of implicated drugs were recorded, along with the temporal relationship between medication initiation and arrhythmia onset. Case identification relied on thorough medication histories and clinical assessments, with inclusion criteria encompassing documented arrhythmic events, electrocardiographic abnormalities, or symptomatic presentations. Drug-induced cases were defined as those where arrhythmias were temporally related to medication use, with no alternative etiology identified.

SPSS version 29 was utilized for statistical analysis which involved descriptive statistics to summarize the patient demographics and clinical characteristics. Categorical variables were expressed as frequencies and percentages, while continuous variables were reported as means±standard deviations or medians with interquartile ranges. The association between implicated drugs and arrhythmia development was assessed using logistic regression analysis, with Odds Ratios (ORs) and 95% Confidence Intervals (CIs) calculated. Logistic regression was selected for this analysis as we were interested in assessing

the association between drug use and the binary outcome of arrhythmia development at a specific time point. The significance level was set at $p<0.05$. A multivariate logistic regression analysis was performed to assess the association between implicated drugs and arrhythmia development, adjusting for the following variables: age, gender, comorbidities (*e.g.*, hypertension, diabetes), and baseline heart rate.

Results

In this retrospective cohort study investigating drug-induced arrhythmias, comprehensive analysis revealed intriguing insights into the epidemiology, implicated drugs, and clinical characteristics associated with this complex phenomenon. Over the study period spanning from January 1, 2021, to December 31, 2023, a cohort comprising 500 patients diagnosed with arrhythmias was meticulously examined (Table 1).

The results revealed that among the 500 patients, 115 cases (23%) were attributed to pharmacological agents, signifying the significant contribution of medications to arrhythmia etiology. Antiarrhythmic agents constituted the largest proportion (15%) of implicated drugs, with amiodarone emerging as the most frequently associated medication, accounting for 10% of all drug-induced arrhythmias. Antibiotics were also commonly implicated, contributing to 7% of cases, with ciprofloxacin and azithromycin being the most frequently prescribed antibiotics associated with arrhythmias. Psychotropic medications, including selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs), accounted for 5% of drug-induced arrhythmias, with sertraline and amitriptyline being the most frequently implicated drugs (Table 2).

Further analysis revealed significant associations between certain drugs and arrhythmia development. For instance, the use of amiodarone was found to be significantly associated with the development of arrhythmias ($p<0.001$, OR=2.5, 95% CI 1.8–3.4), underscoring its arrhythmogenic potential. Additionally, antibiotics were associated with an increased risk of arrhythmias, with ciprofloxacin showing a significant association ($p=0.006$, OR=1.8, 95% CI 1.2–2.7). Psychotropic medications also

Table 1. Demographic characteristics of the study population

	Total	Male	Female
Total Patients	500	280	220
Age (mean±SD)	62±10	63±9	61±11
Comorbidities			
Hypertension	224	139	85
Diabetes Mellitus	151	90	61
Coronary Artery Disease	123	84	39
Congestive Heart Failure	75	49	26
Chronic Kidney Disease	51	35	16
Medication History			
Antiarrhythmics	75	48	27
Beta-blockers	99	59	40
Calcium Channel Blockers	48	29	19
ACE Inhibitors	75	45	30
Antibiotics	52	27	25
Psychotropics	23	14	9

Table 2. Distribution of the implicated drugs by drug class and gender

Drug Class	Implicated Drugs	Total Cases	Male Cases	Female Cases
Antiarrhythmic Agents	Amiodarone, Sotalol, Flecainide	36	20	16
Antibiotics	Ciprofloxacin, Azithromycin, Clarithromycin	25	12	13
Psychotropic Medications	Sertraline, Amitriptyline, Haloperidol	18	9	9
Calcium Channel Blockers	Verapamil, Diltiazem, Amlodipine	10	5	5
Beta-Blockers	Metoprolol, Propranolol, Bisoprolol	9	4	5
Others	Digoxin, Lithium, Diuretics	12	6	6

The percentages in parentheses represent the proportion of cases attributed to each specific drug within its respective drug class.

Table 3. Risk factors for drug-induced arrhythmias

Risk Factor	Odds Ratio (95% CI)	p-value	Clinical Implications
Advanced Age	2.5 (1.5–4.2)	<0.001	Age-related decline in cardiac function, increased vulnerability
Cardiovascular Disease	3.1 (1.8–5.6)	<0.001	Underlying structural heart disease, impaired electrical conduction
Polypharmacy	2.8 (1.6–4.9)	0.002	Drug interactions, cumulative cardiotoxic effects

exhibited a significant association, with sertraline and amitriptyline showing a p value of 0.014 and an odds ratio of 1.6 (95% CI 1.1–2.3) (Table 3).

Advanced age emerged as a significant risk factor for drug-induced arrhythmias, with patients over 65 years old exhibiting a 2.5-fold increased risk compared to younger individuals (OR=2.5, 95% CI 1.5–4.2, p<0.001). Similarly, a history of cardiovascular disease was strongly associated with arrhythmia development, with an odds ratio of 3.1 (95% CI 1.8–5.6, p<0.001). Polypharmacy, defined as the concurrent use of five or more medications, was also identified as an independent risk factor, with patients showing a 2.8-fold increased risk of drug-induced arrhythmias compared to those with fewer medications (OR=2.8, 95% CI 1.6–4.9, p=0.002).

In terms of clinical characteristics, palpitations were the most common presenting symptom (60%), followed by syncope (25%) and fatigue (20%). Electrocardiographic findings revealed QT interval prolongation in 45% of cases, ST-T changes in 30%, and torsade de pointes in 10%. Hospitalization occurred in 35% of the cases, with mortality reported in 10%. In addition to torsades de pointes (15%) and Ventricular Fibrillation (VF) (5%), the study observed a variety of other arrhythmias. These included Atrial Fibrillation (AF), Premature Ventricular Contractions (PVCs), Bradyarrhythmia's (such as Sinus Bradycardia or Atrioventricular Block), and Supraventricular Tachycardia (SVT). The incidence of these additional arrhythmias was not as prominently featured as Tdp and VF, yet they contribute to the overall spectrum of arrhythmogenic potential observed in this population. Complications included heart failure (15%), ventricular fibrillation (5%), and cardiogenic shock (2%). Notably, there were slight differences in clinical characteristics between males and females, with males experiencing

Table 4. Clinical characteristics of drug-induced arrhythmias

Clinical Characteristic	Total (n=115)	Male (n=65)	Female (n=50)
Presenting Symptoms			
Palpitations	69	42	27
Syncope	29	14	15
Fatigue	23	12	11
Electrocardiographic Findings			
QT Interval Prolongation	52	31	21
ST-T Changes	35	18	17
Torsades de Pointes	12	5	7
Outcomes			
Hospitalization	40	25	15
Mortality	12	8	4
Ventricular Fibrillation	6	4	2
Complications			
Heart Failure	17	11	6
Ventricular Fibrillation	6	4	2
Cardiogenic Shock	2	2	0

a higher incidence of certain symptoms and outcomes compared to females (Table 4).

Subgroup analyses further elucidated variations in the risk of drug-induced arrhythmias across different age groups, medication classes, and comorbidity profiles. Elderly patients (>65 years) exhibited the highest risk, particularly when prescribed amiodarone, ciprofloxacin, azithromycin, sertraline, or amitriptyline. Patients with a history of cardiovascular disease showed a significantly increased risk, especially when exposed to multiple medications concurrently. The differentiation between heart failure-induced arrhythmias and those caused by drug consumption was carefully considered. This differentiation was primarily based on the temporal relationship between drug administration and arrhythmia onset. The patients were closely monitored to establish a baseline arrhythmia profile before the initiation of the drug. Any arrhythmias that emerged following the commencement of treatment, particularly those that are known adverse effects of the drug, were classified as drug-induced. The mentioned findings underscore the complex interplay between patient characteristics, medication profiles, and arrhythmia susceptibility. Tailored risk assessment and management strategies are imperative to mitigate the risk of adverse outcomes associated with drug-induced arrhythmias, particularly in high-risk patient populations. Ongoing research efforts are warranted to further elucidate the underlying mechanisms and optimize therapeutic interventions in this clinically challenging domain.

Discussion

The discussion surrounding drug-induced arrhythmias encompasses a comprehensive analysis of various facets, including epidemiology, implicated drugs, clinical characteristics, management strategies, and emerging trends. This multifaceted examination is crucial for understanding the complexities of arrhythmia pathogenesis and optimizing patient care. One of the key findings of this retrospective

cohort study is the significant contribution of medications to the development of arrhythmias, with 23% of cases attributed to pharmacological agents (5,9). This underscores the importance of recognizing drug-induced arrhythmias as a clinically relevant phenomenon and highlights the need for heightened awareness among healthcare providers. Further exploration into the implicated drugs reveals a diverse array of medications associated with arrhythmogenicity. While antiarrhythmic agents, such as amiodarone, have long been recognized for their potential to induce arrhythmias (3,19,20), other therapeutic classes, including antibiotics and psychotropic medications, also exhibit significant arrhythmogenic potential (11,21,22).

Amiodarone, a widely used antiarrhythmic agent, has been consistently associated with drug-induced arrhythmias due to its complex electrophysiological effects (19). While it effectively controls cardiac rhythm disturbances, its propensity to prolong the QT interval and induce torsades de pointes underscores the importance of careful patient selection, close monitoring, and dose optimization (19). Amiodarone administration was largely targeted at controlling pre-existing arrhythmias. However, in cases where the arrhythmia persisted or when a different type of arrhythmia emerged post-administration, a differentiation was made between treatment failure and drug-induced arrhythmia. Persistent arrhythmia of the same type was classified as treatment failure, indicating the need for alternative therapeutic strategies. Conversely, the emergence of a new type of arrhythmia, particularly one known to be associated with Amiodarone, was considered indicative of drug-induced arrhythmia. Ciprofloxacin, a commonly prescribed fluoroquinolone, has been associated with QT prolongation and an increased risk of ventricular arrhythmias (21). Similarly, azithromycin, a widely used macrolide antibiotic, has been implicated in QT interval prolongation and torsades de pointes, particularly in patients with pre-existing cardiovascular risk factors (21). Sertraline, an SSRI, has been associated with QT prolongation and ventricular arrhythmias, highlighting the importance of careful risk assessment and monitoring in patients receiving these agents (21). Similarly, amitriptyline, a TCA, can prolong the QT interval and increase the risk of life-threatening arrhythmias, particularly at higher doses (21).

Patient characteristics play a critical role in modulating susceptibility to drug-induced arrhythmias. Advanced age, a history of cardiovascular disease, and polypharmacy emerged as independent risk factors, highlighting the importance of individualized risk assessment and management strategies (9,22-24). Genetic predispositions further compound this complexity, influencing drug metabolism, ion channel function, and drug transporter activity (25). Pharmacogenomic testing offers a promising avenue for personalized medicine, enabling clinicians to tailor therapeutic interventions based on individual genetic profiles (11,26).

By identifying the genetic variants associated with drug metabolism and sensitivity, pharmacogenomic testing can help predict an individual's response to specific medications and optimize treatment outcomes while minimizing the risk of adverse drug reactions. Effective management of drug-induced arrhythmias requires a multifaceted approach that encompasses medication management, risk stratification, and close monitoring of cardiac function. Clinicians must remain vigilant for potential drug-drug interactions and adverse effects, particularly in vulnerable patient populations (9,27). Individualized management strategies, such as dose adjustments and drug substitutions, may be necessary to mitigate the risk of arrhythmic complications and optimize clinical outcomes (3,9,28). Moreover, patient education and shared decision-making are essential components of comprehensive care, empowering patients to actively participate in their treatment plans and adhere to prescribed therapies (29). By fostering collaborative partnerships between patients and healthcare providers, clinicians can enhance medication adherence, improve patient satisfaction, and ultimately, reduce the burden of drug-induced arrhythmias. Looking ahead, ongoing research efforts are required to further elucidate the mechanisms underlying drug-induced arrhythmias and identify novel therapeutic targets. Longitudinal studies are warranted to assess the long-term outcomes and prognosis of patients with drug-induced arrhythmias, as well as the impact of emerging pharmacotherapies on arrhythmia incidence and management. Collaborative initiatives

between clinicians, pharmacologists, geneticists, and other stakeholders are essential to drive innovation in arrhythmia research and translate scientific discoveries into clinical practice.

Conclusion

In conclusion, drug-induced arrhythmias represent a significant clinical challenge, necessitating a nuanced understanding of their epidemiology, implicated drugs, and clinical characteristics. Insights from retrospective cohort studies, coupled with advances in pharmacogenomics and risk stratification, can inform tailored interventions to mitigate the risk of adverse outcomes associated with drug-induced arrhythmias. By optimizing medication management and implementing personalized monitoring strategies, healthcare providers can enhance patient safety and improve clinical outcomes in this vulnerable population.

Limitations

The study has limitations to be acknowledged. It is retrospective, which introduces biases like selection and information bias, affecting validity. Reliance on medical records may lead to incomplete data and misclassification. The study was limited to a specific healthcare facility, possibly limiting generalizability. Causality between medication use and arrhythmia cannot be established due to the observational design. Additionally, the sample size and duration of follow-up may have limited the ability to detect less common drug-arrhythmia associations or assess long-term outcomes accurately. These constraints highlight the necessity for further prospective research with larger, more diverse populations to validate and expand upon the findings.

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Conflict of Interest

There was no conflict of interest in this manuscript.

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