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Refractory Torsades de Pointes Due to Dofetilide Overdose

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Abstract

Dofetilide, a class III antiarrhythmic, is widely used in the treatment of cardiac arrhythmias. Antiarrhythmic drugs can have a long duration of action that prolongs the QT interval. This causes bradycardia that predisposes to R-on-T phenomenon subsequently leading to torsades de pointes (TdP). This necessitates constant monitoring to prevent or treat ventricular arrhythmias or bradycardia associated with cardiac medications. Although extremely rare, dofetilide overdose has been described in the literature. However, no evidence found in the current literature required prolonged intervention after the initial acute stabilization, leading to scarcity of data for treatment of ongoing dofetilide overdose. We present the case of an intentional dofetilide overdose in a 61-year-old Caucasian woman with a history of congestive heart failure, atrial fibrillation, stage IIIb chronic kidney disease, diabetes mellitus type II, hypothyroidism, morbid obesity, and hypertension that required extensive interventions for refractory TdP that lasted 4 days. Therapeutic as well as excess dosage of dofetilide can lead to TdP, which is usually controlled by decreasing the dose or terminating drug administration. If the arrhythmia is not resolved, guidelines recommend management with activated charcoal if ingestion is within 15 minutes, followed by administration of 2 g IV (intravenous) magnesium and addressing the electrolyte imbalance. However, if the arrhythmia is persistent due to ongoing dofetilide toxicity, isoproterenol is given as a bridge to overdrive pacing and dopamine is used as an alternative to isoproterenol.

Keywords

dofetilide, overdose, torsades de pointes, ventricular arrhythmia

Introduction

Dofetilide, a class III antiarrhythmic, is currently used in the treatment of a variety of cardiac arrhythmias, including atrial fibrillation and atrial flutter, to convert them into normal sinus rhythm. It exerts its action by blocking the rapid component of the cardiac delayed rectifier potassium channel, which results in prolongation of the repolarization phase leading to an increase in the effective refractory period and prolongation of the QT interval, subsequently terminating the arrhythmia.[1,2] It avoids the toxicities of amiodarone while having a preferentially greater effect on prolonging repolarization in the atrial myocytes.[1]

Acute overdose of dofetilide is reported to manifest as QT prolongation, TdP, or complete heart block.[3] The treatment for dofetilide overdose is mainly supportive. Activated charcoal is useful if a patient presents within the first 15 minutes of drug overdose, which is followed by cardiac monitoring and electrocardiogram (EKG).[3] Administration of isoproterenol and magnesium sulfate along with correction of potassium imbalance using potassium chloride is done if the symptoms persist.[3] Usually, these treatment modalities lead to resolution of symptoms without long-term sequelae.

In this report, we present an acute intoxication with 10 g (20 tablets) of dofetilide in a 61-year-old woman who presented with palpitations and TdP on EKG outside the window where gastrointestinal decontamination could be attempted successfully as described in prior case reports.[4,5] She presented approximately 4 hours after ingestion. The United States Poison Control Center recommends lidocaine continuous intravenous infusion as the treatment for dofetilide

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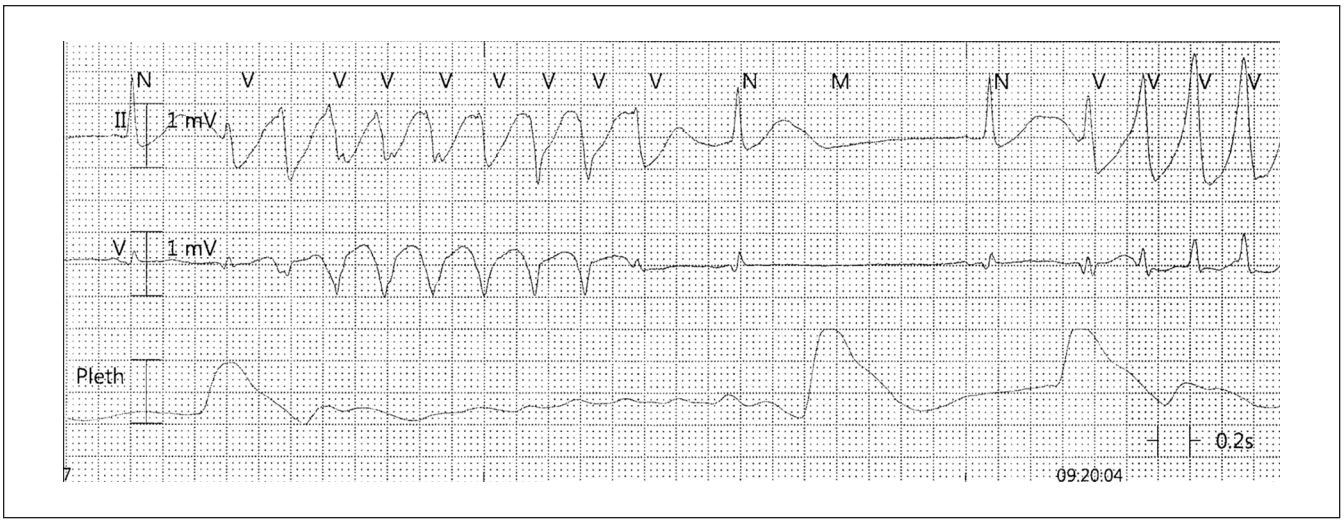

Figure 1. Telemetry strip showing repeated self-terminating episodes of TdP with prolonged QT with R-on-T phenomenon with bradycardia.
Abbreviation: TdP, torsades de pointes.

overdose. However, our patient did not respond to continuous lidocaine infusion and standard pharmacological management, but was subsequently stabilized using additional interventions, which have not been described in the existing literature. Through this case, we aim to expand the knowledge of treatment options in the case of prolonged torsades de pointes (TdP) secondary to dofetilide overdose.

Case

A 61-year-old Caucasian woman with a past medical history of paroxysmal atrial fibrillation, congestive heart failure, diabetes mellitus type II, hypertension, chronic kidney disease (CKD) stage IIIb, and hypothyroidism presented to the emergency department complaining of an acute overdose of dofetilide. She reports she was taking her usual morning medications and accidentally ingested 20 tablets of dofetilide which she confused for her usual morning medications. The dofetilide dose was 500 μg bringing her total ingestion to 10 mg. The patient reported that the event occurred 4 hours prior to presentation; hence, she could not be considered as a candidate for gastrointestinal decontamination with activated charcoal.[6] No further history could be elicited owing to the patient being lethargic. She presented with a temperature of 98.7, heart rate (HR) 68, blood pressure (BP) 184/89 mmHg, and respiratory rate 19. Her physical examination findings revealed a morbidly obese lethargic woman in mild respiratory distress. She was immediately placed on telemetry and was revealed to have several self-terminating episodes of polymorphic ventricular tachycardia (Figure 1).

An EKG was performed immediately, which revealed sinus rhythm with a HR of 82 and frequent premature atrial complexes and occasional premature ventricular complexes. The patient's QTc was 529 ms on day 1 with R-on-T phenomenon (Figure 2), which exceeded the normal QTc interval for women of $\leq$450 ms.[5]

The PR interval and QRS duration were within normal limits. Two grams of intravenous magnesium was given immediately per American Heart Association (AHA) treatment guidelines.[7] Poison Control Center of Kentucky in Louisville was called immediately and a lidocaine continuous intravenous infusion along with direct current cardioversion for unstable TdP was initiated as per their recommendations. Lidocaine has been used successfully in prior overdosages of class III antiarrhythmics such as sotalol.[7] The on-call cardiologist was contacted for a transvenous pacemaker with isoproterenol or dopamine to keep the HR above 85 until the pacemaker could be placed, as our facility did not offer this service.[1,8] This is necessary as QT interval decreases with HR and it decreases ventricular ectopy.[1,8] The patient was intubated as she is lethargic and the need to protect her airway should she develop ventricular fibrillation or pulseless ventricular tachycardia. Patient was transferred to another facility within our system. She remained on the lidocaine infusion for the next 24 hours while continuing to have episodes of TdP with HR $>$ 60 for the next day. She did require defibrillation 5 times on day 2 due to unstable TdP. She became progressively bradycardic on the following day which was treated with atropine to no avail. A dopamine continuous intravenous infusion was subsequently initiated which did not resolve the bradycardia. QTc maximum was 741 ms on day 1 with subsequent shortening to 628 ms after treatment with dopamine for chronotropic effect. She had a maximum QTc prolongation of 770 ms. She was then temporarily placed on transcutaneous pacing until a transvenous pacemaker could be placed in the cardiac catheterization lab (Figure 3). She was set at a rate of 80. This successfully

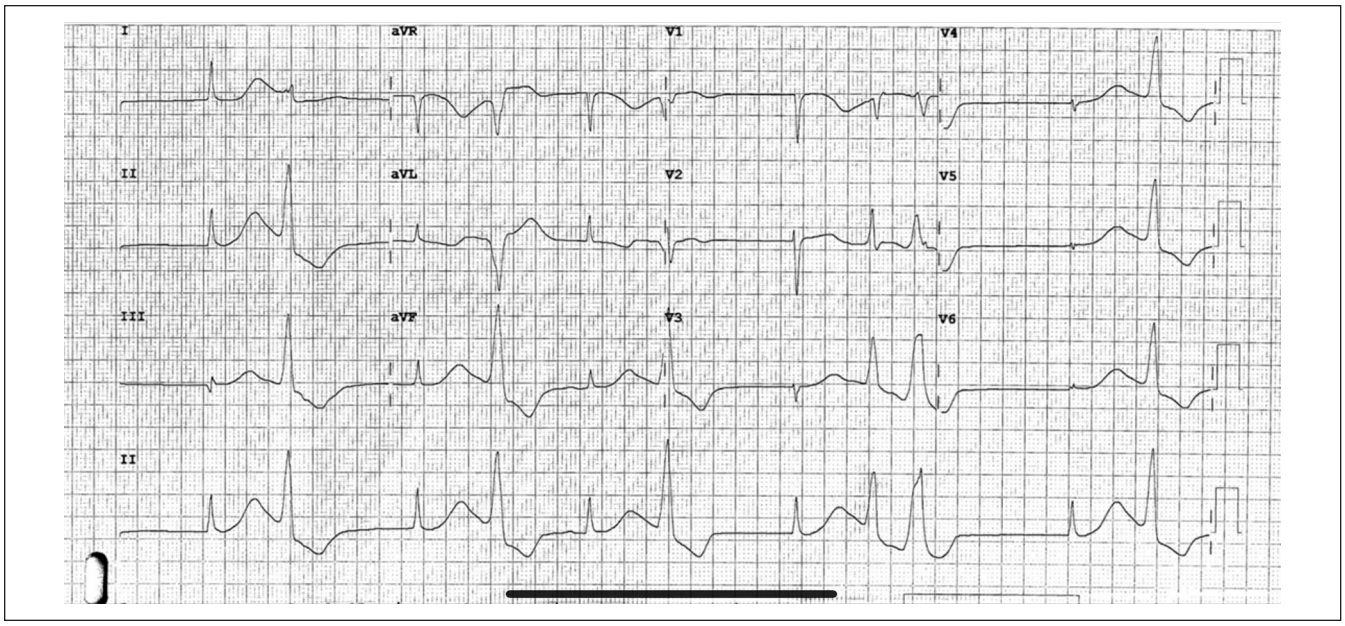

Figure 2. A 12-lead EKG demonstrating EAD occurring during repolarization or R-on-T phenomenon which occurs during bradycardia.
Abbreviations: EKG, electrocardiogram; EAD, early afterdepolarization.

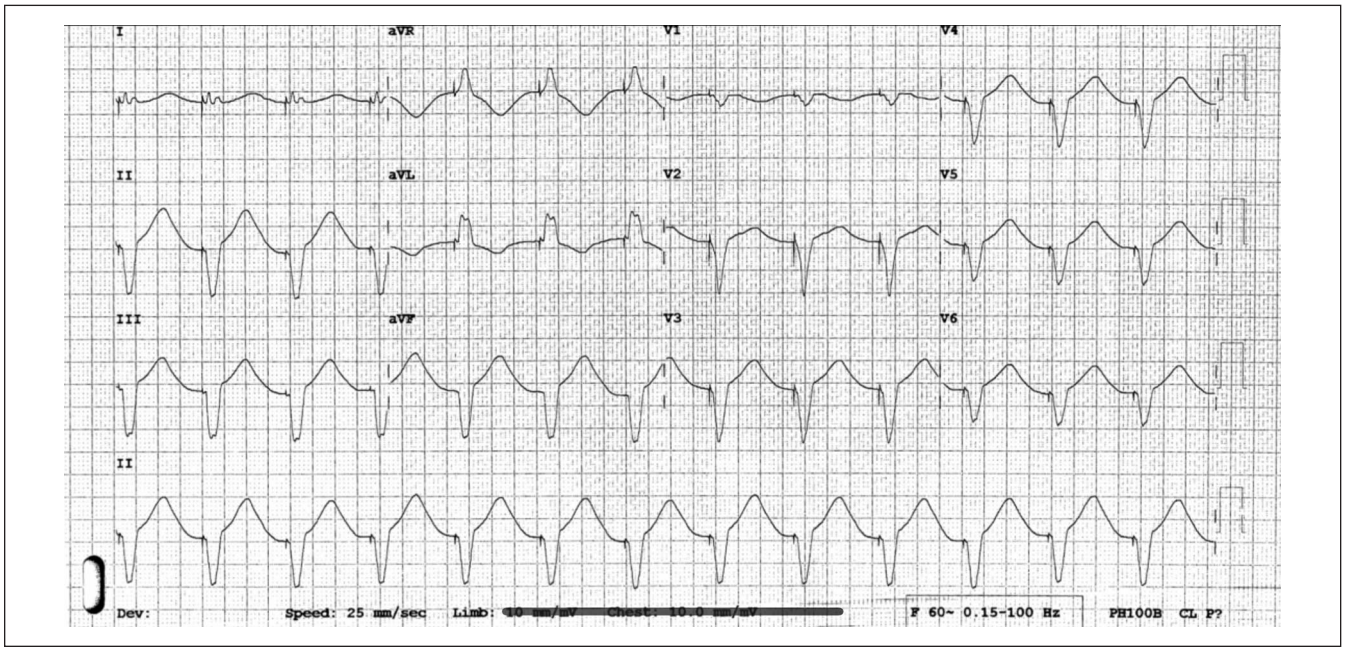

Figure 3. EKG after transvenous pacer is placed, prolonged QTc, but overdrive pacing suppresses ventricular ectopy.
Abbreviation: EKG, electrocardiogram.

Day 1	Day 2	Day 3	Day 4
IV $MgSO_4$ 2 gm	Dopamine CIV	Pacing to 85 bpm	Pacing to 50 bpm
Intubation	Lidocaine CIV	Lidocaine CIV	Pacemaker Removed
Lidocaine CIV	Defibrillation $\times 5$		
	Transvenous Pacemaker		
Day 1 QTc-741 ms	Day 2 QTc-770 ms	Day 3 QTc-550	Day 4 QTc-Normalized

overcame the ventricular ectopy. By the third day, she had no new arrhythmias and had a marked improvement of the QTc interval as compared with her QTc interval of 770 ms on the second day of admission. By day 4, the pacemaker rate was decreased to 50, following which the transvenous pacemaker was removed. Subsequently, she maintained a normal sinus rhythm with a rate of 70 and a normal QTc. Later, she was extubated and discharged. She was discharged on amiodarone 200 mg by mouth twice daily and was advised to follow up with cardiology clinic. She was subsequently lost to follow-up.

Discussion

Dofetilide, a class III antiarrhythmic, is widely used in the treatment of arrhythmias, including atrial flutter and atrial fibrillation.[9] Dofetilide in therapeutic as well as excess dosage can lead to a prolongation of QTc interval which can induce TdP that is managed by immediate interventions.[5,10] However, we present a unique case of dofetilide overdose that needed management of an underlying arrhythmia outside of the acute intervention stage. Our patient ingested 10 mg of dofetilide. Dofetilide is almost completely absorbed with a bioavailability of greater than 90% after oral administration with a t½ of 8 to 10 hours in patients with normal renal function and it has not been studied in those with severe CKD.[1] It is mainly eliminated via the kidneys (80%) and the QT interval has a linear relationship with dofetilide after oral administration.[1] Our patient had a history of CKD stage IIIb with baseline creatinine/glomerular filtration rate (GFR) of 1.3/40 but had acute kidney injury (AKI) on presentation with a creatinine/GFR of 1.7/30 on presentation that responded to fluid administration. This suggests that dofetilide excretion may not be substantially reduced until there is severe kidney dysfunction as this patient had taken 10 mg of dofetilide which was excreted in roughly 10 to 12 t½s over the course of 3 days.[1] This case is complex, in that it challenges existing treatment guidelines by medical toxicologists.

A literature review of PubMed and ScienceDirect databases addressing the risk factors, clinical effects, and treatment of dofetilide overdose was carried out. Keywords "dofetilide" or "Tikosyn" and "overdose" were used, without any language or date filters, which resulted in 6 studies ranging from 1993 to 2020 in the PubMed database and 18 studies in ScienceDirect. From these, 20 studies, including the one conducted in 1993, were excluded due to nonrelevance to our question in discussion. A search of similar articles and the reference lists of the included studies was carried out to look for other potentially eligible studies. In all, a review of 11 studies was carried out to consolidate the knowledge of dofetilide overdose. However, we could not find any study addressing the treatment of prolonged arrhythmia, beyond the acute phase in dofetilide overdose, which would entail requiring treatment beyond gastrointestinal decontamination and magnesium administration, and hence are reporting this case to add to the existing literature.

A study done by Jaiswal et al[1] listed the risk factors predisposing a patient to drug-induced excessive QT prolongation and TdP. This included EKG changes of long QT interval, increased QT dispersion, increased interval from peak to end of T wave, T wave alternans, or the presence of T-U waves. Other predisposing factors include electrolyte abnormalities such as hypokalemia and hypomagnesemia, female gender, older age, HIV-positive status, systolic dysfunction, previous history of drug-induced long QT or TdP, close relatives with a history of drug-induced long QT, recent cardioversion from atrial fibrillation, and decreased elimination/excretion of these drugs.[1] Our patient had 5 of these risk factors.

Usually, patients suffering from an acute overdose of dofetilide present within the first 15 to 30 minutes during which treatment with gastric lavage usually proves to be curative. This was described in a clinical study where despite ingesting 5 mg or 10 tablets of dofetilide, due to timely gastric lavage, the patient was stabilized with no residual adverse effects.[3] A retrospective study done by Hieger et al on 27 patients with dofetilide overdose also showed that the only patient who developed symptoms of nonsustained ventricular tachycardia, frequent multifocal premature ventricular contractions (PVCs), and ventricular bigeminy was the one who had taken 90 times his usual dose in a suicide attempt.[4] He received magnesium sulfate and potassium chloride supplementation, which caused resolution of symptoms. Another study that described an unintentional overdose of 5 mg of dofetilide in a 50-year-old man due to mathematical calculation error reported symptom resolution with the known management protocol of activated charcoal, magnesium sulfate, and potassium chloride.[11] Similarly, a 33-year-old man with a history of cocaine abuse who ingested 5 mg of dofetilide was successfully treated with similar therapeutic interventions that included the administration of activated charcoal and sorbitol by nasogastric tube and potassium and magnesium supplementation.[12] As opposed to these cases described in the literature, despite following guidelines for therapeutic management of TdP, our patient could not be stabilized and further treatment with lidocaine, dopamine, and overdrive pacing had to be done.

The current recommended guidelines for acquired QT prolongation with TdP is to give 2 g of intravenous magnesium immediately as it acts as a calcium channel blocker by blocking calcium influx into the cytoplasm from the sarcoplasmic reticulum.[7] It is this calcium influx from the L-type calcium channels on the sarcoplasmic reticulum that gives rise to early afterdepolarizations and triggered activity that underlies self-limiting episodes of TdP.[13,14] Following this, it is recommended to treat patients showing persistent symptoms with lidocaine, as this was successful in the past cases.[13,15] One study shows that a late sodium current blockade by lidocaine shortens the QT

interval substantially in QT prolongation caused by hERG potassium-channel blocker such as dofetilide.[16] If the patient becomes hypotensive, or unstable, or degenerates into ventricular fibrillation, then immediate defibrillation is recommended as per ACLS (Advanced Cardiac Life Support) protocol. If the patient is relatively stable but continues to have self-limiting episodes of TdP, the next step is to give isoproterenol, which has β1/β2 agonist properties, as an intravenous infusion until transvenous pacing can be performed if the HR < 85.[1,14] This is called overdrive pacing that is ideally set at rates of 90 to 110 beats per minute to overcome the patient's intrinsic ventricular ectopy.[17] Isoproterenol acts as a pharmacological pacemaker to increase the HR and decrease the QT interval.[17] The general pathway for management of acquired QT prolongation–induced TdP was successful in our case of dofetilide overdose. Dofetilide and other class III, Ia, Ic antiarrhythmics have been known to cause QT prolongation and should be avoided in patients with preexisting arrhythmias, cardiac disease, or electrolyte disturbances.[18] Specifically, one article recommends treating dofetilide-induced TdP as TdP from any other cause.[1] Also, electrolyte disturbances such as hypokalemia, hypomagnesemia, and hypocalcemia should be considered as causes of QT prolongation in the patient and corrected subsequently. Potassium is ideally repleted to a level of 4.5 mEq/L although there is no great evidence to support this practice.[1] As with atrial fibrillation though, it is preferential to keep the magnesium above 2 mg/dL and the potassium above 4 mEq/L in patients with underlying heart disease as well as hold or discontinue any QT-prolonging medications until the acute intoxication is resolved.[12]

Other complex issues to consider are that the extreme expense and unavailability of isoproterenol may limit its use in many settings, especially rural. Dopamine continuous IV infusion can be used to increase the HR and serve as a bridge to overdrive pacing as dopamine is used in symptomatic bradycardia to increase the HR, although not specifically to prevent TdP.[19]

Conclusion

We present a rare case of dofetilide toxicity presented as recurrent TdP. This case report provides insight into presentation and management. Ak Jaiswal et al suggested treating dofetilide-induced ventricular tachycardia or TdP similar to TdP from any other cause, which includes 2 g of IV magnesium initially, followed by isoproterenol as a bridge to overdrive pacing even in acute overdose, although data are currently limited. Activated charcoal has a role if patient presents within 15 minutes. Dopamine is an alternative to isoproterenol. Dofetilide toxicity is an acute emergency and can happen even with therapeutic doses and any patient on this medication presenting with TdP should be further investigated.

Authors' Note

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in the article.

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