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Case Report

Diphenhydramine and QT prolongation – A rare cardiac side effect of a drug used in common practice

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ABSTRACT

There have been few cases in recent times where QT interval prolongation has been studied with regards to the use of diphenhydramine. We present a case of a patient who presented because of shortness of breath and needed emergent hemodialysis; during the course of which he developed prolonged QT interval on electrocardiography, which was correlated interestingly with the use of diphenhydramine. Pruritus is a common symptom experienced by dialysis patients. A less known, but rare side effect of diphenhydramine is prolongation of QT interval. The histamine H1 receptor antagonist diphenhydramine inhibits the fast sodium channels and at higher concentrations inhibits the repolarizing potassium channels which leads to prolongation of the action potential and the QT interval. Diphenhydramine toxicity is dose-dependent with a critical dose limit of 1.0 g.

Although a lot is known about the potential side effects of antihistamines, only a few cases have cited the cardiac side effects. Thus, it is important for the clinician to be aware of this potentially serious consequence of a commonly used drug, especially in the end-stage renal disease population. It is important for clinicians to be aware of this rare yet dangerous side effect of diphenhydramine.

<**Learning objective:** Although a lot is known about the potential side effects of antihistamine drugs little is described regarding cardiac side effects. Some antihistamines such as terfenadine have been discontinued from the US market due to prolonged QT interval; therefore, it is important for the clinician to be aware of potentially serious consequences of a commonly used drug such as diphenhydramine. We describe a case of a patient who developed QT prolongation with a temporal association with diphenhydramine usage.>

Introduction

Long QT interval due to prolonged repolarization may be associated with polymorphic ventricular tachycardia known as torsades de pointes (TdP). During marked prolongation of the action potential (long QT), early after depolarizations may occur, which, when propagated may trigger an arrhythmia. The duration of QTc interval is the major determinant of the risk of drug-induced TdP. Congenital long QT syndrome (LQTS), female gender, hypokalemia, and use of sympathomimetics increase the risk of TdP, and potentiate the QT prolonging effects of drugs. Antiarrhythmics that block the potassium channel prolong the QT and increase the risk for TdP (amiodarone, sotalol, quinidine, procainamide, ibutilide, disopyramide). Additionally, some macrolide and fluoroquinolone antibiotics, antipsychotic and antidepressant drugs, serotonin agonists of the triptan class, cisapride, dolasetron, and others have been reported to be associated with QT prolongation or cases of TdP. Drug-induced effects on the QT interval, with the associated possibility of inducing fatal arrhythmias, have become a new challenge for the practitioner, the drug development process, and the regulatory agencies.

The association of diphenhydramine and QT prolongation is extremely rare, and the association is only proposed and not definite [1,2]. Our case demonstrates the proposed rare association of diphenhydramine with prolongation of the QT interval.

Case report

The patient is a 55-year-old male, with a past medical history of hypertension, end-stage renal disease related to hypertensive

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nephrosclerosis on hemodialysis, anemia of chronic disease, obesity, and pulmonary embolus on lifelong warfarin, presented to the hospital with worsening shortness of breath and atypical infraclavicular chest pain. He had a clogged arteriovenous fistula, not allowing the patient to receive dialysis treatments (or as needed doses of diphenhydramine – which he received during dialysis treatments) for a few days prior to admission. Electrocardiogram (ECG) on admission was unremarkable for any acute abnormalities; of note, QTc was minimally prolonged (Fig. 1).

The initial diagnosis was fluid overload due to not receiving dialysis treatments over the previous few days but computerized tomography (CT) with intravenous contrast was performed because of subtherapeutic international normalized ratio. This revealed bilateral multifocal acute pulmonary emboli. He was placed on intravenous (IV) heparin drip for the treatment of pulmonary embolus and scheduled for emergent hemodialysis and ultimately had his arteriovenous fistula revised by vascular surgery. He was then transitioned to warfarin for his anticoagulation. During the course of his stay in the hospital, QT prolongation was intermittently noted on telemetry monitoring, temporally related to dialysis. Initially it was thought to be due to electrolyte fluxes during his hemodialysis, but ECG repeated up to 24 h later still showed persistent prolonged QTc. Later it became apparent that he was given PRN doses of diphenhydramine 50 mg on two consecutive days during dialysis which correlated with prolonged QT intervals of 586 ms and 512 ms on ECGs taken subsequently (Fig. 2). All liver function testing was unremarkable throughout the hospitalization. Magnesium was found to be elevated at 3.0 mg/dL on the first day of hemodialysis but no further levels were drawn. Calcium and phosphorous were normal throughout the hospital course. The serum potassium was normal during the hospital stay.

The half-life of diphenhydramine is 7–12 h; therefore, it is conceivable that it was still present in the system after 24 h. Repeat ECG that was taken after four half-lives of diphenhydramine subsequently showed resolving QT interval with only mild prolongation (Fig. 3).

Fortunately, the patient did not suffer from any arrhythmias which can be a drastic consequence of a prolonged QT interval. Another consideration is that the patient might have a forme fruste of a QT prolonging mutation, which might make him more susceptible to the QT prolonging effects of drugs. This patient denied genetic sequencing of the LQTS genes of the proband. Also, no family members had previously been diagnosed with LQTS.

Discussion

Diphenhydramine and the older antihistamines are known for their anticholinergic and sedative side effects. They also have been proposed to cause arrhythmias. Terfanidine, an antihistamine drug, was removed from the US market due to prolongation of the QT interval less than 20 years ago. At that time, it was a commonly used drug with over 100 million patients taking it. Most reports have focused on the QT interval prolongation, due to an acute overdose of diphenhydramine [3–7], rather than the more commonly used lower doses. Takahara et al. have also documented the occurrence of prolonged QT interval in halothane-anesthetized guinea pigs with the overdose of cloperastine which is an antitussive agent with a chemical structure similar to diphenhydramine [8]. In our case, the patient used only the common low-dose PRN diphenhydramine but interestingly enough, the abnormalities in the ECG correlated well with the time of taking the diphenhydramine, and subsequently subsided after the drug was avoided.

We speculate that our patient showed marked prolongation of QTc after taking these small doses of diphenhydramine due to the possibility of having a channelopathy causing QT prolongation. Although no family members had been previously diagnosed with LQTS, our patient may still carry a sporadic mutation or even have a familial form of LQTS which could, sometimes, have low penetrance in families.

All electrolytes were within normal limits despite being on hemodialysis and the patient's ECG changes were temporally related to the diphenhydramine ingestion.

Diphenhydramine inhibits the potassium channels which can cause QT interval prolongation and abnormal ventricular repolarization, and these changes may be more marked if the patient carries a mutant gene for LQTS. Most reported cases in the current literature document the association of diphenhydramine with QT prolongation at much larger doses, but our case is unique; in that these changes occurred with small and usually administered doses.

It would be prudent for clinicians to be aware of this rare yet potentially dangerous association of the commonly used over-the-counter antihistamine, diphenhydramine.

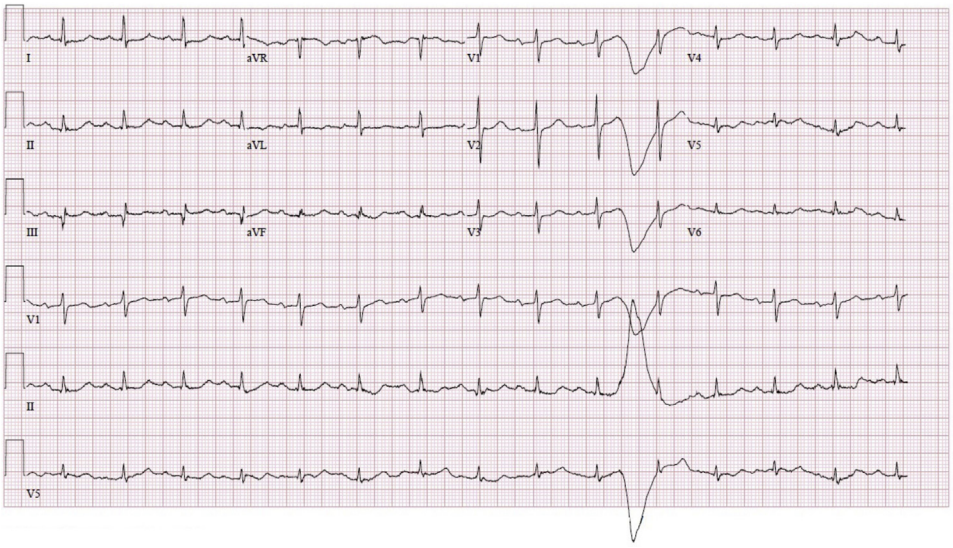

Fig. 1. Electrocardiogram on admission 11/27/2014 @ 10:58. No diphenhydramine given. QT 380 ms/QTc 460 ms (mildly prolonged).