Case of Polymorphic Ventricular Tachycardia in Diphenhydramine Poisoning

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PVT in Diphenhydramine Poisoning. This is the first reported case of torsades de pointes attributable to diphenhydramine, a drug with weak I_{Kr} effects. A 26-year-old, healthy man was admitted to intensive care after a diphenhydramine overdose. Results of physical examination, ECG, and electrolytes were normal at admission. Despite supportive care, he developed typical, sustained, torsades de pointes with a markedly prolonged QT interval requiring cardioversion. Drugs with weak I_{Kr}-blocking effects may cause lethal proarrhythmia in susceptible individuals when delivered in high concentrations. This case illustrates the variation in repolarization reserve that exists in a free-standing population. *(J Cardiovasc Electrophysiol, Vol. 15, pp. 591-593, May 2004)*

diphenhydramine, overdose, QT prolongation, I_{Kr} channel, torsades de pointes

Introduction

Poisoning and overdose with diphenhydramine is common. The 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System ascribes 67,053 overdoses to either H_1 or H_2-histamine receptor blockers.[1] Of these, diphenhydramine is the most common, with 28,263 incidences.[1] Even though the overall fatality rate with all antihistamine overdoses is only 0.07% (44 deaths in total), 59% (26 deaths) of these were due to diphenhydramine.[1]

Over the last decade, multiple case reports have described QTc prolongation and torsades de pointes ventricular tachycardia with the second-generation H_1 blockers astemizole and terfenadine, leading to their withdrawal from the market. Monomorphic ventricular tachycardia has been reported as an uncommon complication of diphenhydramine poisoning,[2] but there is no previous report of torsades de pointes with this agent. We report the first case of torsades de pointes directly attributable to diphenhydramine.

Case Report

A 26-year-old man presented to the emergency room 1 hour after ingesting 50 tablets of diphenhydramine hydrochloride in a suicide attempt. Each tablet contained 50 mg of the drug. He was awake and communicative at admission. He was known to be suffering from depression but had no history of cardiac disease. He was not taking any medication and denied abusing any other substance. Pulse was 68/min, blood pressure 136/70, temperature 98.8°F, and oxygen saturation was 100% on room air. Heart sounds were normal, lungs were clear, and there was no evidence of heart failure. Except for slight drowsiness, all other systems were normal. There was no family history of sudden cardiac death.

Serum potassium was 3.6 mEq/L and magnesium was 1.8 mmol/L. CBC, clotting studies, and comprehensive metabolic panel, including liver function tests, were normal. Blood gases on room air were pH 7.45, pCO_2 39.9, pO_2 123, and CO_2 28.8. A comprehensive drug screen of blood and urine did not reveal any other agents.

ECG obtained in the emergency room approximately 52 minutes after ingestion showed sinus rhythm with a PR interval of 220 ms. The QTc interval was 404 ms (QT 380 ms, corrected by Bazett's formula, Fig. 1). There was no intraventricular conduction disturbance. He was given activated charcoal orally and 20 mEq of potassium chloride intravenously, started on a normal saline drip, and admitted to the intensive care unit.

He initially maintained sinus rhythm and remained hemodynamically stable; however, 4.5 hours later, he suddenly had a generalized seizure. Approximately 15 seconds after the seizure began, he was noted to have a polymorphic ventricular tachycardia (Fig. 2). This was terminated by a single 200-J DC shock. Simultaneously, 50 mL of 7.5% sodium bicarbonate and 2 g of magnesium sulfate were administered intravenously. Blood pressure after cardioversion was stable and sinus rhythm was maintained. He was intubated and placed on mechanical ventilation because he became comatose and had aspirated during the seizure and cardiac arrest. An infusion containing 100 mL of 7.5% sodium bicarbonate in 5% dextrose was started and continued for the next 12 hours. Immediately after cardiac arrest, potassium was 3.2 mEq/L, magnesium 3.8 mmol/L, pH 7.16, bicarbonate 15 mEq/L, and calcium 9.0 mg/dL. The presence of extensive seizure artifact on ECG made it impossible to ascertain how the polymorphic ventricular tachycardia was initiated.

ECG after cardioversion showed a prolonged QTc interval that persisted over the next 2 days. An ECG obtained 13 hours after overdose showed sinus rhythm with a QTc interval of 500 ms and abnormal repolarization in the form of a TU wave (Fig. 3). He remained stable and was extubated the following day. Subsequently, he made an uneventful recovery with no recurrence of cardiac arrhythmia, and the QTc interval returned to 406 ms on day 3, approximately 61 hours after the overdose. An echocardiogram performed on day 5 was normal. He was discharged to an inpatient psychiatric unit.

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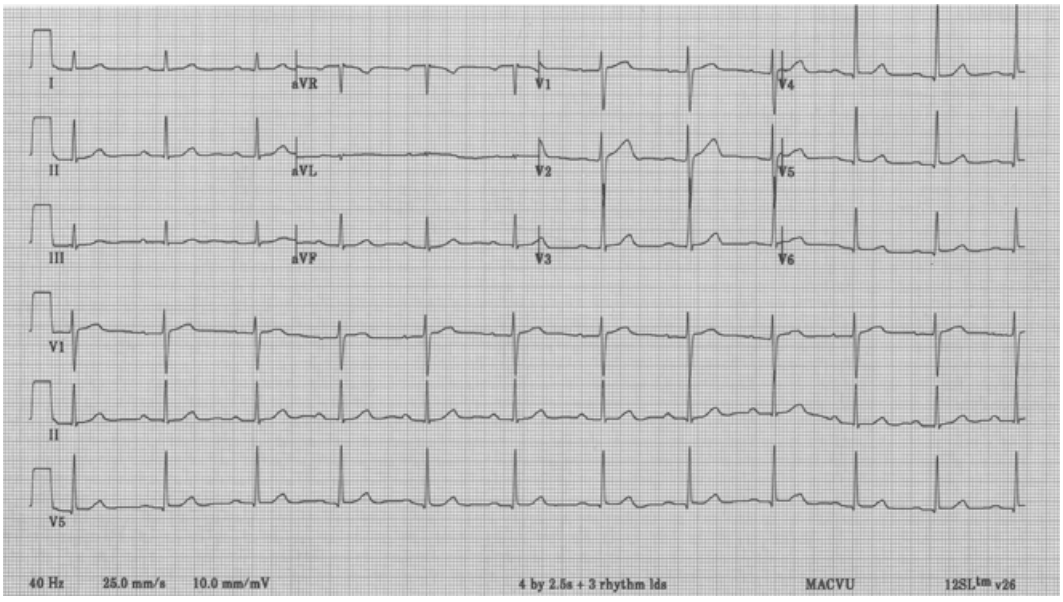

Figure 1. *ECG obtained 52 minutes after ingestion. Note normal QTc interval and T wave morphology.*

Discussion

Diphenhydramine belongs to the ethanolamine group of H_1 histamine receptor blockers. Symptoms of poisoning include somnolence, anticholinergic signs, cardiac arrhythmia, cardiogenic shock, seizures, coma, and death.[3]

ECG changes in diphenhydramine overdose have been studied in 126 consecutive, otherwise healthy subjects.[4] In this series, it produced sinus tachycardia (mean heart rate 103), QTc prolongation, and flattening of the T wave.[4] The mean QTc was 454 ± 43 ms. Half the patients had a QTc $>$ 450 msec, 25% $>$ 480 ms, and 11% $>$ 500 ms.[4]

In a study of 282 patients by Radovanovic et al.[3] and another study of 136 cases of diphenhydramine poisoning by Koppel et al.,[5] no cases of ventricular tachycardia occurred.

In 1955, Weidmann[6] observed that diphenhydramine interacts with cardiac sodium channels. It now is known that diphenhydramine blocks the fast inward sodium current during phase 0 of the action potential, increasing the threshold for excitability and slowing conduction.[7] At higher concentrations, potassium channels also are inhibited. Diphenhydramine has been shown to block the delayed rectifier potassium channel I_{Kr}.[8] Flattening of the T waves in diphenhydramine poisoning is similar to the T waves changes seen in patients with the hereditary long QT syndrome (LQT2), which is caused by the HERG mutation.[9] I_{Kr} blockers share the property of markedly prolonging the QT interval and producing torsades de pointes in a small percentage of patients.[10] We conducted an extensive review of the literature and found no case of polymorphic ventricular tachycardia caused by diphenhydramine.[3,5]

Diphenhydramine in overdose produces sinus tachycardia due to its anticholinergic effect, which makes it unique among potassium channel-blocking drugs. This may protect patients from torsades de pointes by multiple mechanisms. First, it reduces the likelihood of early afterdepolarizations and short-long-short sequences, which characteristically initiate

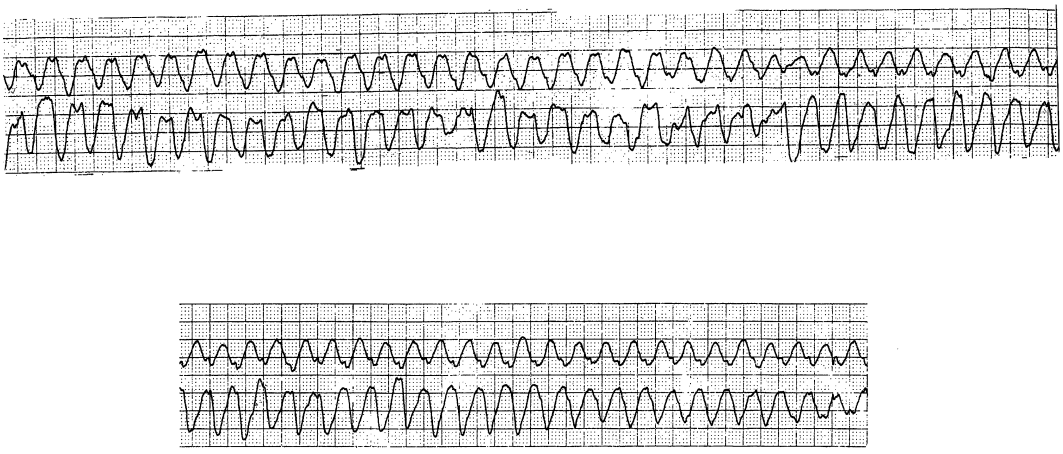

Figure 2. *Continuous ECG tracing recorded after termination of seizure.*

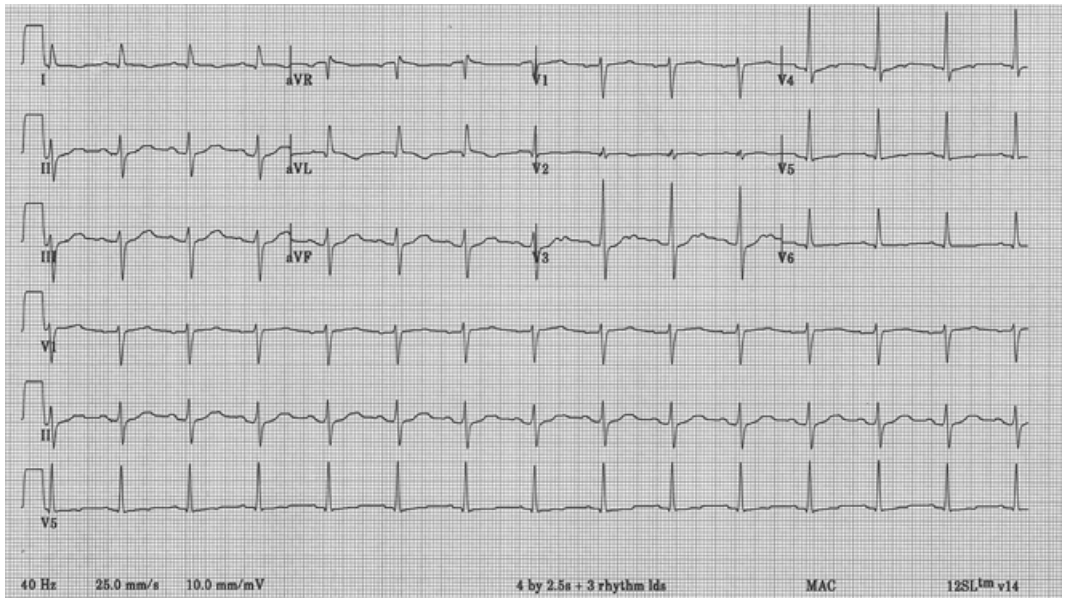

Figure 3. *ECG obtained 13 hours after ingestion. Note abnormal repolarization and prolongation of QTc interval.*

torsades de pointes.[11] Second, drug-induced blockade of the I_{Kr} channel has shown reverse-use dependence.[12,13]

Even with large doses of diphenhydramine, prolongation of the QT interval usually is modest. In the series by Zareba et al.,[4] only 11% of overdose patients had a QTc > 500 ms. This suggests that its I_{Kr} channel-blocking effect may be weak compared with other I_{Kr} blockers.

Our patient's potassium level at admission was low-normal (3.6 mEq/L) and dropped to 3.2 mEq/L when repeated after the seizure, despite being severely acidotic with a pH of 7.16 at that time. Hypokalemia probably played a role in precipitating torsades de pointes. Acidosis induced by the seizure may have potentiated sodium channel blockade caused by diphenhydramine and contributed to the development of torsades de pointes. Acidosis has been shown to decrease the slope of phase 0 of the action potential and worsen toxicity of sodium channel-blocking drugs.[14] In addition, our patient did not have the sinus tachycardia seen in most cases of diphenhydramine overdose, making him more susceptible to torsades de pointes.

There is considerable individual variation in susceptibility to I_{Kr} channel blockers. It raises the possibility that this patient may be a carrier of an allelic variant of a gene encoding one of the congenital long QT syndromes.[15]

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