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Case Report

Long QT syndrome due to Doxylamine overdose

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Abstract:

The list of medications known to induce QT prolongation is long. We report here a case of long QT syndrome (LQTS) caused by use of Doxylamine, which has previously only been reported once. The patient arrived to the emergency department after having ingested two bottles of Doxylamine (roughly 96 tablets) in a suicidal attempt and was noted to have seizure-like activity prior to arrival. Upon admission she was found to have severe rhabdomyolysis and significant QTc prolongation (>650 ms). Her clinical status improved over the course of hospitalization with supportive treatment that included intravenous fluids as well as electrolyte monitoring and replacement. Given the relative ubiquity of Doxylamine, the purpose of this article is to raise awareness of a unique adverse effect of a widely available medication.

Key words: doxylamine; long QT syndrome; arrhythmia; antihistamine; anticholinergic

Introduction

Doxylamine is an antihistamine used to treat allergic symptoms and is often used as a short-term treatment of insomnia. It is also used in combination with pyridoxine (vitamin B_6) to treat morning sickness in pregnant women [1]. Doxylamine is available over-the-counter and is used in nighttime cold medications such as Nyquil, as well as in analgesics containing acetaminophen or codeine. Along with its antagonist effects of the H_1 receptor, Doxylamine also exerts anticholinergic properties and serves as a rather potent antagonist of the muscarinic acetylcholine (M_1-M_5) receptors [2]. In large amounts, Doxylamine can induce hallucinations, seizures, rhabdomyolysis, and death.

LQTS is a condition affecting repolarization of the heart. Many drugs have been implicated in LQTS, including first- and second-generation antihistamines, but the incidence of Doxylamine-induced LQTS has previously only been reported once [3]. The mechanistic basis of acquired LQTS is thought to be due to blockade of the potassium channels, for which many pharmacologic agents have an affinity [4].

Case Presentation

The patient is a 22-year-old female with a medical history of depression and anxiety, with multiple past suicidal attempts by drug overdose, who was brought in by her roommate for a suspected drug overdose. She was unable to provide any history upon arrival in the emergency department due to altered mental status. Her roommate further endorsed that the patient may have had seizure-like activity that lasted for about one minute. Upon further questioning, it was found that the patient had ingested two bottles (approximately 96 tablets) of Doxylamine succinate. In the ED, the patient was hemodynamically stable, but confused, restless, disoriented, and actively hallucinating.

Initial labs revealed significantly elevated CPK levels of 16,775 U/L and a WBC count of 15,000. Her urine toxicology was positive for benzodiazepines. The AST was mildly elevated at 76 U/L. The rest of her labs, including all electrolytes, were within normal limits. She was immediately started on Lactated Ringer's at a rate of 250 cc/hr and a 150 mEq sodium bicarbonate infusion at a rate of 150 cc/hr. Her initial ECG at the time of admission demonstrated normal sinus rhythm and a QTc of 440 ms (Figure 1).

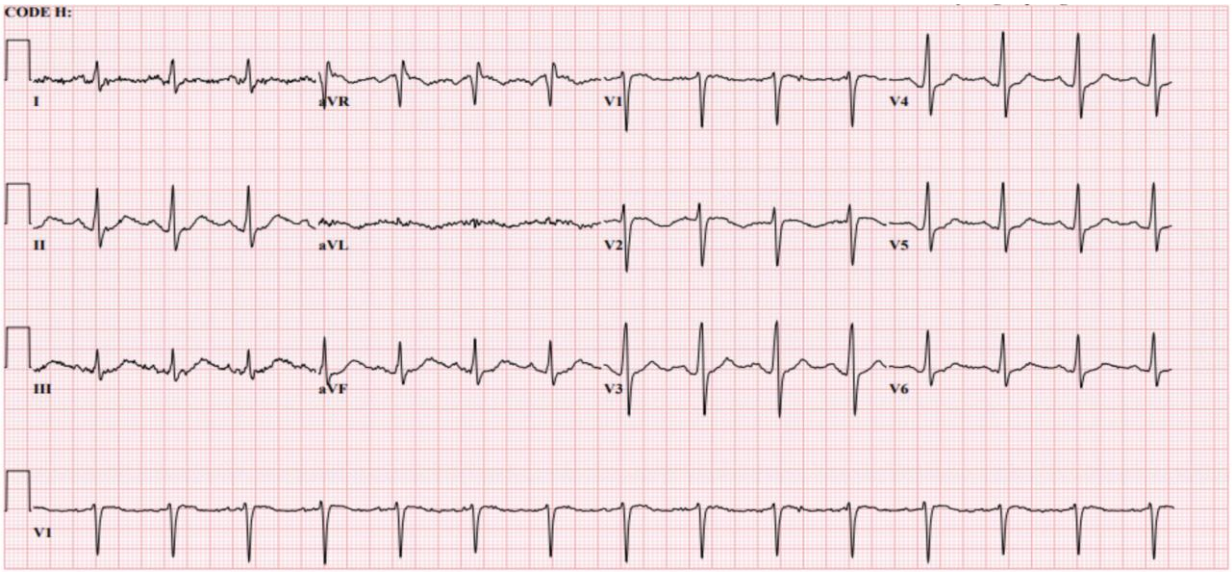

Figure 1: Initial ECG demonstrated normal sinus rhythm and a QTc of 440 ms.

Over the course of the first day, serial BMPs were obtained that showed persistently rising CPK values, which peaked at 54,395 U/L. After treatment with fluids, the CPK gradually downtrended throughout the night. A repeat ECG (Fig 2) was obtained in the morning which showed marked prolongation of the QTc at 661 ms, yet she remained hemodynamically stable. Following the change in ECG, 3g of IV magnesium sulfate as well as 2g of IV calcium gluconate and 1g of IV calcium chloride were administered. A repeat ECG two hours later demonstrated that the QTc had decreased to 507 ms. Upon discussion with the electrophysiologist, it was deemed that there was no acute need for isoproterenol. The etiology of the QTc prolongation was suspected to be due to pronounced H1 antagonism in the context of an anticholinergic toxidrome. Due to concerns for an inherited channelopathy, genetic testing was also performed.

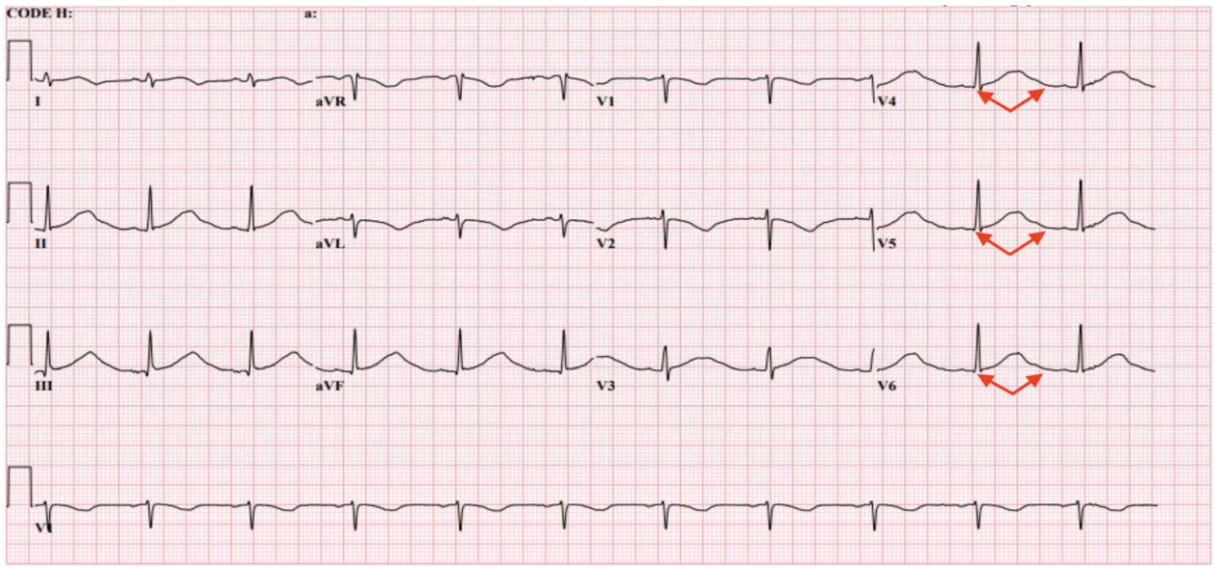

Figure 2: ECG on the second day showed a markedly prolonged QTc of 661ms (arrows).

On the third day, her CPK continued to decrease. The patient however developed significant metabolic alkalosis from the sodium bicarbonate infusion, which was promptly discontinued. Her electrolytes were closely monitored and repleted as necessary. A single dose of IV Acetazolamide 500 mg was administered to correct her metabolic alkalosis. Subsequent ECGs thereafter continued to show improvement in the QTc, until it eventually normalized during the fourth day of hospitalization (Fig 3). After she was medically stable, she was transferred to the inpatient psychiatric unit of the hospital.

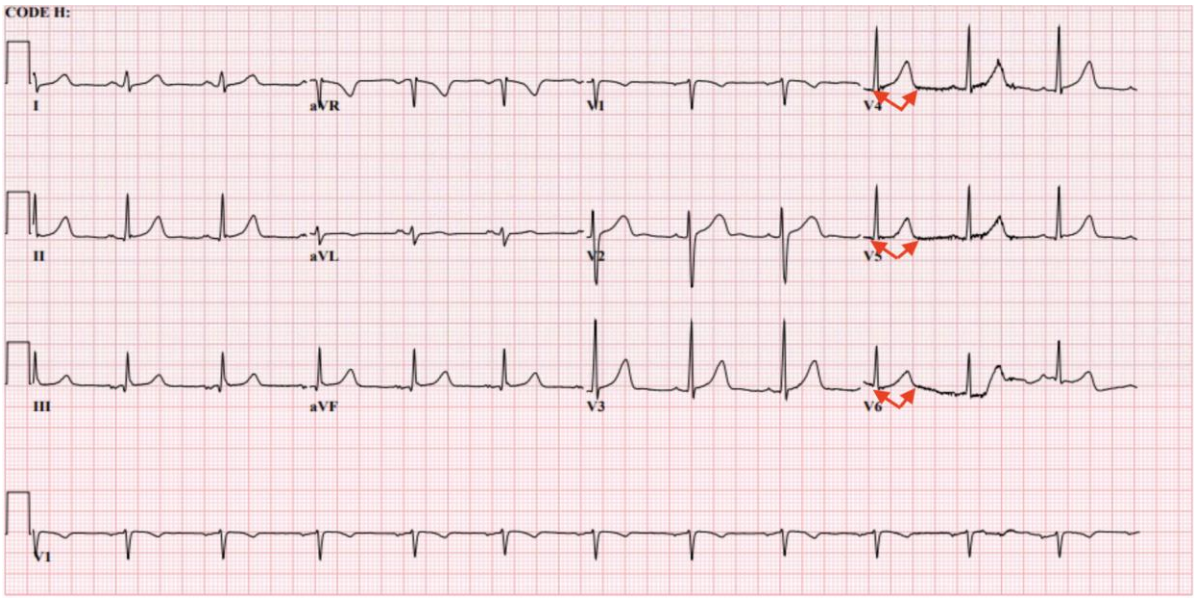

Figure 3: ECG shows resolution of the prolonged QTc (440 ms, arrows).

Discussion

LQTS is a condition affecting repolarization of the heart that leads to an abnormally lengthened QT interval. It results from an increase in inward current (through sodium or calcium channels) or a decrease in outward current through the potassium channels [5]. While there are two mechanisms that can lead to LQTS, myocardial repolarization is chiefly mediated by the efflux of potassium ions. There exist two subtypes of the delayed rectifier potassium current, IKr (rapid) and IKs (slow), that are mainly implicated in repolarization of myocytes [6]. These two currents have different activation and inactivation characteristics and hence different sensitivities to pharmacologic agents, and furthermore are the products of different genes. The typical mechanism of acquired LQTS is through blockade of the IKr by certain drugs, and is the likely biochemical interaction by which our patient's LQTS manifested.

There are also genetic variants of the syndrome, the Romano-Ward syndrome and the Jervell and Lange-Nielsen syndrome, which is the more severe variant and also associated with congenital deafness [7]. Furthermore, there are more than 530 disease-causing mutations associated with the IKs complex, with most being missense mutations. The vast majority occur in the gene KCNQ1, which leads to LQT1 [8]. KCN encodes the α-subunit of the potassium channel, yielding IKs, which is crucial for modulation of the QT interval when there is an increase in heart rate. A defective IKs results in the QT interval not shortening appropriately in tachycardic conditions and thus leads to a highly arrhythmogenic state [9]. Heterozygous KCNQ1 mutations cause the dominant RW LQT1 syndrome and account for the majority of disease-causing variants, whereas homozygous mutations in KCNQ1, cause the recessive JLN variant, characterized by deafness because of the reduced IKs in the inner ear [10].

While inherited LQTS may result from mutations that disrupt any number of ion currents, including (IKs, IKr, and INa) the mechanism by which drugs cause acquired LQTS is almost exclusively due to block of IKr [11]. This KCNH2 channel is blocked by drugs with diverse structures encompassing many different drug classes, including antiarrhythmics, antipsychotics, antibiotics, and antihistamines [12]. Despite the important roles of other potassium (and sodium) channels in the cLQTS, these channels are far less susceptible to block by drugs [13]. This may be due to the structural features of the channel, including the presence of two polar amino acids (Thr623 and Ser624) in the pore region and two aromatic amino acids (Tyr652 and Phe656) with side chains oriented toward the large central cavity of the pore region that provide high-affinity binding sites for a wide range of compounds [14]. It is certainly interesting why some antihistamines, most particularly Diphenhydramine, have been far more commonly implicated in cases of drug induced LQTS than others in the same class. While there may be a molecular basis to this, it is also plausible that it is because Diphenhydramine is much more commonly used.

Conclusion

Many first- and second-generation antihistamines have been implicated in LQTS, the most commonly reported one perhaps being Diphenhydramine. Whether this is due to other antihistamines being more commonly used, or because Doxylamine has a lesser degree of binding affinity to the implicated potassium channels, is difficult to determine. Our case sheds light on a potentially fatal cardiac manifestation of a commonly available drug that clinicians ought to be aware of.

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