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Letter to the Editor

# QTc prolongation due to dextromethorphan

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Dextromethorphan, d-3-methoxy-N-methylmorphine, (DXM) is an antitussive drug. It was approved by the Food and Drug Administration for over-the-counter sale in 1958. DXM, is an active ingredient found in many over the counter cough and cold medications. There are over 140 products which contain DXM along with other agents including: acetaminophen, antihistamines, decongestants, topical anesthetics, guaifenesin, promethazine and ethanol [1]. It is often abused recreationally, especially by teens [2]. When taken in excess it acts as a dissociative hallucinogen. Patients also may present with nausea, vomiting, dizziness, diaphoresis, clumsiness, ataxia, nystagmus, mydriasis, auditory and visual hallucinations, tachycardia, hypertension, seizure, stupor and coma [1]. Withdrawal can also occur from DXM, manifesting as nausea, vomiting, diaphoresis, myalgias, diarrhea, and restlessness beginning approximately 3 days after discontinuation of DXM [3]. DXM is the dextrorotary enantiomer of the methyl ether of levorphanol (a synthetic opioid analgesic). Its pharmocodynamics include: uncompetitive NMDA receptor antagonism, nicotinic and acetylcholine receptor antagonism, serotonin transporter blocker, and NAPDH oxidase inhibition [1]. Time to achieve peak serum concentrations vary from 2 to 3 h and serum elimination half-lives are approximately 3 h in liquid, tablet, or extended-release formulations [1]. Various side effects have been noted in overdose for DXM; however, prolonged QT interval is not one of them.

A 27 year-old Caucasian male with no significant past medical history was brought in by ambulance after he was found altered in a bathroom. He admitted to ingesting four (8 oz) bottles of Robitussin®, 1920 mg of DXM (27 mg/kg) and ethanol. In the emergency department, the patient was alert and oriented. His only abnormal vital sign was his heart rate of 101 beats-per-minute. His physical exam was unremarkable. The patient's initial labs were significant only for potassium of 3.3 mmol/L and a negative acetaminophen level. The patient's initial electrocardiogram revealed a QTc of 506 ms (Fig. 1). After potassium repletion, his QTc was 514 ms. The patient had multiple prior emergency department visits for ethanol and DXM use. His QTcs on prior visits were 468 and 480 ms after DXM; however, after an ethanol binge, his QTc was 432 ms.

This case demonstrates a potential correlation between DXM ingestion in large quantities and prolonged QTc interval. QTc interval prolongation has never been associated with DXM ingestion, although, tachycardia and nonspecific electrocardiographic findings have been associated with ingestions [4]. In a 23-year-old male who ingested 2160 mg DXM (36 ounces of cough syrup) and ethanol an electrocardiogram revealed notched T waves and prominent U waves in leads I, II, and V2 through V6 [4]. However, this case is the first to show DXM's potential effect on QTc interval prolongation.

There are many medications, drugs and electrolye imbalances that can prolong the QTc interval; however, DXM is not a known cause. Alcohol, hypokalemia and other medications in Robitussin® were also present in this case and are possible confounding variables. However, despite the fact that ethanol may directly prolong the QTc-interval independent of electrolyte status, it is noteworthy that in the absence of DXM the patient's QTc interval was normal. In addition, although the patient was relatively hypokalemic his QTc interval did not change upon repletion, suggesting that hypokalemia alone is unlikely to be the cause of delayed repolarization. Moreover, the broad based T-wave morphology has an appearance less consistent with hypokalemia, which more often manifests with concurrent ST-T wave flattening (Fig. 1). Finally, the patient did not exhibit any signs of toxicity from the other ingredients of Robitussin, such as anticholinergic symptoms.

There are other possible limitations to DXM causing prolonged QTc interval. One was the absence of comprehensive urine toxicology screening, though the patient only noted additional alcohol consumption. In addition, DXM levels were not measured.

In conclusion, in spite of the limitations to this case, DXM ranks as a possible adverse event on the Naranjo causality scale [5]. A probable

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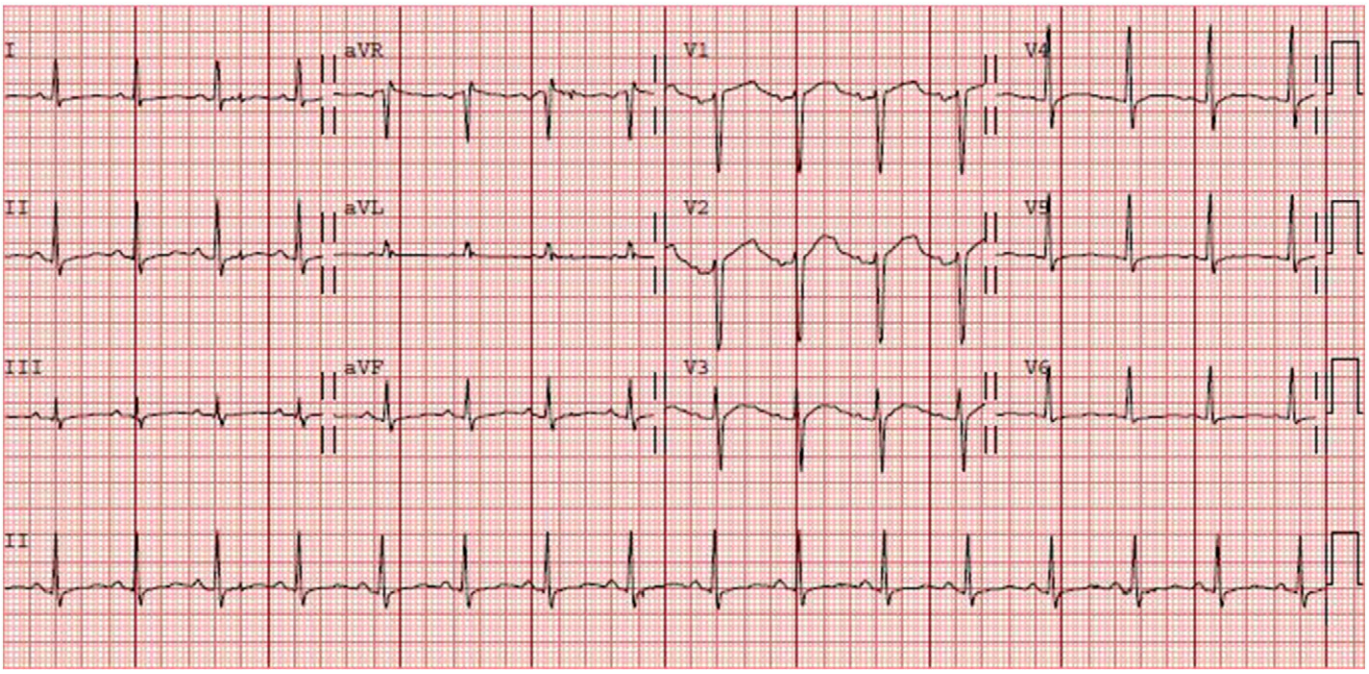


**Fig. 1.** The patient's initial electrocardiogram revealed a QTc of 506 ms. This broad based T-wave morphology has an appearance less consistent with hypokalemia, which more often manifests with concurrent ST-T wave flattening.

mechanism for DXM effecting QTc is that it is a synthetic opioid and known to inhibit the delayed rectifier potassium ion channel which is coded by the human ether-a-go-go gene (hERG) [6]. This property could be associated with HERG blockade, the putative mechanism of QTc prolongation. Therefore, this case demonstrates a potential correlation between DXM ingestion and prolongation of the QTc interval. Given the established QTc-prolonging properties of other synthetic opioids such as methadone , further research is warranted to investigate this association [7].

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [8].

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