Sudden Cardiac Arrest in a Patient on Chronic Methadone After the Addition of Azithromycin

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Abstract: Corrected QT-interval (QTc) prolongation with increased risk of fatal arrhythmia is a well-established toxicity of methadone. In this study, a case of sudden cardiac arrest in a patient on chronic methadone therapy is presented. A 47-year-old man presented unresponsive to the emergency department after pulseless arrest at his home. The patient's wife revealed he was taking methadone as part of an ongoing opioid dependency treatment and that he was prescribed azithromycin for an upper respiratory tract infection 3 days before his presentation. A 12-lead electrocardiogram at the time of presentation showed sinus tachycardia and a QTc of 490 milliseconds. It was concluded that the patient experienced a fatal arrhythmia because of QTc prolongation, precipitated by azithromycin in the setting of ongoing methadone use.

Key Indexing Terms: Arrhythmia; Methadone; Azithromycin. **[Am J Med Sci 2013;345(2):160–162.]**

Methadone is a long-acting opioid used primarily for the treatment of opioid dependence and, for this indication, is dispensed by Food and Drug Administration-approved facilities only. It can also be prescribed by independent practitioners for patients with chronic pain. Methadone carries a "black box" warning of corrected QT-interval (QTc) prolongation with potential for fatal arrhythmia including torsades de pointes. It is the only opioid that carries such a warning. The risk of fatal arrhythmia is significant enough that specific guidelines have been proposed regarding electrocardiogram (ECG) monitoring and careful attention to drug interactions.[1] Our review explores one particular case of methadone-induced arrest, the mechanism of QTc prolongation with regard to methadone and other factors potentiating fatal arrhythmia.

CASE REPORT

A 47-year-old man was brought to our emergency department from an outlying hospital for unresponsiveness. Family was *en route* at the time of presentation to our hospital, so initial history was limited to third-hand information obtained from the transfer report. According to the report, the patient was found cyanotic and obtunded by his wife. Emergency medical services quickly arrived and transported the patient to the outlying facility, whereupon he was transferred to our hospital for higher level of care. Medical history was significant for hypertension and prescription opioid addiction, for which he was enrolled in an accredited treatment program. Home medications were initially reported as methadone 10 mg 3 times daily, lisinopril/hydrochlorothiazide 20/12.5 mg once daily, benzonatate 100 mg every 8 hours as needed, and an over-the-counter cold medicine consisting of acetaminophen, dextromethorphan and doxylamine. The patient had no known allergies. Social history was reportedly negative for tobacco or alcohol use. Review of systems was otherwise unobtainable, and the rest of the known history was unremarkable.

Initial examination revealed a moderately obese man, obtunded with irregular respirations. He had no discernible response to voice or tactile stimulation, and he was aphasic except for sporadic moaning. His body temperature was 36.8°C, heart rate around 130 beats per minute and the rhythm regular. The respiratory rate was 25 breaths per minute and blood pressure 120/80 mm Hg by manual cuff measurement. Oxygen saturation was 100% via non-rebreather mask. His pupils reacted normally to light and his extraocular movements appeared intact. Oral mucosa was moist. Heartbeat was tachycardic but regular; a soft systolic murmur was detected at the left sternal border. He had no jugular venous distention, normal peripheral pulses and no lower extremity edema. His lungs were clear bilaterally. He was mildly tachypneic without retractions. Abdomen was protuberant because of central obesity but otherwise benign. Musculoskeletal examination revealed mildly increased tone throughout with full range of passive motion and no deformities. Neurological examination was limited but revealed no focal deficits other than the aforementioned increased tone; deep tendon reflexes were normal, Babinski reflexes were downgoing and gag was intact. The Glasgow coma scale score was 10. Laboratory evaluation revealed lactic acidosis (lactate 15 ng/dL, pH 7.11) and hyperammonemia (74 mg/dL). Other than a low serum bicarbonate level, electrolytes and renal function were normal. Liver function tests were normal as well, as were cardiac isoenzymes. ECG revealed sinus tachycardia and a QTc of 490 milliseconds. No previous ECGs were available. Chest radiography was normal.

Because of the lack of an immediately discernible cause for his symptoms, and because of his history of drug abuse, the patient's initial diagnosis was presumed to be toxic metabolic encephalopathy. Extended toxicology screening, however, was negative for all substances other than opiates, and his presenting symptoms were not consistent with opiate overdose. Magnetic resonance imaging of his brain was normal, and all cultures (blood, urine and cerebrospinal fluid) were negative. Echocardiogram revealed normal ventricular function and no structural abnormalities. His mental status gradually improved without any therapy other than a few days of empiric antibiotics and supportive care. He had no significant arrhythmias during the rest of his hospitalization.

Details surrounding his precipitating event were elucidated on hospital day 12, after the patient had improved enough to leave the intensive care unit and his wife was re-interviewed. She was present at the time of his arrest. Just before bedtime the night of his arrest, the patient became acutely nauseated and complained of palpitations. His wife checked his pulse and described it as "racing." After a few seconds, he lost

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consciousness and became cyanotic and pulseless, at which point his wife, a trained police officer, called the emergency services and initiated cardiopulmonary resuscitation. He had regained a pulse by the time the emergency services arrived. She added that he was prescribed azithromycin by his primary care provider 3 days before the event, for an upper respiratory tract infection (URI).

The additional information provided by his wife led to our diagnosis of sudden cardiac arrest because of prolonged QT. A few days later, the patient's mental status had improved enough to answer questions reliably. He confirmed that he had been taking both azithromycin and methadone in the days leading up to his arrest. He denied previous diagnosis of arrhythmia including prolonged QT syndrome, and he denied family history of arrhythmia or unexplained sudden cardiac death.

DISCUSSION

More than 200,000 patients are currently enrolled in a methadone treatment program in the United States, making it the most frequently used narcotic for opioid maintenance.[2] Methadone has become a medication of interest because of widespread use of this agent for opioid addiction and management of chronic pain, but more recently, detrimental side effects associated with methadone have been highlighted. Despite the availability of methadone for over 60 years, only in the past 10 years has this medication received attention for its potential to cause QTc prolongation leading to torsades de pointes. One report in 1973 revealed that methadone may affect cardiac function[3] but it would take 30 years for this topic to resurface in the literature. In 2003, Krantz et al[4] were the first to uncover the association of methadone use and QTc prolongation in a retrospective case series of 17 patients. Not only did they identify this association but also risk factors for the development of QTc prolongation were elucidated. Consequently, more studies have emerged in the recent years confirming the link between methadone and QTc prolongation.

Major risk factors predisposing a patient to QTc prolongation include older age, female sex, underlying structural heart disease, electrolyte abnormalities (hypokalemia, hypomagnesemia) and unrecognized long QT syndrome.[5,6] More specifically, patients receiving high doses of methadone (>100 mg/d) or those taking methadone with cytochrome P450 inhibitors or with other medications known to cause QTc prolongation are at a higher risk.[1,4,7] Interestingly, doses of methadone as low as 29 mg/d have been implicated in causing sudden cardiac death.[8] It has been postulated that causes for QTc prolongation are cumulative with regard to the risk of fatal arrhythmia (ie, the more risk factors, the more likely the arrhythmia). However, to our knowledge, there are no published reports that have confirmed this theory. Girolamo[9] alludes to this idea of additive effects in his editorial, stating that the presence of risk factors may have cumulative effects in QTc prolongation leading to torsades.

Our patient was receiving a normal dose of methadone and had no other risk factors predisposing him to QTc prolongation. The addition of azithromycin to this stable patient seemed to be the nidus for the development of sudden cardiac arrest. Of the macrolides, erythromycin and clarithromycin are thought to cause the most significant drug interactions with methadone as a result of inhibition of methadone metabolism via the cytochrome P450 system. In contrast, azithromycin has no effect on methadone metabolism, which decreases the risk of methadone accumulation and subsequent toxicity along with QTc prolongation. Azithromycin, as monotherapy, has been associated with QTc prolongation leading to torsades and, more recently, increased risk of sudden cardiac death.[10–13] Whereas all macrolides have the propensity to induce QTc prolongation, azithromycin has the least incidence because of a rectangular pattern of the monophasic action potential configuration.[11,14] However, azithromycin has become the primary macrolide used because of better tolerability and a decreased side effect profile.

Azithromycin was prescribed to our patient for an uncomplicated URI, which is quite common in clinical practice with up to 50% of all antibiotic prescriptions in the United States being given for URIs.[15] Therefore, we feel a secondary topic of antibiotic prescribing practices merits discussion with regard to this case. Antibiotic overuse is a frequently discussed topic but remains a problem in the primary care setting.[16] Patient satisfaction, avoidance of litigation (in the event of missed bacterial infection) and insufficient time for patient education on antibiotic ineffectiveness are just a few of the reasons physicians cite to justify antibiotic overuse.[15] In the case of our patient, azithromycin was prescribed for a URI in conjunction with chronic methadone, which almost led to the patient's demise. This case reminds us that antibiotic overuse contributes not only to increasing antimicrobial resistance but also to morbidity.

CONCLUSIONS

Methadone's risk of fatal arrhythmia may be underappreciated by the medical community at large because it is not prescribed by most practitioners. Given the frequent use of antibiotics in the outpatient setting, additive adverse effects such as the one described in our patient occur too frequently. Physicians must remain vigilant in recognizing drug interactions or additive adverse effects that may lead to patient harm. Our goal in sharing this case is to advance general awareness of the potentially fatal cardiovascular additive effects between methadone and azithromycin.

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