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J. A. Decerf
B. Gressens
C. Brohet
A. Liolios
P. Hantson

Can methadone prolong the QT interval?

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Sir: The cardiac safety of high doses of methadone has been questioned in recent publications describing the impact of methadone on cardiac conduction [1, 2, 3, 4]. We present a case of prolonged QTc interval in a patient treated with methadone for several years.

A 37-year-old man was found in cardiac arrest (asystole) and was successfully resuscitated. He had been receiving methadone maintenance treatment for more than 8 years at a daily oral dose of 130 mg; it is not known how compliant the patient was during these years. Electrocardiography (ECG) performed in 2000 while the patient was on methadone revealed sinus bradycardia (49/min) with a normal QRS interval and a normal QTc interval of 404 ms. The patient was also taking fluoxetine (20 mg/day), trazodone (10 mg/day), and olanzapine (5 mg/day). According to his wife, he had used cocaine ("sniffing") a few hours before the cardiac arrest, but he was not seen taking an excessive dose of methadone. Toxicological screening showed therapeutic serum levels of fluoxetine, trazodone, and olanzapine, and the presence in the patient's serum of two cocaine metabolites [benzoylecgonine (0.263 µg/ml), methylecgonine (0.012 µg/ml)] and methadone (0.229 µg/ml). Postresuscitation ECG showed sinus rhythm (90/min) with a QRS complex less than 100 ms and a QTc interval of 576 ms; there were no findings consistent with ischemia. No electrolyte abnormalities were noted. The patient developed anoxic encephalopathy with a poor prognosis for neurological recovery. The only medication the patient was receiving was low doses of propofol for fighting the ventilator. ECG changes were monitored daily. Methadone and its metabolites were still detected in the blood until day 7 and in the urine until day 11. Cocaine metabolites were detected in the serum until day 4. The QTc interval gradually decreased from 600 ms (heart rate, HR, 72/min, day 2) to 485 ms (HR 90/min, day 12) while the QRS complex always remained less than 12 ms. The patient was becoming progressively more agitated and as this was interpreted as probable methadone withdrawal, methadone was reintroduced on day 12 at a dose of 130 mg per day. On the next day the QTc interval started gradually increasing. It rose to 552 ms (HR 83/min) on the next day (day 13) and reached 581 ms (HR 91/min) on day 19. Given the poor prognosis, further resuscitation efforts were deemed futile, and the patient died 2 days later from ventilator associated pneumonia.

Methadone is a synthetic opioid widely used for the treatment of narcotic addiction. Tolerance may develop, and the daily maintenance dose must be increased in patients treated by oral methadone for several years. Until recently there was little evidence of the effect of methadone on the human heart. Kornick et al. [5] found in patients treated by intravenous methadone for cancer pain that there is an approximately linear relationship between QTc interval prolongation and the log-dose of methadone. In these patients the presence of chlorbutanol in the commercial solution was considered a possible contributing factor. However, the authors were demonstrated that methadone alone blocked cardiac human *ether a-go-go* related gene (*HERG*) K^+ channels in vitro in comparable concentrations to those observed in the patients receiving intravenous methadone for chronic pain management. A prospective study conducted in 132 drug-addicted patients beginning oral methadone maintenance treatment observed a significant increase in the QTc interval between baseline and follow-up [4]. Men and patients receiving higher methadone doses (110–150 mg) had the greatest prolongation. Gil et al. [1] recently found that four patients infected with the human immunodeficiency virus developed syncope and prolongation of the QT interval while receiving high doses of methadone (>200 mg/day); shortening of the QT interval occurred when methadone doses were reduced.

Among the other drugs or substances taken by our patient, fluoxetine, olanzapine, and cocaine can also cause QT interval prolongation and may be associated with torsades de pointes. The hallmark of cocaine intoxication is wide complex arrhythmia which was absent in our patient [6]. Fluoxetine can cause QTc prolongation in toxic doses. Three clinical studies involving 350 patients treated with fluoxetine showed no significant changes in the QTc interval. There is a single case report of QTc prolongation in a patient taking 40 mg fluoxetine daily which resolved after fluoxetine was stopped. Our patient was taking half of that dose and had therapeutic fluoxetine levels on admission. Additionally the QTc prolongation reappeared despite the discontinuation of fluoxetine [7, 8]. Therapeutic olanzapine and trazodone have mild and clinically nonsignificant effects on QTc prolongation [9, 10].

The QTc interval showed a dose-response relationship consistent with the administration of methadone; it gradually decreased when methadone was stopped and became immediately prolonged after methadone was reinstituted. Our patient had a normal QTc interval 4 years prior to the event while he was taking the same amount of methadone (404 ms vs. 576 ms postresuscitation). The delayed effect of methadone on the QTc interval and questionable compliance of the patient can probably explain this difference. Although cocaine may have contributed to our patient's cardiac arrest, we believe that this effect took place on an already compromised heart secondary to the documented QTc prolongation induced by methadone. This effect was reported to the local drug safety center.

In conclusion, in addition to the experimental evidence supporting the concept that methadone prolongs the QTc interval through a dose-dependent mechanism, there is an increasing number of reports suggesting that this effect can also occur in humans. Consequently the QT interval should be carefully monitored especially when the dose of methadone is increased or when the patient is given other medications which could also affect the QT interval [11].

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J. A. Decerf · B. Gressens · A. Liolios
P. Hantson (✉)
Department of Intensive Care,
Cliniques universitaires St-Luc,
Avenue Hippocrate 10, 1200 Brussels,
Belgium
e-mail: hantson@rean.ucl.ac.be
Tel.: +32-2-7642743
Fax: +32-2-7648928

C. Brohet
Department of Cardiology,
Cliniques universitaires St-Luc,
Avenue Hippocrate 10, 1200 Brussels,
Belgium