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CASE REPORT

False sense of safety by daily QTc interval monitoring during methadone IVPCA titration in a patient with chronic pain

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Abstract: It has been proposed that some deaths attributed to methadone are related to prolongation of the QTc interval; however, there are no clear recommendations on electrocardiogram (ECG) monitoring in patients undergoing intravenous methadone infusion. This is a report on a patient receiving methadone intravenous patient-controlled analgesia titration for the treatment of chronic pain. Initially, her daily ECGs showed QTc intervals within normal limits; however, she experienced a rapid increase in QTc interval from 317 ms to 784 ms within a 24-hour period after methadone had been discontinued for excessive sedation. QTc interval greater than 500 ms is considered to be high risk for the fatal arrhythmia Torsades de Pointes. Daily ECGs did not detect a gradual increase in the QTc interval that would have alerted the medical staff of the need to decrease or stop the methadone before reaching a prolonged QTc interval associated with cardiotoxicity. In selected cases where aggressive methadone titration is required, more intensive monitoring, such as telemetry or ECG determinations every 12 hours, might help detect changes in QTc interval duration that might otherwise be missed by daily ECG determinations.

Keywords: methadone, QTc prolongation, opioids, opioid side effects, IVPCA methadone

Background

The use of methadone for the management of chronic pain has increased in the last decade, as has the number of the deaths attributed to its use.[1] Methadone is a chiral mixture with a variable metabolization rate[2] that contributes to its unpredictable half-life (ranging between 15 and 150 hours), which can lead to drug accumulation and potential cardiac toxicity.[1] Methadone and other opioids, including oxycodone,[3] can block delayed potassium rectifying currents (I_{Kr}), thus interfering with the repolarization of the conductive tissue of the heart[4] and predisposing to Torsade de Pointes (TdP), a fatal ventricular arrhythmia. On electrocardiogram (ECG), prolonged depolarization manifests as QTc interval prolongation.[5] An acceptable QTc interval upper limit has been proposed to be 430 and 450 ms for males and females,[6] respectively, while values beyond 500 ms are considered to be high risk for TdP irrespective of sex.[6]

Although the use of intravenous (IV) methadone in the terminally ill population is considered to be safe,[7] and the QTc prolongation reported by Kornick et al was attributed to the preservative chlorobutanol,[8] many reports suggest that methadone itself may prolong the QTc interval in a dose-dependent manner.[4] Furthermore, coadministration of certain medications may increase the risk of cardiotoxicity, for example, drugs that have the potential to prolong the QTc interval,[9] such as certain antibiotics or antiarrhythmic agents, or drugs that may compete with methadone as substrates for the cytochrome P450 isoenzymes 3A4, 2D6, and 2B6,[10] such as certain antidepressants, resulting in

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elevated methadone plasma levels. To address the risk of cardiotoxicity, some authors have advocated serial ECGs to monitor the QTc interval duration,[11] but the recommendations on frequency of monitoring and medication dose at which the ECG should be done are controversial[12] and range from "ECG is never necessary" to perform ECG "in every patient."[13]

Objective

To promote awareness that daily ECG monitoring during IV patient-controlled analgesia (PCA) with methadone may not be sufficient to anticipate a rapid prolongation of the QTc interval.

Methods and findings

The patient was a 50-year-old woman with chronic abdominal pain for over 10 years due to lupus vasculitis who during hospitalization for opioid rotation, experienced QTc prolongation beyond 500 ms during rapid IV methadone titration in less than 24 hours. The patient's pain had not been managed to satisfaction as an outpatient, and admission for IV opioid titration was recommended. At the time of admission to the Pain Service Inpatient Unit, Beth Israel Medical Center, New York, NY, USA, the patient's medications included morphine sulfate 150 mg intramuscular (IM) every 4 hours and meperidine 75 mg IM every 8 hours, and her pain score was 10/10. During hospitalization, the patient underwent trials with intravenous patient controlled analgesia (IVPCA) hydromorphone, morphine, and fentanyl, which did not alleviate the pain or cause significant side effects and had to be discontinued. Afterwards, the patient received IV methydlprednisolone and ketamine infusion, and both were ineffective. After a baseline ECG that showed a QTc interval of 449 ms, an IVPCA methadone trial was initiated. The 12-lead ECG was obtained with a MAC 5000 machine (GE Medical Systems, Milwaukee, WI, USA). The QT interval was measured manually by a board-certified cardiologist. The interval was corrected for heart rate using the Bazett formula:[6]

$$QTc = QT/Sqrt\ [RR].$$

QTc prolongation was defined as intervals longer than 430 ms for males and 450 ms for females.[14] During the first 7 days of methadone IVPCA titration, the QTc interval duration ranged from 416 to 449 ms (Table 1). On the morning of day 8, the QTc interval was 317 ms (Table 1). That night, due to excessive sedation, the IVPCA methadone was discontinued, so the patient received only 184 mg during the 24-hour period. During this episode, the patient was easily aroused; oriented to self, time, and space; had stable vital signs (BP 134/82; HR 62; RR 12); and had no evidence of arrhythmia (although an ECG was not done). The next morning, a repeat ECG showed a QTc interval of 784 ms (12 hours after the methadone IVPCA had been discontinued). At that point, the sedation was resolved, there was no evidence of withdrawal symptoms, and the electrolytes were within the normal range (K^+ 4.3, Ca^{2+} 9.3, Mg^{2+} 2.0, aspartate aminotransferase (ALT) 17, alanine aminotransferase (AST) 16 for a reference range of 3.7–5.2 mEq/L, 8.5–10.9 mg/dL, 1.7–2.2 mg/dL, 8–37 IU/L, and 10–34 IU/L respectively). The patient remained on nortriptilyne 25 mg in the morning and afternoon and 50 at bed time (plasma level of 81 for a therapeutic range of 70–170 ng/mL), and baclofen 10 mg every 8 hours that she had been taking at the same dose for several months before this admission. It is worth noting that no new medications that could prolong the QTc interval or interfere with methadone metabolism were initiated at this admission, (for a list of medications that can prolong the QTc interval, visit http://www.torsades.org). Twenty-four hours later, the QTc interval duration was 476 ms, and the patient reported a pain score of 8/10. At this time, methadone was resumed as an oral formulation at half the dose of that before discontinuation (30 mg three times a day), which is a dose that had not caused significant QTc interval prolongation a few days earlier. In addition, the patient received hydromorphone 8–16 mg IV every 3 hours as needed to provide additional pain relief and to control withdrawal symptoms. This combination of medications provided inadequate pain relief, as the patient reported pain scores ranging from 6/10 to 10/10.

On day 15, in view of the poor response obtained with IV and oral opioids (the patient continued to report pain scores of 10/10), methadone was discontinued, and a trial of neuroaxial analgesia that included hydromorphone, bupivacaine, clonidine, baclofen, and midazolam was conducted. At day 21, the patient continued reporting pain scores that ranged between 8/10 and 10/10, and the neuroaxial analgesia trial was discontinued. At this point, oral methadone was titrated, up to 30 mg four times a day, and the patient also received transdermal fentanyl 300 µg/hour every 72 hours (dose based on the IVPCA fentanyl trial that the patient had had earlier during this hospitalization). Hydromorphone 8–16 mg every 3 hours as needed was continued to manage breakthrough pain and withdrawal symptoms. On day 24, the patient was discharged on methadone and transdermal fentanyl, with the addition of meperidine IM and morphine IM, which the patient had used for many years, but now at lower doses and with longer intervals between administrations. At discharge, her pain score was 4/10 and the QTc interval

Table 1 Methadone dose over time and daily ECG

Day of IVPCA	Methadone			QTc interval duration (ms)
	Total methadone oral dose (mg/24 h)	IVPCA methadone dose (continuous rate plus demand, mg/24 h) and conversion to PO equivalency dose (IV to PO conversion factor = 2)	Total methadone dose in PO equivalent (mg/24 h)	
Day 1	40	28.8 × 2 = 57.6	97.6	449
Day 2	60	58.8 × 2 = 117.6	177.6	445
Day 3	60	94.8 × 2 = 189.6	249.6	430
Day 4	60	151.6 × 2 = 303.2	363.2	426
Day 5	60	121 × 2 = 242	302	416
Day 6	60	126.9 × 2 = 253.8	313.8	420
Day 7	60	137.3 × 2 = 274.6	334	429
Day 8	60	62 × 2 = 124 (12 h)	184	317
Day 9	20	–	20	784
Day 10	120	–	120	476
Day 11	120	–	120	486
Day 12	120	–	120	477
Day 13	120	–	120	495
Day 14	120	–	120	471
Day 15	None	–	0	485
Day 16	None	–	0	432
Day 17	None	–	0	451
Day 18	None	–	0	418
Day 19	None	–	0	437
Day 20	None	–	0	421
Day 21	30	–	30	404
Day 22	60	–	60	443
Day 23	90	–	90	448
Day 24	90	–	90	467

Notes: QTc duration versus total methadone dose. The first ECG was done to obtain a QTc interval duration baseline. Thereafter, daily ECGs were obtained to monitor the duration of the QTc while the IVPCA methadone titration was conducted. The total methadone dose was defined as the addition of the constant infusion rate, the demand dose, and the IV equivalent oral dose, in 24-hour periods. The methadone IV to oral conversion ratio was 1:2.
Abbreviations: ECG, electrocardiogram; IV, intravenous; PCA, patient-controlled analgesia; PO, per oral.

was 437 ms. We recognize that meperidine IM long-term use is not recommended, and the potential buildup of the metabolite normeperidine can cause seizures. However, the patient expressed anxiety at the prospect of discontinuing this medication, which she had been taking for many years without experiencing significant side effects. Therefore, we developed a plan to gradually switch from the use of injectable meperidine to injectable morphine, with eventual plan to transition to oral medications. After discharge, the patient was evaluated weekly in an outpatient setting for 1 month, at the end of which her pain score was 4/10, and the QTc interval was 372 ms. Four months later, the overall injectable mediations had been reduced by an additional 25% and her QTc interval duration was 410 ms.

Discussion

An ECG is a good screening tool for cardiac arrhythmias;[14] however, in this case, daily ECGs were not sufficient to guide dosing during rapid methadone titration as a gradual prolongation of the QTc interval was not observed. Instead, the QTc interval jumped from what is considered to be low risk for cardiotoxicity to over 700 ms in less than 24 hours, putting the patient at high risk for fatal arrhythmias such as TdP. Since the methadone was preservative-free, and medications that can be substrates of the cytochrome P450 isoenzymes 3A4, 2D6, and 2B6, or those that can block the I_{kr}, were not initiated during this hospitalization, it is likely that the observed prolongation was due to a dose-dependent effect of methadone on the QTc interval caused by drug accumulation. In this report, daily ECGs did not detect a gradual increment of the QTc interval duration that would have guided clinical decisions to either decrease or stop the drug before the QTc interval exceeded 500 ms. Therefore, while daily ECGs may be useful, this should not be the only method used to guide clinical decisions regarding dose adjustments of methadone, as a normal QTc interval can give a false sense of safety.

Telemetry monitoring or ECG determinations every 12 hours should be considered in cases in which aggressive titration of IV methadone is elected. However, since methadone plasma levels were not measured in this case, the conclusions of this report cannot be generalized.

Disclosure

Ricardo A Cruciani is on the speaker board for ENDO, Covidien, and Pfizer; has been coinvestigator in research funded by Ameritox; has organized CME courses funded by Grupo Ferrer; and has been in the advisory board for Depomed and Janssen Pharmaceuticals. The authors report no other conflicts of interest in this work.

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