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The Successful Use of Parenteral Methadone in a Patient with a Prolonged QTc Interval

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Abstract

Recent case reports have raised concerns about the potential for methadone to prolong the QTc interval (QT corrected for heart rate) and predispose patients to torsade de pointes (TdP), a life-threatening arrhythmia. We present a case report that describes the successful use of parenteral and oral methadone in a patient with uncontrolled cancer pain and a history of QTc prolongation. We describe an approach to the use of methadone in this patient and review both case reports and recent prospective studies that have evaluated the risk of TdP and the long term outcome with respect development of TdP in patients receiving methadone for chronic pain or addiction.

Keywords

Methadone; prolonged QTc interval; torsade de pointes (TdP); cancer pain

Introduction

The use of parenteral methadone in the management of pain in patients with advanced cancer is no longer a rarity. While methadone is an effective opioid analgesic for most patients and in general well tolerated, limited data show that there is some risk of QTc (QT corrected for heart rate) prolongation associated with its use.[1,2] QTc prolongation is a risk for a life-threatening arrhythmia, torsade de pointes (TdP) that may potentially lead to a sudden cardiac death.[3] This report illustrates the successful use of intravenous (IV) methadone in a patient with QTc prolongation.

Case Report

A 59-year-old man with advanced renal cell carcinoma involving the left peritoneum, pancreas and lumbar spine was referred to the Pain and Palliative Care Service for management of intractable thigh pain. Past management of his renal cancer included a left nephrectomy and interferon therapy. Subsequent epidural and lumbar spine disease was treated with radiation therapy followed by debulking surgery and a spine stabilization procedure. A second course of radiation therapy was given at a later date for progressive epidural disease and associated severe back pain.

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The patient's past medical history included hypertension, anxiety, depression, benign prostatic hypertrophy, chronic anemia, and mild to moderate renal insufficiency with a serum creatinine level ranging from 1.3 to 1.7. In addition, the patient had an eight-month history of prolonged QTc interval. His most recent QT/QTc value was 450/531msec with a heart rate of 84 beats per minute two weeks prior to this admission. (A normal range of QTc is <450 ms in men and <460 ms in women and a QTc interval of at least 500 ms has been shown to correlate with a higher risk of torsade de pointes.[3])

The patient described his pain as a constant, squeezing and achy pain with some burning and numbing sensation localized around both thighs. He also complained of stabbing pain at his lumbar spine area radiating to both flanks and thighs. His thigh pain corresponded with the L1-3 dermatomes and was consistent with vertebral/epidural disease. There was no evidence of spinal cord compression on MRI scan. During the past year the patient had required several inpatient admissions for pain management. The patient's pain had been managed with escalating doses of controlled release oxycodone and oral hydromorphone for breakthrough pain. He had been rotated to oral methadone several months prior to this admission and achieved pain control on a dose of 60mg every six hours. However, his pain once again escalated despite upward dose titration and the addition of gabapentin to his analgesic regimen.

The patient presented to the Urgent Care Center with severe pain rated at 10/10 on a zero to 10 pain rating scale. Parenteral steroids and bolus doses of hydromorphone were administered, with minimal relief of pain. When seen by the pain and palliative care consultant, he was agitated and restless, and complaining of severe pain. He was administered parenteral lorazepam and haloperidol, with some decrease in his agitation. His pain remained severe. He was evaluated for epidural or intrathecal analgesic approaches to manage his pain but these techniques were not employed because of the extent of his epidural disease and his repeated refusal to consent to these interventional procedures. A bolus dose of parenteral methadone (containing preservative, see below) was administered and the patient reported a meaningful decrease in the severity of his pain.

The pain and palliative care consultant was then faced with the decision of the relative benefit versus risk in starting this patient, who had a persistent history of prolonged QTc, on a parenteral infusion of IV methadone. The relative risk was discussed with the patient, who stated that despite that risk he wanted the methadone infusion to be tried as he could not live with such severe pain. He expressed a desire to commit suicide. Three hours after the initiation of methadone infusion and rapid dose titration up to 8mg/h, his pain had decreased significantly. His ECG, however, showed an increased QTc (591msec). The patient was transferred to a telemetry bed. A cardiology consultant's initial recommendation was that the patient's methadone be discontinued (both parenteral and oral), as well as all other potentially QT prolonging drugs. However, after a discussion among the patient's primary team, the cardiology consultant, and the pain and palliative care consultant, with clarification of goals of care, closeness to death and the patient's priority of pain relief, the decision was made to continue the methadone infusion as the most effective way to control pain. Eight hours after initiation of the IV methadone infusion, the IV medication was converted to an oral preparation and his pain remained under good control. He was discharged home on oral methadone 100mg every six hours. His pain remained adequately controlled with oral methadone until he died six months later.

Discussion

Although most cancer pain can be controlled with dose titration of first-line opioids, some cancer pain, in particular neuropathic pain, remains a significant challenge, despite the addition of adjuvant drugs such as anticonvulsants and antidepressants. Preclinical and in vitro studies

have identified properties of methadone that are not found in most clinically-used opioids. Methadone potentiates the analgesic effects of morphine,[4] has antagonist activity at NMDA receptors,[5, 6] and inhibitory effects at catecholamine uptake transporters.[7] Although it remains to be determined whether any of these effects occur in patients with pain, an increasing number of case reports describe improved pain relief after rotation to methadone.[8–13]

These potential advantages of methadone must be weighed against relative risk of QTc prolongation and the development of TdP as a consequence of methadone therapy.[14] Recent case reports have associated methadone with the development of TdP.[14–16] In a retrospective report, Krantz et al.[14] describe 17 patients who developed TdP while taking high doses (average equal to approximately 400 mg/day) of oral methadone for chronic pain or methadone maintenance. Most of the patients in these case series had a predisposing risk factor other than methadone for arrhythmia.[14–16]

As with other non-antiarrhythmic drugs, the effect of methadone on cardiac repolarization appears to be mediated through blockade of the human ether-a-go-go (HERG) potassium channel.[17] However, the extrapolation to a clinically relevant methadone concentration from in vitro data[17] failed to account for the extensive protein binding of methadone in human plasma[18] and, therefore, overestimated the in vivo QT prolongation potency of methadone.

A prospective study by Krantz et al. [19] evaluated 180 methadone maintenance patients at entry to the program and at six months after the start of methadone therapy. The ECG evaluation included a measure of QT dispersion, a predictor of drug-induced TdP. No occurrences of TdP were observed. Methadone modestly increased both QTc interval and QT dispersion. The authors concluded that the magnitude of this effect appears to be substantially less with methadone than with antiarrhythmic drugs known to produce TdP. Three additional recent prospective studies that included follow-up at two weeks to 12 months did not observe TdP and concluded that chronic oral methadone poses little risk of serious QTc prolongation except when other predisposing factors are present.[20–22]

A retrospective study by Kornick et al [2] compared the ECG of inpatients who had received IV methadone or IV morphine by continuous infusion. In this selected group of patients, the QTc prolongation in IV methadone patients was significantly greater than in IV morphine patients. The association was complicated by the in vitro observation that chlorobutanol, the preservative in parenteral methadone preparations, blocks the HERG potassium channel at relevant concentrations and potentiates the blocking action of methadone in vitro. Thus, the QTc prolongation in these patients may have been caused by a direct cardiotoxic effect of either methadone or chlorobutanol, or by a synergistic interaction of the two compounds. None of the 47 patients who received iv methadone developed TdP.[2]

When, as in this report, a patient has a history of a significant QTc prolongation (>500 ms) and parenteral methadone is the most effective means of controlling the patient's pain, the following considerations will reduce the potential for the development of life threatening TdP:

1. Awareness of non-drug-related causes of QTc prolongation, including hypokalemia, hypomagnesemia or hypocalcemia, or underlying cardiac disease.
2. Avoidance of other drugs that can prolong QTc.[19]
3. Avoidance of other drugs that can inhibit the biotransformation of methadone such as CYP3A4 inhibitors.[23]
4. Availability of preservative-free parenteral methadone. Since the current standard practice does not mandate the use of preservative-free methadone, this preparation is not yet generally available and must be ordered from and outside source. This limits

our ability to use this preparation to manage a pain crisis. In this case, parenteral methadone (with preservative) was rapidly titrated and then converted to the oral route before we were able to obtain the preservative-free methadone. However, based on a growing concern about the potential contribution of the chlorobutanol preservative to QTc prolongation with parenteral methadone, we recommend that preservative-free methadone be available for patients with a predisposition to or higher risk of QTc prolongation.

5. Determination of the patient's QTc at specified time intervals during parenteral methadone therapy.
6. The goals of care, including the risk and consequences of TdP, should be discussed.

Given the limited data on the risk of QTc prolongation and TdP associated with methadone infusions, there is no definitive answer that is adequate for all patients. The decision must be tailored to the individual clinical situation and goals of care. Good communication among the patient, family and providers is a critical component of the decision process. For the patient in this case report, initiating and continuing a methadone infusion during the patient's pain crisis and then converting to the oral route of drug administration when the pain had been brought under control was a reasonable decision. In retrospect the benefit far outweighed the risk.

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