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INITIATION AND RAPID TITRATION OF METHADONE IN AN ACUTE CARE SETTING FOR THE TREATMENT OF OPIOID USE DISORDER: A CASE REPORT

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Abstract

Background: Although methadone is an effective treatment for opioid use disorder, its initiation requires prescribing at a subtherapeutic dose with subsequent titration to a therapeutic dose over many weeks. Accordingly, the methadone induction period can be a challenging one for individuals and can be associated with an increased risk for ongoing illicit drug use and consequently overdose. Given its capacity for regular clinical assessments, acute care settings may offer a unique opportunity to reduce the duration of the induction period for methadone maintenance therapy.

Case summary: We report a case of an individual who successfully completed initiation and rapid methadone titration for treatment of opioid use disorder in an acute care setting.

Discussion: Utilizing divided dosing intervals and regular monitoring for toxicity, the patient received a cumulative daily methadone dose of 70 mg within 48 hours of admission with continuation of this dose subsequently. No adverse events occurred over a 9-day follow-up period. The case report described here highlights the potential acute care settings may offer for the successful initiation and rapid titration of methadone for the treatment of opioid use disorder. Such an approach could significantly reduce the induction period associated with methadone maintenance therapy and its associated negative outcomes including ongoing illicit substance use and risk for overdose.

Keywords

methadone; opioid substitution treatment; opioid-related disorders

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INTRODUCTION

North America is in the midst of an opioid crisis. In 2017, almost 4000 opioid-related deaths were reported in Canada, with almost 71,000 people dying from a drug overdose the same year in the United States (Ahmad et al., 2018; Belzak and Halverson, 2018). Accordingly, significant efforts have been made to improve access to evidence-based medication for the treatment of opioid addiction. Buprenorphine/naloxone and methadone are both medications with demonstrated efficacy in the treatment of opioid use disorder (Mattick et al., 2014). Despite recent Canadian guidelines recommending buprenorphine/naloxone as first-line therapy, methadone remains an effective second-line treatment option among individuals not able to tolerate a buprenorphine/naloxone induction, or for those who have been unsuccessful with this medication in the past (Bruneau et al., 2018).

Despite its effectiveness, significant challenges exist around the induction period associated with methadone maintenance treatment that currently limits its use more broadly. Specifically, initiation of the medication requires starting at a subtherapeutic dose, given the individual variation in elimination half-life and potential for dose accumulation over several days. Titration of methadone commonly occurs over weeks to months before a therapeutic dose can be reached (Kampman and Jarvis, 2015; World Health Organization, 2009). Not surprisingly, this period can be an especially challenging time for patients, where the risk of relapse and/or ongoing illicit drug use can be high given persistent cravings, opioid withdrawal symptoms, and associated stresses (Belding et al., 1996; Dyer and White, 1997). Consequently, until dose stabilization can be achieved, individuals are at an increased risk for both nonfatal or fatal overdoses (Modesto-Lowe et al., 2010). These challenges could be mitigated if the time to achieve therapeutic levels of methadone was decreased.

Although some research suggests more aggressive methadone titration can be utilized under closer monitoring or inpatient settings, the existing literature is scant to date and makes no direct recommendations (Gowing et al., 2014; Noska et al., 2015). To address this, we describe a case report of a patient with severe opioid use disorder who safely underwent initiation and rapid methadone titration in an acute care setting.

CASE PRESENTATION

A 36-year-old male was admitted to hospital in Vancouver, Canada for management of *Streptococcus pneumonia* bacteremia secondary to bacterial sinusitis. His past medical history was significant for a remote bilateral below-knee amputation secondary to meningococcemia. His substance use history revealed daily smoking of both heroin and crack-cocaine (approximately 1 gram of each per day) for the past 2 years. His last use of both substances was just prior to hospital presentation. He denied any injection drug use or previous overdose events. His addiction treatment history revealed a period of abstinence from all illicit substances while on methadone maintenance therapy, but further details regarding the timing or duration of this were not provided. He was not on any regular medications, did not follow-up with any primary care provider, was homeless, and was financially supported by income assistance.

At the time of presentation to hospital he was febrile with a temperature of 38.3 degrees Celsius, tachycardic at 127 beats per minuate, and normotensive with a blood pressure of 121/67 mmHg. His physical examination was notable for yawning, piloerection, and emesis. A CT head performed as part of his workup was suggestive of significant dental infection. His blood cultures returned positive for gram-positive cocci and he was placed on broad-spectrum antibiotics. His urine drug screen was positive for fentanyl, cocaine, amphetamines, and opioids.

The hospital's inpatient addiction medicine consult team was involved in his care to help manage the patient's ongoing polysubstance use. At the time of their consultation, the patient was found to be in acute opioid withdrawal. He was offered treatment with buprenorphine/naloxone or methadone and, given his previous success with methadone, he elected to restart on methadone maintenance therapy while admitted to the general medicine ward for treatment of his infection. Once clinically stable, the patient was started on 30 mg of methadone, with an additional 10 mg prescribed every 3 hours, up to 4 times per day as needed for ongoing withdrawal symptoms (maximum total daily dose 70 mg). Before each methadone dose, the patient's level of consciousness and respiratory rate was assessed by a nurse, and a decision to withhold the dose could be made if he exhibited any signs of methadone toxicity (eg, sedation, hypoventilation). Daily vitals were recorded and daily O_2 saturations did not demonstrate a drop below 92% on room air. In addition to his methadone, the patient was also prescribed short-acting oral morphine (10mg every 2 hours) on an as needed basis to manage any acute pain or remaining symptoms of opioid withdrawal, as assessed by his nurse. If the patient self-reported symptoms of opioid cravings or withdrawal, methadone doses were administered preferentially if available, followed by morphine as needed for any ongoing symptoms.

For a detailed breakdown of the patient's opioid use, see Table 1. On day 1 the patient received 60 mg of methadone (30 mg initial dose plus 3 × 10 mg doses) as well as 50mg of short-acting morphine. On day 2 the patient received 70 mg of methadone (30mg daily plus 4 × 10 mg doses) and 50 mg of short-acting morphine. On day 3, his daily methadone dose was increased to 50 mg from 30 mg, based on his total daily methadone dose on days 1 and 2, and he received an additional 2 doses of 10 mg (70 mg total) as well as 20 mg of short-acting morphine. Throughout the remainder of his admission, the patient remained on methadone 50 mg scheduled regularly, and used between 1 to 2 × 10 mg as-needed doses daily (for a total daily dose of between 60 to 70 mg). Each dose was provided at least 3 hours apart, allowing for time to reach peak serum methadone concentrations prior to the next dose. Of note, no doses were withheld. As seen in Table 1, as the patient's methadone dose stabilized, his short-acting morphine requirements reduced (50 mg on day 1 to 0 mg on day 9).

At the time of discharge, the patient was receiving a stable total daily dose of 60 to 70 mg of methadone daily for sufficient time to achieve steady plasma levels (>5 half-lives). He was linked to an outpatient clinic for ongoing dose titration, long-term treatment, and primary care follow-up. Before discharge, informed consent was obtained for the publication of a case report.

DISCUSSION

Methadone is a long-acting full μ-opioid receptor agonist, with a robust evidence-base supporting its effectiveness in the treatment of opioid use disorder (Mattick et al., 2014). The medication is administered orally, with peak plasma levels achieved 2 to 4 hours following ingestion (Kampman and Jarvis, 2015). The elimination half-life of methadone varies considerably due to genetic variability in the CYP 3A4 enzymatic system (a cytochrome P450 oxidizing enzyme which metabolizes methadone in the liver), ranging between 5 to 59 hours (Modesto-Lowe et al., 2010). Consequently, the period of methadone initiation and titration is associated with some risk, as toxicity can occur if the medication is allowed to accumulate in the body over several days. Because of the potential harms of dose stacking, current methadone prescribing guidelines suggest initiation at a low dose (e.g., 30 mg) and slow titration over time (e.g., 10 mg increase every 4 to 5 days) until cravings are reduced and the euphoric effects of any additional opioids are minimized (Kampman & Jarvis, 2015; World Health Organization, 2009).

While caution should be employed during the methadone induction period, this must be balanced against the need to provide timely, effective treatment for opioid use disorder. A low initiation dose and slow titration schedule results in a prolonged subtherapeutic window prior to stabilization (generally at 60 to 120mg, or after 4 to 6 weeks on average) (Kampman and Jarvis, 2015; World Health Organization, 2009). During this time, individuals with opioid use disorder are at increased risk for ongoing illicit opioid use, medication non-compliance, and both nonfatal and fatal overdose (DeMaria et al., 2000; Gottheil et al., 1993). In the wake of North America's opioid crisis, strategies that can minimize or eliminate this high-risk period should be further explored.

Current methadone guidelines are written to target community care settings, where split dosing and/or regular monitoring for signs of toxicity is impractical. The resulting recommendations err on the side of safety, and offer a very conservative approach to methadone initiation and titration. Monitored settings (e.g., acute medicine wards, inpatient detox facilities, or residential treatment facilities) offer an opportunity to take advantage of resources not available in the community, allowing greater flexibility in the dosing schedule and the ability to regularly monitor for early signs of toxicity.

In this case report, we have demonstrated the rapid titration of methadone in a safely monitored, inpatient setting. By providing smaller doses in 3 hour windows, we allow time for methadone to reach peak plasma concentration between doses. This permits the nursing staff to determine if it safe to continue with a further dose of methadone, or hold if there are any signs of toxicity. Utilizing our protocol, the patient described in this case was able to be titrated to a dose of methadone 60 mg total daily within 24 hours in a safe manner. He was then maintained at this dose for greater than 5 days, allowing his plasma methadone levels to achieve steady-state concentrations. Finally, he was linked to an outpatient methadone provider on discharge so that his medication could be continued and further titrated once his acute illness had resolved.

Several limitations to this approach are important to note. Although these windows of time present an opportunity to accelerate the schedule for methadone stabilization, the individual variability in serum half-life necessitates close monitoring during initiation. Nurses must have adequate training to recognize early signs of opioid toxicity, so that physicians can be alerted if there are any signs of accumulation. Likewise, all physicians, pharmacists, and allied healthcare workers also benefit from an understanding of the principles of methadone maintenance therapy and the induction process to help ensure patient safety. This type of induction protocol also requires a minimum time in hospital to ensure that serum levels of methadone have achieved a steady-state (at least 5 – 7 days), and any early discharge would require a return to more traditional schedules for titration in order to prevent dose stacking. Concurrent pain management presents another barrier, as it can be difficult to adjudicate whether symptoms are related to acute pain and/ or opioid withdrawal. In circumstances where the source of acute pain is not expected to improve rapidly, this scenario may require a more cautious approach to methadone dose increases. Lastly, this approach depends on the ability to link a patient to a community methadone provider at the time of discharge, for continuation of the prescription and ongoing dose titration as needed. This need for swift outpatient follow-up is especially critical with our protocol, given the fluctuating daily doses of methadone provided. Imminent outpatient follow-up (ideally 3 – 4 hours after the patient's daily methadone dose) post hospital discharge is required to ensure avoidance of opioid toxicity and to adjust dosing regimens accordingly. In Canada, methadone is available for dispensing from a community pharmacy. A crucial component to expanding access to methadone in other settings includes an exploration of alternative methods of administering this medication outside of specialty addiction treatment settings.

In light of the rising prevalence of highly potent synthetic opioids and the epidemic of opioid-related deaths sweeping across North America, it behoves us to maximize the benefit of every tool available for the treatment of opioid use disorder. Methadone remains an effective treatment modality, but has several important limitations to its use. If rapid initiation and titration of methadone in a monitored setting can be performed safely in patients admitted to hospital, it could greatly reduce some of the dangers associated with the induction phase. This approach may expand the pool of patients that could benefit from this potentially life-saving medication.

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TABLE 1

Methadone Regular, PRN and Morphine PRN Dosing for the patient in this report

Admission day	Methadone scheduled (mg)	Methadone PRN (mg)	Total daily methadone (mg)	Morphine oral liquid (M0S) (mg)	Total daily MOS (mg)	Total Morphine Milligram Equivalent (MME), mg*
Day 1	30	3 × 10	60	5 × 10	50	530
Day 2	30	4 × 10	70	5 × 10	50	610
Day 3	50	2 × 10	70	2 × 10	20	580
Day 4	50	10	60	2 × 10	20	500
Day 5	50	2 × 10	70	2 × 10	20	580
Day 6	50	10	60	10	10	490
Day 7	50	10	60	10	10	490
Day 8	50	0	50	3 × 10	30	430
Day 9	50	2 × 10	70	0	0	560

*Methadone dose used to calculate morphine milligram equivalent (MME) based on morphine : methadone ratio of 8:1 (Wong and Walker, 2013).