Managing Short Methadone Half-life in the Perinatal Period: A Case Report of a Patient Requiring 900 mg Daily

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Abstract: Using serum methadone levels to calculate methadone clearance can help providers individualize dosing, particularly in patients displaying clinical symptoms of rapid clearance, such as peak sedation with concomitant trough withdrawal. Multiple factors may impact methadone dose requirements and serum levels, necessitating deviation from standard methadone titration protocols. The physiologic changes of pregnancy generally shorten methadone's half-life due to CYP450 enzyme induction and increased volume of distribution. Additionally, the emergence of fentanyl—a far more potent opioid than its predecessors—has led to increased opioid tolerance among individuals who use it. As a result, these individuals may require higher methadone doses to effectively manage their opioid dependence. We present a case of a pregnant patient with opioid use disorder, primarily using fentanyl, who presented to labor and delivery at 36 weeks 6 days of gestation. She delivered at 37 weeks 1 day and remained admitted for 4 weeks while undergoing methadone induction. At the time of discharge, she endorsed ongoing opioid withdrawal and required ongoing methadone dose escalation at her outpatient methadone clinic after discharge. Laboratory testing one month postpartum indicated a methadone half-life of 9.22, and she was determined to need thrice daily dosing to maintain therapeutic serum levels, with her total daily dose ultimately reaching 300 mg 3 times daily. In patients who do not respond to standard methadone titration protocols, laboratory testing can support individualized dosing strategies to achieve therapeutic levels while maintaining patient safety.

Key Words: methadone, pregnancy, half life

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Methadone, one of three Food and Drug Administration (FDA) approved medications for the treatment of opioid use disorder (OUD), was first approved by the FDA in 1972. Despite its long history of use, our understanding of this medication continues to evolve, and changes in the drug supply (with high-potency synthetic opioid fentanyl replacing heroin as the primary illicit opioid) have required changes in our approach to methadone induction and dosing. Fentanyl is a more potent opioid than its predecessors and may require higher methadone doses to adequately address users' opioid tolerance.[1] Individual responses to a given methadone dose vary widely, with one study reporting a 17-fold variation in methadone serum levels for a given dose.[2] The half-life of methadone at steady-state ranges between 8 and 59 hours.[3] This interindividual variability can lead to methadone accumulation and side effects, including sedation in patients with relatively long elimination half-life, while a shorter half-life can lead to subtherapeutic medication levels, opioid withdrawal, and associated return to opioid use. In addition, pregnancy impacts the pharmacokinetics of methadone through multiple mechanisms, including the progesterone-mediated upregulation of hepatic cytochrome p450 enzymes and expanded volume of distribution.[4] While there is not a clear consensus, historically (when heroin was the primary opioid), a typical "therapeutic range" for serum levels was considered to be 150–600 ng/mL.[5] Peak levels exceeding 1000 ng have historically been considered potentially toxic.[6]

CASE

Informed consent was obtained from the patient for the publication of her case details. A 36-year-old female with OUD presented to labor and delivery at a tertiary care hospital at 37 weeks 1 day gestation and was admitted for induction of labor due to known heart failure with reduced ejection fraction. Past medical history was notable for endocarditis with mitral valve repair, hypertension, methamphetamine use, anxiety, a left femoral deep vein thrombosis, previously treated syphilis, hepatitis C with sustained virologic response, an emergency cesarean delivery for placental abruption three years prior, and homelessness. She reported that her opioid use began at age 15. Her past treatment history for OUD included several prior episodes of methadone treatment, about which she reported that she had been told that she was a methadone "rapid metabolizer" and had received methadone 369 mg PO daily. At the time of admission to labor and delivery, she was enrolled in a community opioid treatment program (OTP) with a methadone dose of 162 mg daily. She reported that this methadone dose was insufficient, and she had continued to use fentanyl daily, multiple times throughout each day. She also reported concurrent methamphetamine use. The day after admis-

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sion, her methadone dose was increased to 172 mg twice daily, and she delivered a healthy infant by planned repeat cesarean section the following day. Over the next 4 weeks inpatient, she reported ongoing withdrawal symptoms, which were managed by a combination of methadone dose increases and supplemental intravenous and oral hydromorphone. Her medications were reviewed to ensure that she was not on any medications that impacted methadone metabolism. An attempt was made to transition to TID dosing. Before this transition, her COWS scores (on methadone 200 BID) were typically 6–7. After her dose was divided TID (initially 135 TID, uptitrated to 150 TID, over 10 d), her COWS scores were typically 9–12, and the patient said she never felt relief from withdrawal, stating that each individual dose was too low when divided into 3. Her dose was then reconsolidated to 250 BID, with immediate improvement in her COWS in the subsequent days, back to a range of 5–8. By the time of her hospital discharge, 34 days postpartum, she was receiving methadone 335 mg PO twice daily with ongoing reports of withdrawal and COWS ≥ 8. Throughout her admission, her pulse oxygen levels remained between 95% and 100% without episodes of respiratory sedation; her QTcF at the time of her admission was 526 ms; it decreased to < 500 the following day and remained between 438 and 489ms throughout the remainder of her admission.

She was discharged with her newborn to a local perinatal residential substance use treatment program and enrolled at a licensed opioid treatment program. Despite her relatively high dose of methadone, she reported withdrawal symptoms, and she had signs of opioid withdrawal before each dose, including dilated pupils, diaphoresis, and irritability. To try to clarify the picture, the OTP obtained methadone serum peak and trough levels at the time of intake. The results showed a serum methadone peak of 1312 ng/mL and trough of 649 ng/mL with a calculated half-life of 9.2 hours (Table 1). Given this short half-life, her methadone dosing was adjusted to three times daily (TID). Initial recommendations were given to split her total daily dose of 670 mg at that time to 3 equal doses, to maintain steadier serum methadone levels. The patient declined this intervention, as she feared that each individual dose would be too low to control her withdrawal symptoms at any point of the day based on her experience with TID dosing during her postpartum admission, and the dose was split to 300-125-300 instead. Over the next 5 weeks, she continued to participate in the residential treatment programming, parent her newborn, abstain from non-prescribed substance use, and visit with OTP medical staff weekly. Her dose was ultimately titrated to 300 mg 3 times daily, for a total daily methadone dose of 900 mg. She reported improved opioid withdrawal symptoms after this intervention and had objective improvement in signs of opioid withdrawal with no sedation observed between doses. Repeat methadone serum labs drawn after reaching steady state on this dosing regimen showed serum peak 1732 ng/mL and serum trough 1344 ng/mL with an estimated half-life of 14.4 hours. At the time of repeat laboratory testing, she was 3 months postpartum.

DISCUSSION

This case presents a perinatal patient receiving unusually high doses of methadone to treat her opioid use disorder. While her care involved methadone doses well outside of the expected range, it illustrates several important points that are more generalizable. First, a growing body of clinical experience, expert opinion, and reports from drug users suggest that fentanyl use is associated with higher tolerance and the need for higher methadone doses than commonly seen in individuals who use heroin.[1,7,8] Second, methadone serum levels vary substantially between people receiving the same methadone dose[9]—due to factors such as individual differences in metabolism and volume of distribution (demonstrated by the changes in methadone dosing often required in pregnancy as both metabolism and volume of distribution increase). Obtaining serum methadone levels can be useful in situations in which the clinical picture (ongoing withdrawal, cravings, or fentanyl use) suggests the need for higher doses of methadone than expected. The availability of both peripartum and 3-month postpartum serum methadone levels illustrates the impact of enhanced methadone metabolism and changes to the volume of distribution during pregnancy and the postpartum period, as the patient's methadone half-life increased from 9 to 14 hours as her pregnancy-related physiology resolved. It is also important to note that many laboratories will report serum methadone levels above 1000 ng/dL as "toxic," which can be alarming to clinicians, although the evidence used to establish this cutoff is limited,[10] and its applicability in people with prior fentanyl use has not been studied. Finally, this case shows how a confluence of factors (pregnancy[4] superimposed on apparent baseline rapid metabolism and relatively high tolerance related to fentanyl[8]) can result in the clinical need for higher methadone doses.

TABLE 1. Methadone Dose and Serum Levels Throughout the Perinatal Period

Gestational age	Methadone dose (mg)	Peak MTD	Peak EDDP	Serum trough MTD	Trough EDDP	PTR	MTD/metabolite ratio peak	MTD/metabolite ratio trough	Half-life (h)
Prepregnancy	369*					NA			
Delivery	172.5 BID*					NA			
1 mo postpartum	335 BID*	1312	465	649	261	2.02	2.8	2.48	9.2
3 mo postpartum	300 TID	1732	811	1344	673	1.29	2.14	1.99	14.4

*Pt reports untreated withdrawal symptoms at these doses. Withdrawal symptoms reported as adequately treated on 300 TID.

While serum methadone levels are not routinely used in practice, they yield a calculated half-life and can be useful in guiding management for patients who exhibit withdrawal and/or sedation on standard dosing. They can be particularly helpful in managing patients during pregnancy and the postpartum period. For patients whose half-life is < 20 hours, split dosing can improve patient symptoms and keep methadone serum levels more stable throughout the day. Most pregnant people will require split dosing, and those with short half-lives prior to pregnancy can be anticipated to have even shorter half-lives due to the physiologic changes of pregnancy[11] In these cases, objective laboratory testing is helpful for guiding methadone dose titration, as dosage numbers can appear very high, but may correlate to relatively typically therapeutic serum levels.

CONCLUSIONS

Finding an appropriate methadone dose for patients who clear methadone quickly can be difficult even under optimal conditions, and the physiologic changes of pregnancy and the postpartum period may compound the problem. The high total daily dose may be disconcerting for providers, and the time required to titrate up to the dose required to resolve withdrawal symptoms can cause frustration for patients who continue to experience symptoms of opioid withdrawal while their doses are subtherapeutic. Laboratory values can help provide objective data to support the need for ongoing methadone dose escalation despite seemingly high doses. For patients whose methadone metabolism yields a half-life of < 10 hours, dosing every 8 hours can help stabilize methadone serum levels and relieve opioid withdrawal.

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