EDITORIAL

The use of methadone "as needed", is it justified?

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Methadone has enjoyed a resurgence of use in both pain and palliative medicine over the past 5-10 years. Unfortunately, this use has not been accompanied by good clinical trials, research, or wise application of this treatment modality. Although methadone can be a tremendously effective analgesic in experienced hands, it has a significant down side. The increase in deaths from the use of methadone has even roused federal interest and concern.[1] These deaths are correlated with a substantial increase in legitimate prescribing. The use of methadone has risen to 715 percent since 2001, per Drug Enforcement Agency (DEA) statistics.[1] Deaths have occurred not only due to abuse, but also when methadone is prescribed appropriately. A study on methadone overdose found 42 percent of the deaths occurred in patients taking the drug as prescribed.[2] Morbidity and Mortality Weekly Report (MMWR) has stated that 32.7 percent of unintentional deaths were due to nonillicit drug poisonings with methadone between 1999 and 2003.[3] Substance Abuse and Mental Health Services Administration (SAMHSA), in conjunction with the DEA and other federal agencies, is developing training for healthcare professionals on the use of methadone for pain with the suggestion that this training be mandatory.[4] One distinct problem, from this author's perspective, which may have contributed to some of the deaths described earlier, is the use of methadone on an "as needed" or PRN basis.[5] Intuitively, this is a widespread practice and is even a suggested dosing by the Drugdex,[6] although the exact amount of PRN methadone usage remains unclear. As with any medication, the prescriber must understand the pharmacokinetics, pharmacology, drug and disease interactions, and side effects before prescribing. Once the prescriber understands this, the question "Does the prn use of methadone logically fit with its pharmacology?" can be answered.

Methadone was originally developed in Germany in 1938, and was unused until picked up by Eli Lilly and named methadone based on its chemical formulation. In the United States, methadone comes as a racemic mixture. The R-enantiomer(R-MET or l-isomer) has opioid activity, while the S-enantiomer (S-MET or d-isomer) has seritonergic and norepinephrine reuptake inhibition activity.[7] The R-enantiomer accounts for most of the opioid effects of methadone. Both enantiomers noncompetitively inhibit the binding of NMDA receptor ligands with a potency comparable with that of ketamine.[8]

Although there is little data on clear dosing schedules for analgesia with methadone, most experts in the field suggest every 8 hours as a means for initiating therapy.[9] It must be strongly emphasized that there are significant inter-patient variations that can make any dosing schedule dangerous if patients are not monitored closely. Bioavailability can range from 41 to 99 percent. Methadone serum levels are measurable within 30 minutes of dosing, but serum levels range widely (11-146 ng/mL).[10,11] Methadone has a biphasic elimination with an alpha phase of 2-3 hours and beta phase that is extremely variable. The beta phase has been reported as ranging from 9 to 87 hours in postoperative patients, 8.5 to 75 hours in opioid-dependent individuals and up to 120 hours in duration in cancer patients.[12] This characteristic of methadone could be advantageous and allow for wider dosing intervals. However, Lugo and colleagues state that "the short duration of analgesia early in therapy is often counter-intuitive to clinicians, especially in view of the very long half-life of methadone."[7] The rapid alpha elimination is largely responsible for this shortcoming, as the medication is continued and compartments equilibrate, the dosing interval may need to be changed. Therefore, what is seen clinically is a short "analgesic half life," whereas pharmacologically the metabolic half life is much longer.[5] This potential "disconnect" between methadone pharmacokinetics and pharmacodynamics is one of the explanations for the significant variability in the time to steady state serum concentrations. If this concept is not understood, increasing initial doses of methadone too quickly can result in potentially fatal consequences.

When determining if methadone can be used on a PRN basis other characteristics of the drug should be considered as well. One advantageous characteristic is that methadone has no active metabolites.[8] Methadone is very lipophilic and highly protein bound (60-90 percent) to alpha-1-acid glycoprotein (AAG). AAG is elevated in cancer patients and in those who are opioid dependent and reduced in those who are significantly malnourished.[13] Changes in this transport protein have the potential to

affect the efficacy and potential toxicity of methadone. The major metabolic pathway of methadone is through the cytochrome P450 (CYP) enzyme system, specifically CYP 3A4 (major) and CYP2D6 and CYP1A2 to a lesser extent.[14] Substances that inhibit or stimulate these enzymes will affect the serum levels and therefore, potentially impact the efficacy and toxicity of methadone. Even combining methadone with low doses of a tricyclic antidepressant can result in toxicity due to a number of reasons, one of which is the inhibition of CYP3A4 metabolism.[8] Numerous medications including antidepressants, tobacco, and alcohol can also affect methadone clearance and therefore serum levels. Patients with genetic polymorphisms of the CYP2D6 can also be at risk for side effects or toxicity from increased methadone exposure based on their metabolizer status. Patients with such polymorphisms can be differentiated into poor, extensive, or ultra-rapid metabolizers; poor metabolizers would be at the highest risk for toxicity and ultra metabolizers at the highest risk for failure of therapy.[8] Thus, each of these groups may require changes in their methadone dosing. Further, methadone reabsorption from the various body compartments, once equilibrated, may continue for weeks after administration of this drug, which could necessitate reduction in dose over time.[12] Additionally, there may also be gender differences in elimination, with women having lower methadone serum levels than men.[15] Higher urine pH enhances excretion of methadone thereby reducing serum levels. And finally previous opioid exposure, and length of that exposure, may also alter the pharmacokinetics of methadone.[12]

Conversion ratios are another problematic aspect of initiating and titrating methadone therapy. Opioid conversion tables are not based on good science or research and should be used as a "rule of thumb" only rather than an absolute approach to conversion.[16,17] However, this is even more problematic with methadone. In the article by Weschules on conversation ratios from or to methadone, he states, "No universally safe or effective conversion ratio or method currently exists, and because of the large variability in opioid ratios, it is not possible to derive a simple conversion method for rotating to or from methadone."[18] Therefore, the ratios of morphine equivalent to methadone of 1:1 can be extremely dangerous and a much more conservative approach should be taken. Although it is true that many commonly used methadone conversion protocols in the primary literature have an "as needed" component for initiating and titrating therapy, most of these studies are small and lack details regarding the PRN use and adverse events occurring during the dose titration period or thereafter once a stable dose has been reached. Added to the above complexities, methadone has been shown to increase the QT interval to potentially dangerous levels and this must be monitored in all patients on this drug.[19] Further, long-term use of opiates places patients with hypoventilation syndromes and sleep apnea at risk. Methadone specifically may increase the risk of development of *de novo* central sleep apnea as well.[2,20,21]

The use of methadone as an analgesic has given many patients relief from intense suffering. It is an efficient and cheap analgesic. However, this drug can be a dangerous and lethal medication in the hands of the uninformed. The extreme variability and inconsistency in bioavailability, serum levels, conversion ratios, metabolism, long metabolic half-life, and apparent short analgesic half-life, potential interactions with other medications and past opioid exposure all make estimations on safety and patient accommodation to a specific dose of methadone difficult. This would include parenteral methadone regimens using PRN doses as well. Other authors have also condemned the PRN usage of methadone, stating that, "it is dangerous to prescribe additional 'as needed' doses of methadone."[7]

Recommendations for the dosing of methadone have been outlined in other publications, specifically Fishman's 2002 article.[9] I would add the following:

- Read and understand all aspects of this medication, including its pharmacology, pharmacokinetics, and pharmacodynamics before prescribing this drug.

- Any increase in methadone dose should be done no sooner than 5-7 days.[9] During this time, patients can have their rescue medications liberalized, if necessary.

- Conversion ratios should be based on those recommended by the American Academy of Hospice and Palliative Medicine or those with more conservative conversion tables,[18,22] <500 mg equivalents of oral morphine 10:1, 500-1000 mg equivalents 20:1, and >1000 mg equivalents 50:1. Although not specifically studied, they offer the benefit of very conservative ratios that should be a safer option.

- Always err on the side of conservatism. You can always increase the dose, but if you overshoot the mark you may be placing the patient at significant risk.

- Inform your patients taking methadone to always check with you before starting any new medications.

- Provide your patients with cards indicating they are on methadone and asking that new medications be checked for the potential to cause toxicity.

- Strongly inform your patients and their caregivers to take the medication exactly as directed and to report to you any somnolence or side effects immediately.

- Do not mix methadone with other long acting opioids without a good and clear rationale.

- Finally: Do not use methadone on an "as needed" basis and discourage this practice in others.

As Lugo states, "notwithstanding its advantages, the complexity and variability of methadone's pharmacokinetics make it a potentially dangerous drug if used by the uninformed."[7] It seems clear, at least to this author, that the PRN use of methadone is done based on ignorance of this medications pharmacology and complexity. The previous discussion suggests that the use of PRN methadone is not justified based on the pharmacology and pharmacokinetics. Although not a popular suggestion and beyond the focus of this editorial, this author also recommends (in agreement with some governmental agencies, *vide supra*) that prescribers be licensed to use methadone for analgesia (as they are when this drug is used in addiction treatment) and that they be given instruction in the pharmacology of this drug before being allowed to use this medication for the management of pain.

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