Potential for Precision Medicine in Methadone Treatment of Opioid Use Disorder

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The paper by McCarthy et al. (2019) opens a potential new opportunity to apply precision medicine to the use of methadone to treat opioid use disorder (OUD). McCarthy and colleagues analyzed data from 1700 blood specimens provided by patients receiving methadone maintenance treatment for OUD and sent to a single clinical laboratory for assays of serum methadone concentrations. This analysis found that the ratio of serum methadone concentration to the concentration of its inactive metabolite ethylidine-dimethyl-diphenylpyrrolidine (EDDP) could be used to divide the samples into 4 categories closely corresponding to the 4 categories of metabolic activity classically defined in the pharmacokinetic literature to describe the human variation in metabolism of a given pharmacologic compound: poor metabolizers (called ultra-slow metabolizers in the paper), intermediate metabolizers, extensive metabolizers, and ultra-rapid metabolizers.

The analysis further showed significant associations between these categories and the methadone serum concentration peak to trough ratio which already has recognized clinical utility and is obtained when patients demonstrate a poor response to methadone, particularly when patients complain of pre-dose withdrawal symptoms no matter how high the daily dosage goes. Patients with this clinical profile and a peak to trough ratio greater than 2 are presumed to be extensive or ultra-rapid metabolizers in whom methadone has a short half-life, and who will therefore require split dosing, having their total daily dosage divided into 2 separate administrations, to keep the trough serum level above the range at which withdrawal symptoms supervene.

For background and as briefly noted by McCarthy et al, the metabolism of methadone is quite complex and not yet fully elucidated. Current understanding indicates that multiple CYP 450 enzyme systems, including CYP3A4, CYP2B6, CYP2C19, CYP2D6, CYP2C9, and CYP2C8, likely contribute to N-demethylation of methadone to EDDP, and so metabolic pathways might be different across different individuals (Volpe et al., 2018). CYP 450 enzyme activities are determined largely by genetics with some contribution by environmental effects, for example enzyme inhibition or induction by various substrates. The science of understanding genetic effects on methadone metabolism remains in its infancy, but preliminary data suggest that polymorphisms in CYP2B6 may indeed contribute to rate of metabolism, whereas polymorphisms in CYP2D6 appear not to do so (Victorri-Vigneau et al., 2019). When one considers the plethora of enzymes involved, the number of potential polymorphisms that could contribute to alterations in methadone metabolism, and the potential interactions between different genetic influences in a single individual, it seems quite apparent that clinically useful genetic testing to place patients receiving methadone in 1 of 4 metabolizer groups described above is not on the current horizon. Thus, a simpler biomarker that could serve a similar function, such as the methadone/EDDP ratio propounded by McCarthy et al, holds considerable allure.

What clinical advantages might such a biomarker offer? McCarthy et al point out that, to the best of our current awareness, extensive and ultra-rapid metabolizers make up at most about 10% of the population of individuals receiving methadone treatment for OUD. Thus, during ongoing routine clinical care the vast majority of patients can be well managed without obtaining serum methadone levels or any other biomarker and simply using clinical judgment to determine a therapeutic methadone dosage when withdrawal signs and symptoms are absent, use of illicit opioids has ceased, craving for opioids is eliminated, and side effects are minimized.

However, McCarthy et al argue that if the methadone/EDDP ratio can accurately identify the roughly 10% of extensive and ultra-rapid metabolizers who might need split dosing, it could replace the use of peak to trough ratio which requires 2 separate blood draws rather than a single draw. A single draw could have some modest logistical advantages because obtaining a peak level requires the patient to remain in the clinic for 3 to 4 hours after ingesting the day’s methadone dose and going for the blood draw in the correct timeframe.

McCarthy et al also suggest that the methadone/EDDP ratio could be applied at the outset of an episode of methadone treatment, as early as day 2 to predict which patients are poor
(ie, ultra-slow) metabolizers. If this potential to predict poor metabolizers from a single, readily available biomarker were conclusively demonstrated, it could have wide clinical application to make precision medicine for methadone treatment a reality. Individuals with opioid use disorder already have considerably increased risk for mortality compared to the general population, but the initial weeks of methadone maintenance treatment represent a time of even more heightened risk (Sordo et al., 2017). Because of methadone’s average long half-life, some of these deaths have occurred iatrogenically when the daily dosage of methadone was titrated upward too rapidly (Caplehorn, 1998), presumably in poor metabolizers in whom, because of its long half-life, methadone can accumulate over sequential doses until steady state has been achieved. Given this serious risk and our current inability to distinguish poor metabolizers, all patients starting methadone treatment must undergo a slow, painstaking, stepwise increase in dosage that often requires 4 to 6 weeks to reach a therapeutic dosage. The bulk of the patients who are not poor metabolizers could probably tolerate a more rapid titration, over a week or 2. While patients wait many weeks to arrive at a stable dosage, they continue to experience withdrawal, and many continue illicit opioid use, which in itself increases risk for overdose and death. The long wait to achieve stability most likely also contributes to early treatment dropout because patients understandably fall prey to the misapprehension that the treatment is not working. If a single biomarker could indeed identify poor metabolizers, we could then apply this precision to individualize the initial titration of methadone doses, by titrating only poor metabolizers slowly and titrating the other patients more rapidly, making this early component of treatment safer and more effective for everyone. However, McCarthy et al’s hope that the methadone/EDDP ratio could serve as such a biomarker as early as day 2 of treatment demands considerably more rigorous study before it could come into regular clinical use, as McCarthy et al acknowledge.

Overall McCarthy et al do an excellent job of conveying the limitations of their current work which mainly revolve around the fact that no clinical information was available on the patients who provided the serum specimens for analysis. So, what further work might support the application of methadone/EDDP ratio to routine clinical care? Clearly, studies are needed that examine methadone/EDDP ratio in the context of full sets of clinical information including patient demographics, medical and psychiatric history, concurrent medications, methadone dosage, electrocardiograms to assess the QT interval, indices of liver and kidney health, and urine drug screen results. Longitudinal studies that investigate the stability of methadone/EDDP ratio over time, particularly comparisons of this biomarker during the first few days in treatment with methadone to the interval when a stable, effective dose has been reached. Since future work on the genetics of methadone metabolism will likely occur, it would be ideal to collect methadone/EDDP samples in that context.

It is worth noting that, in addition to its use in treatment of OUD, because of its long half-life and its effects on N-methyl D-aspartate receptors (Inturrisi, 2005) and on serotonin and norepinephrine reuptake (Codd et al., 1995), methadone has considerable utility as an analgesic in the palliative care setting. A biomarker such as methadone/EDDP ratio that could help to predict safe and adequate dosing could also serve a valuable function in that context.

While much work remains to be done, McCarthy et al deserve praise for bringing the methadone/EDDP ratio to the attention of the field as a possible biomarker that conceivably might allow us to treat our patients with OUD with more precise, individualized, scientific exactitude.

REFERENCES


Inturrisi CE. The role of N-methyl-D-aspartate (NMDA) receptors in pain and morphine tolerance. Minerva Anestesiol 2005;71:401–403.


