

Practical Pharmacology of Methadone: A Long-acting Opioid

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Abstract

Methadone is a naturally long-acting analgesic with unique pharmacodynamic and pharmacokinetic properties compared to other opioids, available now in India, to treat severe pain. It has the potential to dramatically relieve suffering among patients with serious illness who are living with persistent physical pain. However, clinicians must appreciate its unique pharmacologic properties and its use in clinical practice safely and effectively. The available formulation in India is a racemic mixture of the S- and R-enantiomers, and as such, it will have a propensity for drug-drug and drug-genetic interactions that can increase the risk of Torsades de Point and respiratory depression. Appropriate patient selection, careful dosing and thorough monitoring of methadone will mitigate these risks.

Keywords: Drug interactions, India, methadone, pharmacology

INTRODUCTION

Pain is one of the most common symptoms experienced by patients living with serious illness and is often a combination of persistent, around-the-clock pain with additional intermittent or “breakthrough” pain, which is sometimes incidental to routine body movements, such as coughing, or more strenuous physical activity. In cancer pain, experts recommend using long-acting opioids to control persistent pain and short-acting opioids dosed as-needed for breakthrough pain.^[1] This combination improves pain control and quality of life.^[2] From a pharmacokinetic perspective, using as-needed or scheduled short-acting, immediate-release opioids to control severe pain results in wide fluctuations in plasma levels, causing a roller-coaster of pain severity, and pain-related anxiety. In addition, this dosing strategy results in higher peak plasma levels, which are theoretically associated with a higher risk of side effects [Figure 1].^[3] In the United States and Canada, elegant, controlled-release solid-dosage formulations of naturally short-acting opioids, such as morphine and oxycodone, have been engineered to provide sustained, steady analgesia over 8–12 h. However, there are limitations in using these formulations in patients with serious illness, as these long-acting oral preparations can be difficult to ingest. Methadone is a naturally long-acting analgesic, with a duration of analgesic effect of 8–12 h after repeated dosing.^[4] Therefore,

it can provide sustained analgesia through a variety of dosage forms (tablet, liquid, subcutaneous, and intravenous), allowing versatility in administration through the oral, buccal, rectal, and intravenous routes. This makes it an ideal analgesic to treat persistent pain in patients with the advanced serious illness.

PHARMACODYNAMICS: WHAT METHADONE DOES TO THE BODY

Therapeutic effects

Methadone formulations in India include 5 mg oral tablets and 5 mg/ml syrup which contain racemic mixtures of R-methadone and S-methadone. The R-enantiomer is approximately 50 times more potent than the S-enantiomer for analgesia, in part due to 10-fold greater affinity for the mu opioid receptor. Methadone also activates the delta and kappa opioid receptors.^[5,6] In addition to opioid receptor agonism, both R-methadone and S-methadone equally antagonize the N-methyl-D-Aspartate (NMDA) receptor. Since activation of

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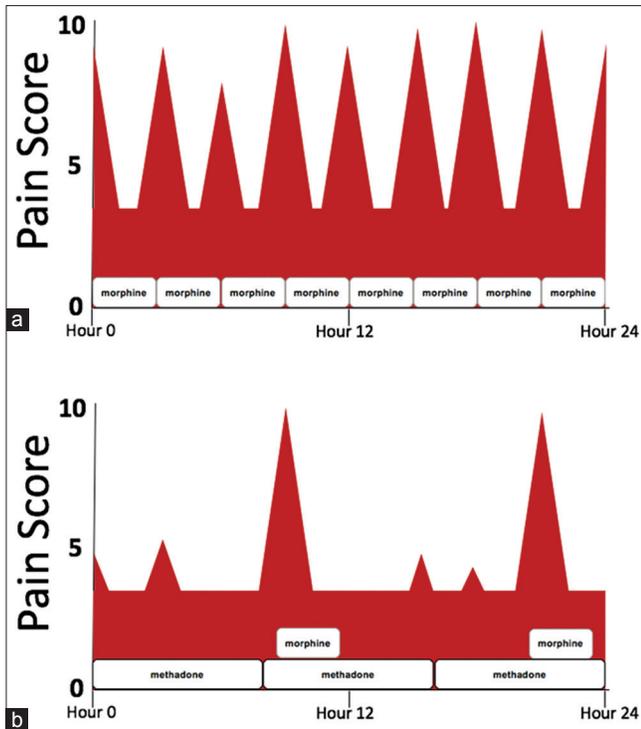


Figure 1: Using schedule short-acting opioids such as morphine versus methadone with rescue morphine available. (a) Pain score pattern for a patient with severe, persistent pain taking scheduled morphine every 3 h. (b) Pain score pattern for a patient with severe, persistent pain taking scheduled methadone every 8 h with morphine available every 3 h as needed for moderate-to-severe pain

NMDA leads to central sensitization, windup, and tolerance, methadone's blockage of this receptor can prevent and reverse acquired tolerance to pure opioid agonists such as morphine. Methadone improved pain control in patients with severe pain who were taking high doses of opioid agonists such as morphine and oxycodone.^[7-12] S-methadone also prevents the reuptake of serotonin and norepinephrine.^[4,6] This, combined with NMDA antagonism, makes methadone more effective for neuropathic pain than other opioids such as morphine and fentanyl.^[13,14]

Adverse effects

The action of methadone at opioid receptors can lead to opioid-related side effects including sedation, respiratory depression, and constipation. These effects are additive with other medications that cause these effects as well as with concomitant medications that increase methadone levels. In particular, most patients in the United States who experienced serious respiratory depression resulting in death while taking methadone were also taking benzodiazepines, which have an additive effect on respiratory depression.^[4] Benzodiazepines, barbiturates, and alcohol should be avoided in patients taking methadone. Sleep apnea, central nervous system injury, and severe lung disease can increase the risk of respiratory depression in patients taking methadone, perhaps the "deep sleep" as a result of neuropathic pain, amelioration. Initiation in such patients should weigh safety risks with the patient's

goals of care and should only be done with conservative dosing and careful monitoring.

Methadone can cause serotonin syndrome when given with other serotonergic medications such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRI), and certain tricyclic antidepressants (TCAs).^[15-19] Methadone should not be used with MAOIs. When methadone is used with SSRIs, SNRIs, or TCAs, it should be dosed conservatively with careful monitoring for serotonin syndrome, which can range in severity from agitation, clonus, and hyperreflexia to confusion, lethargy, coma, and seizures and is accompanied by autonomic instability, particularly hyperthermia.

In addition to its activity at the NMDA receptor and serotonin and norepinephrine reuptake transporters, S-methadone binds to the human Ether-a-go-go (hERG) to cause QT-prolongation, which can lead to Torsades de Point (TdP) and sudden cardiac death. Drug interactions that also prolong the QT interval or result in increased levels of S-methadone increase the risk of QT prolongation. Risk of TdP begins at corrected QT interval (QTc) >500 ms or an increase of QTc >60 ms from baseline.^[20] In outpatient palliative care patients, QTc >500 ms only occurred in 1 of 64 patients after initiation of methadone.^[21] Patient risk factors for QT prolongation must also be considered for initiation and ongoing methadone therapy. These include hypokalemia and hypomagnesemia.^[20] A recent case-control study among palliative care patients identified congestive heart failure, peptic ulcer disease, hypokalemia, rheumatologic disease, malignancy, hypokalemia, total daily dose of methadone >45 mg, concomitant QT-prolonging medications, and concomitant medications that increase methadone levels as significant risk factors for QT-prolongation in this patient population.^[22] The Heart Rhythm Society and American Pain Society recommend obtaining ECGs before starting methadone in patients with the following risk factors: electrolyte abnormalities, Impaired liver function, age >68, female gender, structural heart disease, genetic predisposition, concomitant QT-prolonging drugs, history of syncope, and previous QTc >450 ms. Follow-up ECGs are recommended in 2-4 weeks after initiating methadone for patients with these risk factors, and again if the total daily dose of methadone reaches 30-40 mg and 100 mg.^[20]

PHARMACOKINETICS: WHAT THE BODY DOES TO METHADONE

Methadone's basicity and high lipophilicity largely contribute to its long half-life. On oral ingestion, it is absorbed by the stomach and is 36%-100% (mean 75%) bioavailable, with a peak plasma concentration 2.5-4 h postdose.^[5] In addition to commercially available 5 mg/mL syrup, methadone can be compounded into an oral syrup or solution.^[23] 34% of methadone can be absorbed sublingually from a concentrated

oral solution or syrup.^[24] In addition, methadone oral solution administered rectally has approximately 80% bioavailability equivalent to the oral route. In contrast, methadone suppositories have a lower absorption efficacy of 35%–58%.^[25] Absorbed methadone quickly moves out of the blood compartment, where it can act on its target receptors, and into lipophilic tissues (alpha-phase). An equilibrium of methadone concentration between the tissues and blood compartment is reached after saturation of lipophilic tissues, and the slow beta-phase of elimination begins, with a variable elimination half-life of 5–130 h (average of 22 h).^[26,27] For this reason, it can take 5–14 days to reach steady state and see the full impact of a dose initiation or increase. While methadone's half-life is long, the duration of analgesic effect after repeated dosing is 8–12 h.^[28] The risk of side effects, however, including respiratory depression, persists beyond this analgesic window.

As methadone is released into and circulates in the blood, it is 90% bound to alpha-1 acid glycoprotein, with 4-fold variation among individual patients, further contributing to variability in dosing needs among patients.^[5] Methadone and its metabolites are excreted into the urine and feces, with excretion rate increasing and shifting to the renal route when urinary pH is <6. Typically, 11% of a methadone dose is renally eliminated, but this can increase up to 57% in urine acidification.^[5,6] Even so, methadone is a preferred opioid in end-stage renal disease. Whereas morphine is metabolized into active glucuronides that accumulate and increase risk of toxicity, including neurotoxicity, methadone is safe even in severe renal impairment.^[29] It is not appreciably removed by dialysis.^[30]

Metabolism adds additional variability to safe and effective doses of methadone among patients. Due to its extensive hepatic metabolism, conservative dosing is warranted in liver failure. Methadone is primarily metabolized to inactive metabolites, including 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, by cytochrome P (CYP) 2B6, followed by CYP 3A4 and CYP 2C19. Methadone is metabolized to a lesser extent by CYP 2D6, 2C9, and 2C8.^[31–34] S-methadone, which causes 3.5-fold blockade of hERG, is preferentially metabolized by CYP 2B6, and R-methadone, which has up to 50x more analgesic activity, is preferentially metabolized by CYP 2C19. Both are equally metabolized by CYP 3A4.^[31,33] Methadone's extensive metabolism by CYP enzymes can lead to drug interactions with allopathic and ayurvedic medications that inhibit or induce these enzymes. In addition, consumption of grapefruit juice could increase methadone levels. Depending on the drug interaction, levels of one or both of S-methadone or R-methadone may be impacted and could result in decreased analgesia or increased toxicity. Furthermore, CYP 2B6, CYP 2C19, and CYP 2D6 are polymorphic, with some genetic variants resulting in increased metabolism of methadone and some resulting in decreased metabolism. In India, Ancestral North Indians (ANI) and Ancestral South Indians (ASI) have

distinct pharmacogenetics from each other as well as from ethnic groups in whom methadone has been used to date, including Caucasians. Whereas 13.3% of Caucasians have a poor metabolizer genotype (*CYP2C19* * 2) of CYP 2C19, 33.1% of ANI and 36.8% of ASI do. The poor metabolizer genotype *CYP2D6* * 3 was found in 9.2% of ANI and 0% of ASI compared to 2.8% of Caucasians. More ANI (29.3%) and ASI (34.8%) have the fully functional *CYP2D6* * 2 allele than do Asians (14%) and Caucasians (4%).^[35] A poor metabolizer phenotype for CYP2B6 was discovered in 20.56% of ANI and 40% of ASI, compared to 6%–39% of Caucasians.^[36,37] These genetic variants in our population make it paramount to exercise caution when using this new medication.

HOW PHARMACOLOGY IMPACTS METHADONE USE

Given methadone's complicated pharmacodynamic and pharmacokinetic properties, “starting low and going slow” with close follow-up is central to safely using methadone. Numerous methods and conversion ratios are used for initiating methadone in patients already taking opioids, such as short-acting morphine.^[38] Recent data indicate lower doses than those calculated with the most conservative conversion methods may be effective.^[39] It is unknown if this may be due to patient-related factors or drug interactions not captured in the study. Case reports indicate frail, elderly patients should be initiated on much lower doses of methadone, even as low as 0.5 mg daily.^[14] This could be due to age-related changes including increased fat composition and age-related decreases in activity of phase I CYP enzymes responsible for methadone metabolism, both of which would contribute to a prolonged half-life for methadone. Due to methadone's long and variable half-life, it can take 5 days or more to see the full effect of a given dose. Therefore, the starting dose of methadone should not be increased for at least 5 days in ambulatory patients to avoid early dose stacking. Readers are referred to the manuscript by Palat *et al.* within this issue for a comprehensive discussion of dosing methadone.

As outlined above, methadone has numerous pharmacodynamic and pharmacokinetic drug interactions. Consultation with a pharmacist knowledgeable about methadone may be helpful in identifying and managing drug interactions, including selecting therapeutic alternatives or adjusting doses. Whenever possible, avoid drug interactions with methadone by deprescribing the interacting medication or selecting a therapeutic alternative to the interacting medication when possible. It is particularly important to avoid using methadone with medications which have previously been shown to cause TdP if taken with methadone. Such medications are highlighted with an asterisk (*) in Table 1.^[40,41] Many medications can increase or decrease levels of methadone in the body [Table 2].^[42–44] Therapeutic alternatives may be selected when clinically appropriate [Table 3]. If a patient is taking a medication that lowers methadone levels, monitor carefully and adjust the dose of methadone as needed based on short-acting opioid use. It may take 2 weeks to see

Table 1: Medications that increase the risk of QT-prolongation and Torsades de Pointes when taken with methadone

Risk	Level of Risk	
	Possible	Conditional
Amiodarone	Atazanavir ^a	Metoclopramide
Azithromycin ^a	Saquinavir	Itraconazole ^a
Ciprofloxacin ^a	Aripiprazole	Ketoconazole
Clarithromycin ^a	Asenapine	Posaconazole
Erythromycin ^a	Clomipramine	Voriconazole ^a
Fluconazole	Clozapine	Ritonavir ^a
Levofloxacin ^a	Famotidine	Quetiapine ^a
Chlorpromazine	Dolasetron	Trazodone
Citalopram	Granisetron	Ziprasidone
Cocaine	Risperidone	Furosemide ^a
Droperidol ^a	Tizanidine	Hydrochlorothiazide
Haloperidol, IV greater than oral	Venlafaxine	Torsemide
Escitalopram	Nicardipine	Pantoprazole
Fluoxetine ^a	Mirtazapine	Diphenhydramine
Sertraline ^a	Doxepin ^a	Hydroxyzine
Ondansetron ^a	Co-trimoxazole ^a	Fluvoxamine
Cocaine ^a	Olanzapine	Paroxetine ^a
	Nortriptyline	

A medication is designated as having risk if substantial evidence exists that it prolongs the QT interval and increases risk of Torsades de Pointes, even when used as directed. A medication has possible risk if there is substantial but insufficient evidence of this risk. Medications are listed as conditional if there is substantial evidence they prolong QTc interval and increase risk of Torsades de Pointes only in certain conditions, such as hypokalemia or in combination with other QT-prolonging medications. Regardless of designated risk level, medications denoted with an asterisk(*) have been reported to cause Torsades de Pointes when taken with methadone in cases or case series. It is advisable to avoid using these medications with methadone. Other medications are expected to cause increased risk, but, to date, there are no actual reports of Torsades de Pointes when they are used with methadone. If no therapeutic alternative is available, these medications should be used cautiously with close monitoring. For a complete list of medications that may prolong the QT interval and cause Torsades de Pointes, visit crediblemeds.org

the full effect of a drug interaction that decreases methadone levels. If a medication increases methadone levels, the dose of methadone should be preemptively reduced by 25%–33% and the patient should be carefully monitored. When a patient needs methadone and another serotonergic medication together, choose a medication with lower serotonergic effect when possible. In any case, if a drug interaction is present, it is important to gain informed consent from the patient after communicating the risk of the drug interaction and how patient safety will be maximized and monitored.

SUMMARY

Methadone requires training, knowledge of its unique pharmacology, and careful clinical consideration. When knowledgeable clinicians judiciously add it to short-acting opioids for severe pain in a patient with serious illness, pain control, and quality of life improve without decreasing overall survival.^[46]

Table 2: Medications that may raise or lower methadone levels

Medications that may increase methadone levels		Medications that may decrease methadone levels
Amiodarone	Cimetidine	Ritonavir
Diltiazem	Esomeprazole	Efavirenz
Verapamil	Lansoprazole	Modafinil
Nifedipine	Omeprazole	Nelfinavir
Nicardipine	Pantoprazole	Nevirapine
Clopidogrel	Cotrimoxazole	Rifampin
Ticlopidine	Ciprofloxacin	Rifabutin
Amitriptyline	Clarithromycin	Primidone
Amprenavir	Erythromycin	Phenytoin
Citalopram	Fluconazole	Carbamazepine
Desipramine	Itraconazole	Phenobarbital
Escitalopram	Ketoconazole	St. John's Wort
Fluoxetine	Posaconazole	Estradiol
Fluvoxamine	Voriconazole	
Sertraline	Isoniazid	
Nefazodone	Telithromycin	
Clomipramine	Troleandomycin	
Desipramine	Cobicistat	
Paroxetine	Alprazolam	
Bupropion	Diazepam	
Duloxetine	Midazolam	
Diazepam	Doxorubicin	
Chlorpromazine	Anastrozole	
Aprepitant	Abiraterone	
Haloperidol	Imatinib	
Celecoxib	Darifenacin	
Cannabinoids	Diphenhydramine	
Cinacalcet		

Table 3: Possible alternatives to common medications that interact with methadone

Interacting medication (s)	Possible alternative (s) ^a
Azithromycin, Clarithromycin, Erythromycin	Penicillins
Levofloxacin, Ciprofloxacin	Penicillins
Fluconazole, Itraconazole, Posaconazole, Voriconazole	Micafungin, clotrimazole, single-dose fluconazole for thrush ^[45]
Droperidol, Ondansetron, Chlorpromazine, IV haloperidol	Prochlorperazine, oral haloperidol

^aClinical appropriateness of possible alternatives must be evaluated for each individual patients. Alternatives are not comprehensive

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Conflicts of interest

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