Methadone in end-of-life pain management

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INTRODUCTION

Pain is a complex symptom which, at times, challenges even the best clinician.[1,2] In patients with cancer, pain is a pervasive and difficult problem[3] that encompasses psychological, social, spiritual, and physical realms.[4] Palliative care clinicians must understand the psychosocial and spiritual domains in addition to the physical aspects of pain treatment to truly alleviate suffering. Thus, being adept with opioid dosing and titration is essential in comprehensive palliative care,[5] as it often requires rapid escalation and continual reevaluation. There is a general lack of comfort and understanding concerning the use of many opioids, however, which often leads to undertreatment of pain—even among patients receiving care for terminal diseases.[6] This is particularly true of methadone. Methadone is well known among addiction specialists for its use as maintenance therapy in opioid-dependent patients.[7] Increasingly, methadone's unique properties and economic advantages[8-10] are being realized by those within the palliative care community, whose practice settings often involve homebound patients with limited funds or difficult-to-control terminal pain. Because of its potential for serious adverse effects, however, methadone should only be prescribed with knowledge of its intricacies.

PHARMACODYNAMICS AND PHARMACOKINETICS

Methadone is a synthetic opioid, which exists as a racemic mixture. L-methadone provides analgesia in part via activation of the body's endogenous analgesia system: μ-, δ-, and κ-opioid receptors in the ascending pain pathway are agonized. L-methadone also modulates the descending pain pathway via inhibition of serotonin and norepinephrine reuptake. This monoamine reuptake inhibition dampens pain pathways. Finally, both D- and L- enantiomers are noncompetitive antagonists of the N-methyl-D-aspartate (NMDA) receptor. The reverse process, agonism of the NMDA receptor in the spinal cord, contributes to opioid tolerance. Hence, methadone's unique property of antagonizing this untoward process contributes to its notably higher milligram-for-milligram equianalgesic potency compared to morphine.[11]

Methadone has been used to treat neuropathic pain.[12] As well, some authors have theorized that NMDA receptor antagonism could offer a unique mechanism of added efficacy for neuropathic pain, whereas opioids without NMDA activity would not. However, a retrospective chart review suggested methadone affords no additional efficacy for neuropathic pain versus non-neuropathic pain when compared to equianalgesically dosed hydromorphone.[13] An evidence-based review of the current limited literature of eight randomized trials has revealed no research support for methadone's theoretical benefit in neuropathic pain treatment.[14] Whereas methadone has the complex pharmodynamics already mentioned, morphine is almost exclusively a μ-receptor agonist. Such variability among individual opioid analgesic receptor profiles contributes to the phenomena of incomplete opioid cross-tolerance. Occasionally a change in opioid agent will yield notably better analgesia, even when equianalgesic dosing is taken into consideration.[15]

Clinical onset of analgesia is within 30 to 60 minutes after oral administration; the plasma level peaks in four hours, and peak analgesia is achieved in 2.5 to 4.0 hours. Because methadone is stored in tissues and then subject to redistribution, repeat dosing may extend the initial analgesic effect from three to six hours initially to eight to 12 hours after a steady state is achieved. Methadone's tissue binding (to muscle, liver, kidney, lungs, and brain) is more extensive than its plasma binding. Methadone in the plasma is highly protein bound via α-1-acid glycoprotein (AAG). AAG is an acute-phase reactant, which is often elevated in cancer patients. Unbound methadone is metabolized in the liver primarily via cytochrome P-450 (CYP) 3A4, CYP2C8, and CYP2D6. Hence, hepatic clearance of methadone is decreased and half-life is increased among cancer patients.[17] CYP activity is important when considering potential drug interactions (Table 1). Numerous drugs that either inhibit or activate the CYP system can lead to opioid toxicity or withdrawal with methadone. The elimination half-life has a mean of 22 hours, but an extremely variable range of 15 to 190 hours has been reported.[18] This comparatively long half-life is beneficial for chronic pain management.[19] Elimination is predominantly via liver

Table 1. CYP activity and potential drug interactions								
2C8 substrate	**2C8 inducer**	**2C8 inhibitor**	**2D6 substrate**	**2D6 inducer**	**2D6 inhibitor**	**3A4 substrate**	**3A4 inducer**	**3A4 inhibitor**
repaglinide	rifampin	gemfibrozil	amitriptyline	dexamethasone	amiodarone	alprazolam	barbiturates	amiodarone
torsemide		glitazones	aripiprazole	rifampin	bupropion	amlodipine	carbamazepine	cimetidine
		montelukast	carvedilol		celecoxib	aripiprazole	glucocorticoids	ciprofloxacin
		trimethoprim	chlorpromazine		chlorpromazine	atorvastatin	modafinil	diltiazem
			clomipramine		cimetidine	buspirone	oxcarbazepine	erythromycin
			codeine		citalopram	cisapride	phenobarbital	grapefruit juice
			desipramine		clomipramine	clarithromycin	phenytoin	norfloxacin
			duloxetine		diphenhydramine	diazepam		verapamil
			flecainide		doxepin	erythromycin		
			fluoxetine		duloxetine	estradiol		
			haloperidol		escitalopram	felodipine		
			imipramine		fluoxetine	fentanyl		
			metoclopramide		hydroxyzine	finasteride		
			metoprolol		metoclopramide	haloperidol		
			risperidone		paroxetine	hydrocortisone		
			thioridazine		quinidine	lovastatin		
			tramadol		sertraline	nifedipine		
			venlafaxine			ondansetron		
						propranolol		
						quinidine		
						testosterone		
						trazodone		
						verapamil		
						zaleplon		
						zolpidem		

metabolism and subsequent renal and fecal excretion. There are no active metabolites. Methadone needs to be titrated with additional caution in patients with hepatic or pulmonary impairment. Approximately 40 percent of methadone is eliminated renally. If urine pH is less than 6, then the percent renal elimination increases. Nonetheless, renal dosing is almost never clinically necessary.

FORMULATIONS

In the United States, methadone is commonly dispensed as a tablet, dispersible tablet, liquid, or liquid concentrate for oral administration. Additionally, it may be administered via sublingual (SL), intravenous,[20,21] rectal, subcutaneous (SC), epidural, or intrathecal routes. Given orally, methadone has

a bioavailability of 80 percent (range, 41 to 99 percent), whereas morphine's is approximately 25 percent. In palliative care, providing pain relief in the least invasive manner is preferred. The oral route is used when at all possible. Most lipophilic drugs such as methadone can be given via the SL route. Methadone's SL bioavailability can be 75 percent when taken with bicarbonates.[22] Methadone can be given rectally as a suppository or microenema solution. Microenema preparations of methadone can have onset of action at 30 minutes and duration of effect up to eight hours.[23] Rectal administration has the potential to provide increased bioavailability compared to oral routes; however, many palliative patients experience constipation or impaction. The presence of fecal material in the rectal vault can severely affect absorption. Although many patients may refuse this route of administration, it does provide an alternative in difficult clinical management situations. For patients who have no other means of pain control, such as in cases of bowel obstruction, hospice care uses SC routes for opioids in place of painful intramuscular or invasive intravenous routes. In these settings, SC is reserved for opioids such as morphine and hydromorphone. Methadone is usually not given SC, as it can cause adverse skin reactions and increased pain at the site of administration[24]; however, if needed, this route is available and useful. Dexamethasone added to the methadone syringe has been reported to increase the interval between changing the needle from 2.6 days in the methadone-only group to 4.9 days in the dexamethasone plus methadone group.[25] In particular cases in which acute inpatient hospice care is provided for intractable pain intolerant to other opioids, injectable methadone may have a strong role. Rotating patients onto injectable methadone in a hospitalized setting has been shown to be safe and effective.[26]

DOSING

There are many options for methadone dosing. Choice for dosing is dependent on the clinical scenario, ability to monitor a patient, and experience of the provider. Many clinicians are familiar with common methadone initiation strategies, but rotation with rapid titration is often fraught with confusion for providers due to differing published equianalgesic conversions and ratios. The following are some commonly accepted schematics.

Initiation

Methadone can be the initial opioid used to mitigate severe pain. Initial dosing can vary from 2.5 to 5.0 mg by mouth every four hours, as needed (p.r.n.), for several days. The total p.r.n. doses consumed over those days are then converted to scheduled doses, divided over every eight or 12 hours. An alternative to this consists of beginning with both scheduled and p.r.n. dosages. A recent prospective randomized trial by Bruera involving 103 patients compared the initiation of oral methadone 7.5 mg every 12 hours and 5.0 mg every four hours p.r.n for breakthrough pain versus slow-release morphine 15 mg twice daily and immediate-release morphine 5.0 mg every four hours p.r.n. for breakthrough pain in cancer patients.[27] The primary objective of the study was to evaluate the difference in pain intensity at four weeks. Methadone was not found to be superior to morphine and had higher dropout rates at eight days owing to side effects such as sedation, vomiting, and myoclonus. The investigators postulated that the true dose ratio between methadone and morphine may be lower than the ratio of 0.5 (7.5:15) used in the study. Moreover, they added that it is possible methadone is more toxic than morphine when it also is used as a breakthrough opioid at the doses used in the trial.

Opioid rotation

Often a clinician may find a need to rotate from one opioid, such as morphine, to another. For example, when a patient develops renal insufficiency, neurotoxic morphine metabolites may accumulate, leading to myoclonus. Switching from one opioid to another is a worthwhile strategy, because incomplete cross-tolerance between the two agents may mitigate better analgesia at a lower dosage with the second agent. Toxicity owing to methadone occurs more commonly among patients using high-dose opioids, not among the opioid naïve.[28] Cross-titration, consisting of discontinuing the current analgesic and beginning methadone, is done in a so-called slow or rapid manner.[29]

Slow rotation. Changes occur over three days for patients on > 100 mg morphine equivalent (ME) at baseline. A progressive substitution of one-third of the previous opioid, using an equianalgesic dose ratio based on the prior morphine dose, is used as follows:

- Day one: The current opioid is decreased by 30 to 50 percent over 24 hours. Equianalgesic methadone dosage is given orally or rectally, divided over every eight hours.
- Day two: The original opioid is decreased by another 30 to 50 percent. Scheduled methadone is increased if the patient has moderate to severe pain. Breakthrough pain is addressed with a rescue dose of short-acting opioids or methadone at 10 percent of the daily dose, given as frequently as every two hours if needed, up to three doses.
- Day three: The original opioid is discontinued.

Variations of this slow-rotation scheme are used around the world. Among patients on < 100 mg ME, however, rapid rotation is used.

The conversation ratio of morphine to methadone

Table 2. Equianalgesic ratios of oral morphine to oral methadone			
	Method	**Initial daily morphine equivalence**	**Morphine:methadone conversion ratio**
Model 1	slow route	0 to 1,000 mg per day	10:1
		> 1,000 mg per day	20:1
Model 2	stop-go	30 to 90 mg per day	4:1
		90 to 300 mg per day	8:1
		> 300 mg per day	12:1
Model 3[29]	fixed	< 400 mg per day	5:1
Model 4[30]	fixed	< 300 mg per day	10:1

varies inversely per the current magnitude of MEs. Various authors suggest differing equianalgesic ratios. Table 2 is adapted from work by Bruera and colleagues, Ripamonti and colleagues, and others. Of note, there are many additional equianalgesic tables not reported here.

Rapid rotation. The current opioid is completely and abruptly stopped. In a randomized trial using this method, there was a reported effectiveness of the stop-and-go method when rotating from morphine to methadone in patients with uncontrolled pain.[30] A dose ratio of 1:4 (1 mg of oral methadone = 4 mg of oral morphine) was used for patients receiving less than 90 mg of morphine. Patients receiving 90 to 300 mg per day received methadone at a ratio of 1:8. Finally, a ratio of 1:12 was used for patients receiving morphine doses greater than 300 mg per day. The authors concluded that higher doses of methadone are not dangerous initially, because the pharmacokinetics of methadone require priming before achieving a pharmacologic effect. Appropriate monitoring of methadone dosing is necessary in the days that follow, however, when methadone accumulation could occur and dosing may need to be reduced. Eighty percent of the patients were successfully converted using this method and had improved pain and adverse symptom reports (assessed via the self-reported Visual Analog Scale for pain and a self-reported four-item, 4-point Likert scale devised by the authors, respectively). Constipation was also noted to be less in the methadone group.

Fixed-dose rotation

Conversion to methadone is set at a fixed ratio. Mercadante examined the feasibility of a rapid substitution of morphine with methadone at 20 percent (ratio of 1:5) of the previous morphine dosage to assess if this could improve the opioid response in terms of global effect (i.e., balance between analgesia and adverse effects) in patients with poor pain control.[31] Most of the patients in this study were on lower-dose morphine (< 90 mg per day) and tolerated the switch with efficacious analgesia and low morbidity. It was noted that patients on higher doses of morphine (median, 256 mg) required methadone dose reduction. There is no significant literature support for use of this method among patients using high-dose morphine.

Morley offers an alternative fixed-dose rotation using one-tenth of the previous morphine dose with a maximum initial dose of 30 mg, dosed not more than every three hours.[32] After six days, the amount of methadone taken over two days is converted to a daily dose given in 12-hour intervals. Additionally, there are many more fixed-dose models that are reported among European communities but are not commonly used in the United States.

SIDE EFFECTS

As with all opiates, methadone can exhibit side effects that limit its use by the general community. Methadone is highly lipophilic and easily accumulates in tissues. Among clinicians naïve to methadone prescribing, this tissue accumulation can lead to iatrogenic sedation, respiratory depression, delirium, and seizures. Other reported adverse effects include constipation, hallucinations, QTc prolongation,[33,34] and torsades de pointes.[35] Reports of QTc prolongation in the literature have not been correlated with any linear relationship to the methadone dose. Currently, there are no consensus recommendations on electrocardiogram monitoring among cancer patients on chronic methadone therapy.

Additionally, sexual dysfunction and decreased sex hormone levels have been reported with chronic methadone use. A clinical trial of heroin addicts treated with a single daily dose of methadone reported decreased levels of testosterone and increased levels of erectile dysfunction.[36] Additionally, a study of 92 opioid-dependent men using methadone surveyed reported a direct correlation with increased orgasm dysfunction and methadone dose.[37]

COSTS

Methadone is generally reported to be less expensive

than other long-acting opiates. As of 2004, methadone costs a fraction of sustained-release morphine, oxycodone, or transdermal fentanyl.[8] Sample wholesale prices for morphine sulfate controlled-release tablets (MS Contin, Purdue Pharma LP, Stamford, CT) at 100 mg every 12 hours for one month averages $328, whereas methadone hydrochloride (Methadose, Mallinckrodt, Inc., St. Louis, MO) 40 mg every 12 hours for the same period averages $17. With the availability of methadone in scored form, it can be easily fractionated, which further decreases the financial costs in most formulary-limited hospice systems.[38]

CONCLUSION

Methadone is an old drug that is increasingly providing new meaning among the pain community. It can be a powerful tool in the treatment of terminal pain symptoms. With knowledge of its pharmacokinetics, drug interactions, and variable equianalgesic potency, it can prove a powerful analgesic in our armamentarium against end-of-life pain.

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