Review article: Perioperative pain management of patients on methadone therapy

[Exposé de synthèse : Traitement de la douleur périopératoire chez les patients sous thérapie à la méthadone]

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Purpose: Methadone, an opioid traditionally associated with the management of opioid addictive disorders, has been prescribed increasingly as an analgesic for the management of various chronic pain conditions. Despite the increasing popularity of methadone, most anesthesiologists are not familiar with its complex pharmacology. The purpose of this article is to review the pharmacology of methadone and to suggest a management algorithm for the perioperative care of methadone patients.

Source: A Medline search was performed to obtain the published literature on the pharmacology of methadone and its use perioperatively.

Principal findings: The complexity of methadone's pharmacology is characterized by a high inter-individual variability, a potential for interaction with other medications, and a long elimination half-life. The postoperative management of methadone patients may be difficult as they are often 'opioid-tolerant' but may be 'pain-intolerant'. For those patients who are taking part in methadone-maintenance programs, there is a potential for the problematic use of opioids or other substances. The management plan for patients taking methadone may differ depending on the type of surgery and the associated perioperative differences in fasting status and gastrointestinal function. In consideration of all the factors listed above, a management algorithm is outlined for the perioperative care of methadone patients.

Conclusion: Methadone is an opioid with complex properties, and a patient that is taking methadone can represent a unique challenge to the anesthesiologist. A good understanding of the pharmacology of methadone and of the type of patients on this medication will help to improve their perioperative care.

Objectif : *La méthadone, opiacé habituellement associé au traitement des dépendances aux opiacés, est prescrite de plus en plus comme analgésique pour diverses douleurs chroniques. Malgré sa popularité croissante, la plupart des anesthésiologistes n'en connaissent pas la pharmacologie complexe. Nous avons revu la pharmacologie et recommander un algorithme de traitement périopératoire pour les patients traités avec la méthadone.*

Source : *Une recherche dans Medline a été réalisée pour obtenir les publications sur la pharmacologie de la méthadone et son usage périopératoire.*

Constatations principales : *La complexité de la pharmacologie de la méthadone est caractérisée par une grande variabilité inter-individuelle, un potentiel d'interaction avec d'autres médicaments et une longue demi-vie d'élimination. Le traitement postopératoire des patients sous méthadone peut être difficile, car ils présentent souvent une «tolérance aux opiacés», mais ils peuvent être «intolérants à la douleur». Dans les cas de traitements d'entretien à la méthadone, il y a des problèmes possibles avec l'usage d'opiacés ou d'autres substances. Le plan de traitement des patients sous méthadone peut différer selon le type de chirurgie et les différences périopératoires associées de l'état de jeûne et de la fonction gastro-intestinale. En considérant tous ces facteurs, un algorithme de traitement est tracé pour les soins périopératoires des patients sous méthadone.*

Conclusion : *La méthadone est un opiacé aux propriétés complexes et l'anesthésie d'un patient sous méthadone peut représenter un grand défi. Une bonne connaissance de sa pharmacologie et du type de patients qui en consomment aidera à améliorer les soins périopératoires.*

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METHADONE, a synthetic long-acting opioid, has been used since the 1960's for the stabilization and maintenance of patients suffering from addictive disorders.[1,2] Because of this lengthy association with opioid addiction, methadone carries a negative connotation with the public. However, it has recently been 'rediscovered' as an analgesic in the treatment of chronic pain[2] and cancer pain.[3] A recent survey revealed that the prevalence of chronic pain in Canada is 29%. Of those chronic pain sufferers taking medications, 22% take opioids as an analgesic.[4] Because of its various advantages (Table I), it is estimated that the use of methadone for chronic pain patients will increase.[2,5]

A recent survey of Canadian anesthesiologists practicing chronic pain management reveals that less than 6% of respondents are prescribing methadone.[6] This lack of familiarity with methadone within the anesthesiology community can lead to difficulties in the perioperative management of these patients. Patients admitted to the hospital on methadone treatment can present a challenging problem due to tremendous inter-individual variability in pharmacokinetics, lack of reliable equianalgesic conversion ratio to other opioids, and the potential for multiple drug interactions.

The purpose of this article is to review the pharmacology of methadone and to apply this knowledge in order to develop a strategy for the perioperative management of methadone patients.

TABLE I

Advantages of methadone
- Inexpensive compared to other long acting opioids
- Intrinsically a long-acting opioid; leading to stable inter-dose opioid levels
- High oral bioavailability
- Lack of any significant active or toxic metabolites
- Does not accumulate with renal insufficiency. Effective in hemodialysis patients
- Non-opioid pharmacology such as NMDA antagonist activity and prevention of re-uptake of serotonin and norepinephrine
- Can be taken as a liquid or pill form orally
- Liquid formulation allows for easy dose adjustments by pharmacy
- 'Relatively' low street value as an illicit drug, especially when dispensed as a liquid in flavoured drink

Disadvantages
- Highly variable metabolism related to the cytochrome P450 system leading to a long and unpredictable half-life
- Potential for accumulation and overdose during titration
- Unpredictable equianalgesic potency compared to other opioids
- Variable protein binding related to AAG levels
- Social stigma because of its association with drug addiction treatment
- Parenteral formulation not available in Canada
- Subcutaneous route associated with localized adverse reactions[52]
- High doses and *iv* formulation carries potential risk of QTc interval prolongation and Torsades de pointes

NMDA = N-methyl-d-aspartate; AAG = α_1 acid glycoprotein.

Use of methadone in Canada and the United States

In Canada, as well as many other countries in the world, methadone is a uniquely controlled substance. Physicians who wish to use methadone in their practice must seek an exemption under section 56 of the Controlled Drugs and Substances Act. Exemptions for treating pain and/or addiction are granted under federal authority by the Office of Controlled Substances. However, exemptions to prescribe methadone for methadone maintenance therapy (MMT) are typically made upon recommendation of the provincial medical authorities. Similarly, exemptions to prescribe methadone for pain have been delegated to the provincial level in four provinces: British Columbia, Alberta, Quebec and Manitoba. As of 2003, the total number of physicians in Canada actively prescribing methadone for pain was 1,368, a significant increase compared with 396 in 1998. (Personal communication, Kim Barber, Office of Controlled Substances, Health Canada).

If a MMT patient is admitted to hospital, a physician can obtain an emergency, temporary license after contacting the Office of Control Substances. However, the license is specific for that physician, patient and institution and will expire following the discharge of that patient or after a period of two months. These temporary exemptions allow for continuation rather than initiation of methadone.

In the United States, methadone is considered a schedule II drug according to the drug Enforcement Agency (DEA) Schedule of Controlled Substances. Schedule II drugs are those the DEA considers to carry the highest potential for physical or psychological dependence and abuse. Other examples of schedule II drugs include morphine, meperidine, codeine, and fentanyl. Any of these medications can be prescribed by a DEA licensed Health Care Professional. In this sense, methadone used for the treatment of pain is regulated no differently than any other schedule II drug. In the United States, the use of methadone for the treatment of opioid addiction is highly restricted and in a state of transition. Since the Harrison Narcotic Control Act of 1914, it has been illegal for physicians in the United States to supply patients suffering from opioid addictive disorders opi-

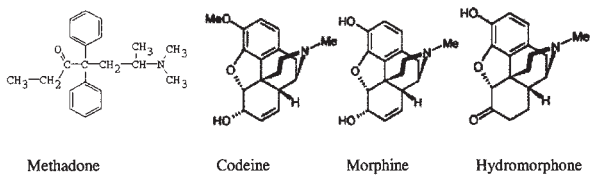

FIGURE 1 Chemical structures of different commonly used opioids and methadone.

oids for the treatment of their addiction. At the present time, the majority of practitioners who prescribe methadone for use in MMT models do so under the institutional authority of a narcotic treatment program. Pilot projects for methadone maintenance in the office-based setting are underway in several sites. The preliminary results are encouraging.

Basic pharmacology

General

Methadone was developed as an analgesic by German scientists, and began clinical trials under the code name "Amidone" in 1942. There is no evidence that it was ever available in large enough quantities to have been used in WWII. Only after its arrival in the United States in 1947 did it take on the name of 'methadone'. Methadone is a synthetic opioid and its structure is quite different from the opium-derived alkaloids such as morphine (Figure 1). Formulated as the hydrochloride powder, it can be reconstituted for oral, rectal or parenteral administration. When used in methadone maintenance for the treatment of opioid addiction, the oral stock solution is often mixed with orange drink or cherry syrup to deter aberrant use via the parenteral route. In Canada, it is also available as a prepared oral solution and more recently, in tablet form (Metadol® Pharmascience, Montreal, QC, Canada). In the United States, the liquid preparation of methadone hydrochloride for injection (10 $mg \cdot mL^{-1}$) is also available (aaiPharma, Wilmington, NC, USA) and can be administered via the *iv*, *im* or *sc* route. However, the FDA has only given approval for the *sc* and *im* routes.[7] There are reports of methadone being used for its analgesic properties by continuous epidural administration in children as well as adults.[8,9] Intrathecal analgesic use has also been reported.[10,11]

Methadone, a lipophilic basic drug (pKa 9.2), exists as a racemic mixture of two enantiomers, R-methadone (R-Met or l-isomer) and S-methadone (S-Met or d-isomer). R-Met is a potent mu and delta opioid-receptor agonist. Methadone in the form of the isolated R-Met (l-isomer) is available in Germany.[3,12] The S-Met enantiomer is inactive as a μ agonist. Nonetheless, it is a non-competitive N-methyl-d-aspartate (NMDA) antagonist and prevents 5-hydoxytryptamine and norepinephrine reuptake.[2,5] The effect on NMDA contributes to methadone effects on neuropathic pain and mitigation of opioid-induced tolerance.[13] The degree of NMDA antagonism produced by methadone is similar to that of ketamine.[14]

Methadone is characterized by its high inter-individual variability. A good understanding of the pharmacokinetics and pharmacodynamics is imperative to the safe use of this medication.

Pharmacokinetics

Following oral administration, time to achieve peak plasma drug concentration is 2.5 hr and three hours for methadone in solution and in tablet form respectively.[15] The oral bioavailability is 85% (range: 67–95%), which is three times that of morphine.[13] Although there is no data of tissue distribution for methadone in humans, the distribution to various tissues has been shown to be extensive in animal models. This is consistent with the high volume of distribution in humans (4.2–9.2 $L \cdot kg^{-1}$ in opioids addicts and 1.7–5.3 $L \cdot kg^{-1}$ in chronic pain patients).[16,17]

At physiological pH, 86% of methadone is bound to plasma proteins, predominately to α_1-acid glycoprotein (AAG). AAG is an acute-phase reactive protein and the plasma level fluctuates with various physiologic and pathologic conditions such as stress, opioid addiction, cancer, and concomitant administration of certain medications. The clinical implication of increased levels of AAG is that such an individual may be protected from the toxic effects of a dose of methadone as compared to a healthy casual user of methadone that would not have elevated levels of AAG.[15]

Unlike morphine, methadone is biotransformed rather than conjugated in the liver and at daily doses less than 55 mg, the majority of the metabolites are cleared via the fecal route. Methadone is metabolized by the type I cytochrome P450 group of enzymes. The main enzyme responsible for N-demethylation of methadone is CYP3A4, with lesser involvement from CYP1A2 and CYP2D6.[2,18] Current evidence suggests that CYP2B6 may play a very significant role in metabolism as well.[19] The main product of N-demethylation, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), is inactive. The activities of these cytochrome enzymes, especially CYP3A4, can be induced or inhibited by other drugs or by the methadone itself, accounting for

TABLE II Interactions of methadone with other medications or medical conditions

Mechanism	*Drugs or conditions*	*Consequence*
Cytochrome enzymes induction*	Antiviral agents: nevirapine, ritonavir Anticonvulsants: carbamazepine, phenobarbitol, phenytoin Antituberculosis agents: rifampicin Antiobiotics: fusidic acid Chronic alcohol ingestion and smoking	Increase clearance, resulting in poor analgesia and may precipitate withdrawal
Cytochrome enzymes inhibition*	Antifungal agents: fluconazole, ketoconazole SSRI: fluvoxamine, paroxetine, fluoxetine† Acute alcohol ingestion	Decrease clearance, resulting in increased serum levels
Competition for cytochrome enzymes*	Tricyclic antidepressants: desipramine	Increase desipramine level
Pharmacodynamic interaction	Benzodiazepine:	↑respiratory depression & sedation
↑plasma level of AAG	Stress reactions, cancer, opioid addiction and concurrent administration of amitriptylline	Inadequate analgesia or withdrawal
Unknown mechanism	Neuroletpics: resperidone	Precipitate withdrawal

*Different medications may induce or inhibit specific cytochrome enzyme subtypes, in which CYP3A4 plays a major role. For simplicity, the drugs are grouped according to the overall effects on the whole cytochrome enzyme system rather than a specific enzyme subtype.
†See text on the details of effects of SSRI on methadone. AAG = α_1-acid-glycoprotein; SSRI = serotonin selective re-uptake inhibitors.

the large individual variations in methadone pharmacology (refer to section on drug interaction). While the primary metabolite of methadone is inactive, methadol and normethadol are two minor metabolites produced in small amounts that have similar pharmacologic activity to methadone.[15,20]

Renal excretion is variable and is pH dependent. At a urine pH above 6, renal clearance is only 4% of the total drug elimination. When urine pH drops below 6, the unchanged methadone excreted by the renal route is approximately 30% of the total administered dose. Despite this, methadone does not accumulate in patients with renal failure and is poorly removed by hemodialysis.[2,5,15] The renal excretion of the primary metabolite, EDDP is not pH dependent.

Methadone undergoes a biphasic pattern of elimination: slow distribution or α-elimination phase (8–12 hr) and a ß-elimination phase (30–60 hr). The α-elimination correlates with the duration of analgesia that is typically six to eight hours.[2,13] The plasma level in the ß-elimination phase is subanalgesic but is sufficient to prevent withdrawal symptoms. Thus, it accounts for the three or four times daily dosing typically needed when prescribed for analgesia compared to the once a day dosing used in MMT.

Interactions of methadone with other medications

CYP3A4 has been the major enzymatic subtype described in methadone metabolism although recent evidence suggests an even bigger role for CYP2B6.[19] There is a tremendous inter-individual variability in cytochrome P450 activity and this variation can be attributed to genetic polymorphism as well as the profound alterations due to certain medications (Table II).

It is not uncommon for a methadone patient to be taking a concomitant medication such as a tricyclic antidepressant, selective serotonin re-uptake inhibitor (SSRI) or anticonvulsant. A SSRI will inhibit the activity of all three hepatic enzymes, i.e., CYP3A4, CYP1A2 or CYP2D6. The activity of CYP3A4 is inhibited by nefazadone, fluvoxamine, paroxetine, fluoxetine and sertraline in this descending order of potency. Both fluoxamine and paroxetine are potent inhibitors of CYP2D6.[21] Carbamazepine, phenobarbital and phenytoin are potent inducers of CYP3A4.[5] Co-administration of these drugs can significantly decrease the plasma level of methadone and precipitate withdrawal in those who are physically dependent. Furthermore, both carbamazepine and methadone can induce their own metabolism in a time-dependent fashion via CYP3A4. Gabapentin and valproic acid have not been shown to interact with methadone.[5,22,23] It is important to remember that although many CYP 450 drug interactions are possible, the significance in any given patient may or may not be clinically important.

Since methadone dose is titrated to effect, it is tempting to think that drug interactions are of limited significance. In some cases, it may not be the addition of a CYP 450 active drug that causes problems but rather the discontinuation of the active inhibitor or inducer. If a patient is titrated to effect with methadone while on a stable dose of a potent CYP3A4 enzyme inducer such as carbamazepine, discontinuation of the inducing agent may result in a clinically significant elevation in serum concentration of methadone as the patient returns to his/her pre-

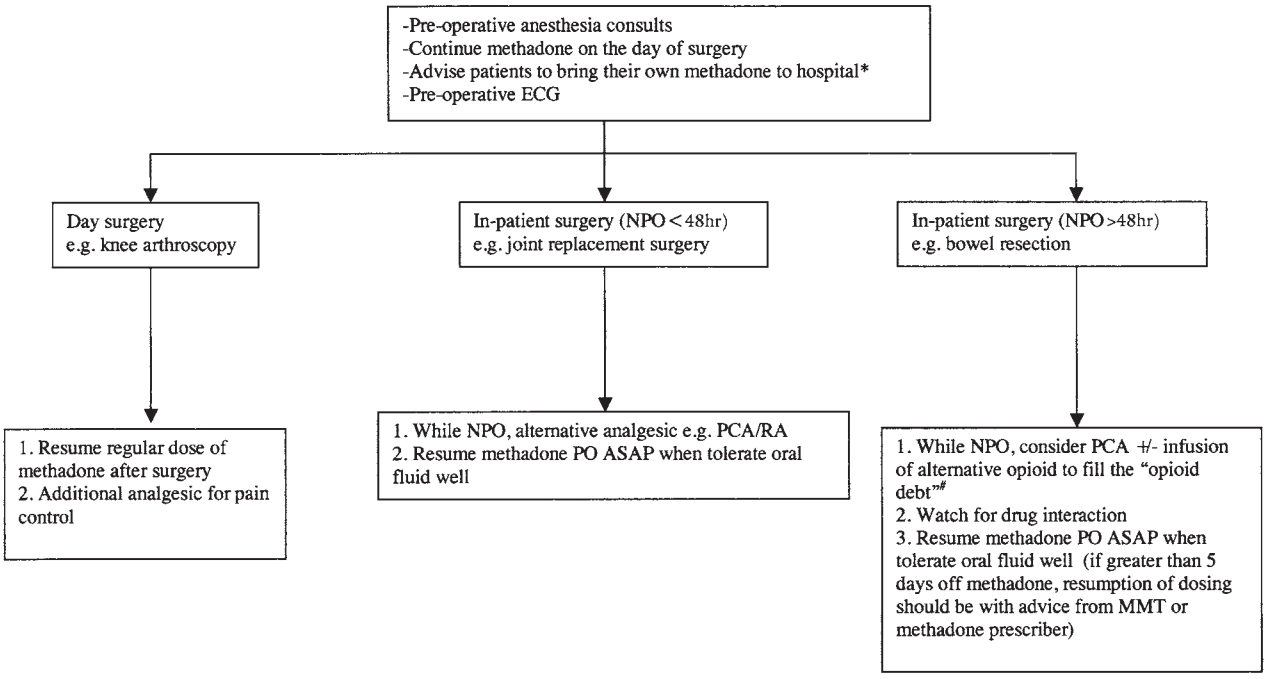

FIGURE 2 Algorithm of managing methadone patients for elective surgery in the perioperative period.

induced metabolic state. In a similar fashion, discontinuation of a potent CYP3A4 enzyme inhibitor such as fluvoxamine or erythromycin may lead to clinically significant reductions in methadone due to an apparent rapid metabolic state as the previously inhibited 3A4 pathway normalizes.

Drug interactions may also occur independently of the cytochrome system. One mechanism of drug interaction is related to AAG, an acute-phase reactant protein. The circulating levels of AAG may be elevated with concurrent administration of medications such as amitriptyline.[17,24] Elevated AAG levels may decrease the effects of methadone leading to inadequate analgesia. Another mechanism is related to the co-administration of a benzodiazepine, a potential respiratory depressant exerting its inhibitory effect through γ-amino-butyric acid (GABA) receptors. Generation of the respiratory rhythm requires phasic activation and inhibition. Within the respiratory centre, the neurotransmitters for excitation and inhibition are mediated through excitatory amino acids such as NMDA and GABA receptors respectively.[25] Concurrent administration of a benzodiazepine and methadone can result in enhanced GABA-mediated inhibitory activity and reduction of NMDA-mediated excitatory activity. Fatal overdose from this drug combination has been reported.[5]

Risk of improper use of methadone in the perioperative setting

Improper use of methadone can potentially result in either a life-threatening overdose or withdrawal phenomena associated with inadequate analgesia. In general, such complications result from one of the following improper uses of methadone.[26]

Single-dose overdose

In the opioid-naïve adult, a single oral dose of methadone in excess of 40 mg has resulted in death.[27] Patients currently on methadone likely have developed some tolerance to all opioids although cross tolerance is variable. However, medication errors can occur when methadone patients receive their methadone dose while hospitalized in the postoperative period. In general, most of the medication errors occur at the stages of ordering and administration.[28] Most of the patients who take methadone in liquid form for pain management do so at a fixed concentration such as 5 $mg \cdot mL^{-1}$. While most physicians describe the dose in mg, many patients communicate in mL. A miscom-

munication in the concentration can potentially result in overdose. In the case of MMT patients, the standard is to dispense a quantity of drug diluted to a fixed volume of 100 mL. As such, there is no specific concentration of methadone used in this setting.

Accumulated toxicity

Unlike morphine or other short-acting opioids commonly used in the postoperative setting, methadone has a very long elimination half-life, even though its duration of action as an analgesic is markedly shorter. Therefore, life-threatening complications may not result from any one single dose but rather from the accumulation of previous doses.[26] This is typically seen in overly aggressive dose titration. The phenomenon of accumulation is not seen with sustained-release preparations (e.g., MS Contin® or OxyContin®) of relatively short-acting agents. In the management of acute postoperative pain, extreme caution should be exercised to titrate the methadone dose according to its analgesic effect while monitoring for signs of sedation, which may be due to methadone accumulation.

Drug-drug interaction

During the perioperative period, medications may be added that can adversely interact with methadone. Sedative-classes of drugs are the most obvious example of medications that can increase the depressant effects of methadone. In some cases the drug interaction occurs not by the addition of a CYP450 active drug but rather through the discontinuation of such an agent.

For example, in the case of the discontinuation of a potent inhibitor such as erythromycin, methadone levels may fall significantly over a matter of days due to a relative increase in methadone metabolism as the 3A4 inhibiting effects of erythromycin abate. This may lead to a state of relative opioid withdrawal, which will make pain management more difficult.

Perhaps more dangerous is the situation when a potent inducer such as rifampin or carbamazepine is discontinued. In this case, the patient will become a relatively slow metabolizer as the 3A4 pathway falls back to its normal metabolic rate. What was previously an adequate dose of methadone may now become excessive leading to clinically significant sedation and respiratory depression.

Suggested algorithm for managing methadone patients in the perioperative period

Preoperative assessment

A preoperative consult is necessary for patients on methadone for chronic pain or MMT. All patients on methadone, whether for MMT or pain management, should continue the dose before and on the day of the surgery to avoid unnecessary fluctuations of the drug level (Figure 2). The practice of abrupt discontinuation of methadone before surgery is unjustifiable.

Patients who present to the hospital and are part of a MMT program pose a particular challenge since they may be at risk of relapse, are often 'opioid tolerant' and yet 'pain-intolerant'.[29,30] Whenever possible a history pertaining to dose, frequency of ingestion, time of last dose and in the MMT patient, level of stability (as indicated by take-home dose level), should be obtained. This information will help in the assessment of opioid tolerance. It is imperative to take a detailed history from these patients and establish a good rapport. In some cases, patients may not be taking their medication as directed. Unfortunately, a minority of patients may be diverting some or all of their methadone for sale or trade. In questionable cases, a portion of the MMT dose may be given repeatedly over the course of a day rather than simply giving a large, potentially dangerous single dose until actual drug tolerance can be established. It has been our experience that these patients appreciate honesty and a clear description of expectations both from the surgical service and the nurses. These patients also appreciate a direct line of communication with the Acute Pain Service whom they see as a valued resource. Some of these patients may have ingested illicit drugs prior to coming to the hospital and thus a urine drug screen, complete blood count, electrocardiogram, liver and renal function tests may be indicated. MMT patients may be able to recount successful analgesia regimes from previous admissions for surgery and reviewing old charts may assist in determining how opioid tolerant these patients have been. With patients on MMT, especially those who are relatively unstable, poly drug use is the norm. In these cases, a detailed history of recent benzodiazepine use can be helpful to prevent a potentially complicated postoperative sedative withdrawal syndrome from occurring. During the hospital stay, communication with the MMT program will facilitate follow-up and discharge planning. Thus, it is advisable to obtain a contact number for the MMT program before admission for patients expected to stay in hospital for a few days. It is also important to contact the dispensing pharmacy whenever possible to establish the time and date of the last actual dose consumed.

Patients on higher doses of methadone may develop a prolonged QT interval, which may then lead to the development of Torsades de pointes.[31] The risk appears to be greatest with the following conditions: *iv* administration of methadone, oral administration of doses greater than 200 mg·day^{-1}, and medical condi-

tions or medications that predispose patients to QTc interval prolongation.[7A] Medications to be aware of perioperatively include chlorpromazine, clarithromycin, disopyramide, erythromycin, haloperidol, amiodarone and some of the other antiarrthymic agents that are known to increase QT interval. A preoperative electrocardiogram and vigilance are recommended when dealing with patients on high doses of methadone, especially in patients who are debilitated or have cancer.

Postoperative pain management

It is not advisable to adjust the methadone dose in these patients, so alternate opioids are used for pain control and then tapered as clinically indicated according to the expected convalescence.[29] The exception to this would be the case where the patient's regular MMT dose of methadone has been interrupted for five or more days.[32] In these cases, the patient should be restarted on methadone by a practitioner knowledgeable in MMT induction, since there may be a marked change in methadone tolerance as a result of this period of methadone abstinence. Cross-tolerance with other opioids is unreliable, so it cannot be assumed that a patient on even large doses of an alternative opioid will tolerate their original methadone dose.

The use of regional anesthetic techniques for pain control is encouraged, but these patients will often also request the systemic administration of opioids. These patients may have persistently high pain scores despite all interventions and so alternate measures of analgesia may be necessary to facilitate postoperative rehabilitation such as ability to deep breathe, cough and ambulate. Patients may lose faith in their postoperative pain management plan, especially if they experience any degree of opioid withdrawal due to inadequate dose equivalence as may be seen in the fasting patient who is switched to another opioid due to their inability to ingest their regular daily dose of oral methadone.

An opioid agreement may be necessary to make the treatment plan with opioids explicit. In this case, the expectations for how long opioid analgesics will be provided, a plan for discontinuing these medications, outpatient contact numbers and follow-up should be discussed. It is important to use analgesic and adjunctive agents appropriately. Use of short acting immediate-release opioids should be limited to a minimum to control pain occurring with activity; sustained-release preparation of opioids are used to manage the pain preferentially in opioid tolerant patients. In general, in the outpatient setting, it is wise to avoid drugs that previously proved problematic for the patient. Some patients will need outpatient dispensing of medications on a daily or every other day basis, especially if there is no reliable third party at home to help regulate medication intake. These patients often need close follow-up as outpatients compared to the usual postoperative patient, especially if they require the use of high doses of long acting opioids. The Acute Pain Service may need to give advice to the primary care physician and/or the MMT program physician. In some cases, the patient may need to be referred to a pain and addiction medicine specialist. In Ontario, a telephone consultation with the Addiction Clinical Consultation Service of the Centre for Addiction and Mental Health may suffice.[B]

Patients undergoing an ambulatory or day surgical procedure can resume their regular dose of methadone following discharge on the same day without experiencing withdrawal symptoms. They should be treated as other opioid-tolerant patients and be prescribed pain medication on discharge appropriate for the type of surgery they received, although tighter limits may be necessary (Figure 2). Since a preadmission dose of methadone offers nothing in the way of acute pain relief, and likely leads to a decrease in the pain threshold,[33] additional opioids will often be necessary depending on the clinical scenario and the presence of opioid responsive pain.

Patients receiving surgery as in-patients should resume oral methadone as soon as they can tolerate *po* fluids well (Figure 2). Because of its long half-life, withholding methadone for one or even two days is unlikely to result in withdrawal. However, alternative analgesia is required as the duration of analgesia from a dose of methadone is six to eight hours. During the period of fasting in the postoperative period, patients should receive alternative analgesia such as *iv* patient-controlled analgesia (PCA) or regional analgesia/anesthesia. Alternative opioids are usually necessary to prevent the development of an "opioid debt" (see below) although methadone can also be administered via nasogastric tubes or even rectally.[3] Alternatively, with dose adjustment, *iv* methadone can be used if available.

When the patient is unlikely to resume *po* intake within 48 hr (Figure 2) and the administration of an

A aaiPharma product monograph.

B 1-888-720-2227 is a warm-line answered Monday through Friday, 9 to 4 p.m. out of the Centre for Addiction and Mental Health, 33 Russell Street, Toronto, Ontario M5S 2S1, Canada.

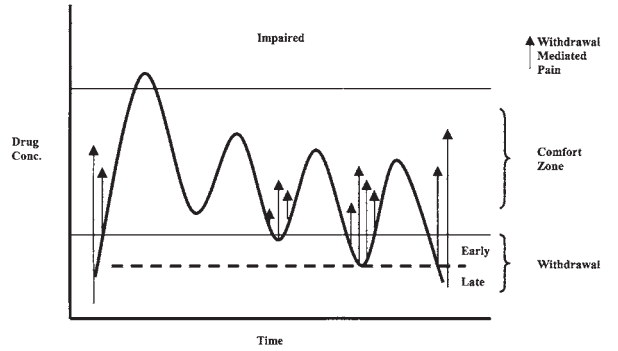

FIGURE 3 Discontinuation of opioids in a opioid-tolerant patient will result in a lowering of the opioid plasma level below the "comfort zone" and may lead to either early (subjective) or late (objective) withdrawal, thus amplifying the patients perceptions of pain.

alternative opioid is considered, PCA is the preferred method. Analgesic efficacy of PCA compared with traditional *im prn* opioid administration is well established.[34] Addition of a background infusion to the on-demand bolus is not commonly used with PCA, because it does not necessarily improve analgesia and sleep.[35,36] On the other hand, it increases the overall opioid consumption and contributes to a higher incidence of side effects such as sedation and respiratory depression.[34,37] Addition of a background infusion is usually considered for patients with known pre-existing opioid tolerance.[34]

Patients who regularly use opioids are likely opioid tolerant and may be predisposed to the development of an "opioid debt" preoperatively if their previous daily opioid requirements are not met. "Opioid debt" may be thought of as the daily amount of opioid medication required by an opioid dependent patient to maintain their usual, pre-hospitalization opioid levels. Discontinuation of opioids in a patient who is opioid dependent will result in a lowering of the opioid plasma level below the "comfort zone" into either early (subjective) or late (objective) withdrawal (Figure 3). Furthermore, abnormal pain sensitivity such has hyperalgesia has been observed in association with opioid withdrawal.[38] PCA is designed to maintain analgesia, not to establish analgesia.[34] In opioid tolerant patients, if the "opioid debt" is not covered, the repeated bolus doses from a PCA pump are unlikely to achieve an analgesia effect (Figure 4a). A background infusion should be considered in opioid tolerant patients currently on a high dose of opioid therapy (Figure 4b). Therefore, we advocate loading the opioid tolerant patient with opioids in the operating room as the patient is awakening from surgery. At our institution, hydromorphone is used in place of morphine if patients have a history of morphine intolerance or allergy. Hydromorphone may also be utilized if the patient comes to the hospital on high doses of another opioid as part of an opioid rotation. Opioid tolerant patients who undergo major surgery are often administered a low dose of intraoperative ketamine ($0.25\ mg{\cdot}kg^{-1}$ *iv*, up to 20 mg) for the potential reduction in opioid tolerance and improved postoperative pain control.[39,40]

In countries other than Canada, methadone can be administered via *iv* PCA.[12,41] Similar PCA settings as morphine can be used initially as the analgesia from an *iv* dose of methadone occurs within three to four minutes.[17] Further, there is evidence that a single loading dose of up to 20 mg intravenously can provide prolonged analgesia without postoperative respiratory depression.[42–44] Details of *iv* use of methadone will not be reviewed here but interested readers may refer to a recent review article on this subject.[45] A recent report found that substantial histamine release occurred in two of 23 patients administered a 20 mg *iv* methadone bolus without hemodynamic sequelae.[46] With the added concern over QTc interval prolongation (see above) and the possibility of drug accumulation with repeated doses, one has to be particularly careful when administering methadone intravenously.

Conversion of methadone to other opioids

Changing from methadone to another opioid is a complex conversion, which requires close follow up of the patient to ensure efficacy and lack of toxicity. The authors recommend consultation with a pain clinician, especially when dealing with opioid conversions involving high doses of opioids (e.g., greater than 150 mg per day of oral morphine). The equianalgesic conversion for methadone to other opioids is known to be less predictable when compared with conversions between other opioids.[47] The conversion ratio from morphine to methadone is usually quoted as being 1:1. This data was obtained from single dosing studies that were performed more than 20 years ago.[2] Recent studies suggest that methadone is more potent than it was originally thought, with a median morphine to methadone ratio of 7.75:1 (2.5:1 to 14.3:1).[22] When converting morphine to methadone, the ratio is highly variable and is dependent upon the previous morphine dose. Patients receiving higher doses of morphine were more sensitive to the analgesic effects of methadone.[22]

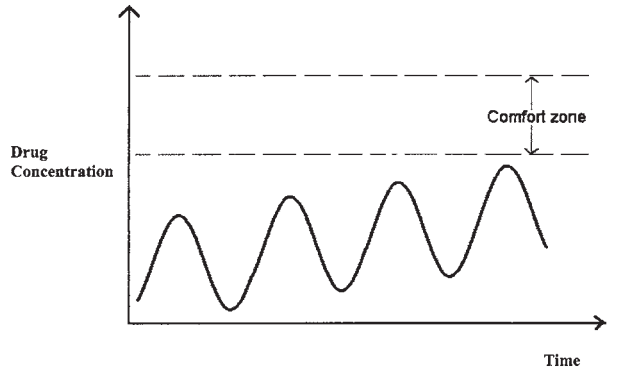

FIGURE 4a Repeated boluses of opioid from patient-controlled analgesia fail to achieve analgesia in opioid-tolerant patients when the "opioid debt" is not filled.

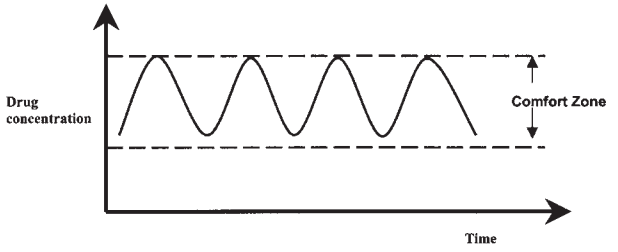

FIGURE 4b With continuous infusion to fill the normal opioid requirement, repeated opioid doses keep the plasma opioid level within the comfort zone.

When converting methadone to other opioids in the postoperative period, two issues need to be considered. The first is the incomplete tolerance between opioids, the second is that the conversion ratio between opioids is not bi-directional.[13,48] Conversion of methadone to other opioids appears to be more problematic[49] and is associated with worsening pain and dysphoria. Since there is no uniformly accepted conversion ratio for substituting methadone with another opioid, a conservative approach should be adopted. In the authors' experience, a conservative methadone to morphine ratio (4 or 5:1) is used. For instance, a patient previously on 30 mg methadone per day will be equivalent to roughly 120 mg oral morphine per day. Factoring the oral bioavailability (33%) and a 50% cross-tolerance, the hourly morphine requirement is approximately 1 mg·hr^{-1} intravenously. On the first day, the maximum background infusion rate of morphine should not exceed 3 mg·hr^{-1} due to the highly unpredictable nature of the equianalgesic conversion. A PCA device is used separate from the *iv* infusion if there is an underlying pain condition. After the patient is loaded with adequate amounts of morphine, reassessments of pain, sedation and respiratory rate are made at least once every two hours as the patient approaches a steady state with the morphine and as the methadone continues to clear from their system. The ward nurses and clinicians looking after the patient are informed of the patient's unique requirements.

Conclusion

In summary, methadone is a unique opioid that is used to treat opioid addiction as well as a number of pain conditions including chronic non-cancer[50] and cancer pain.[3] Recent attention has served to highlight its use in neuropathic pain as well.[50] Methadone has also demonstrated good utility in cases of opioid tolerance and in situations where an opioid rotation serves to assist in difficult to treat pain states.[41,51] The use of methadone perioperatively takes special care and attention to detail in order to avoid inadequate analgesia or adverse effects including sedation and respiratory depression. Pain clinicians who use methadone as part of their armamentarium can attest to its utility as a second line opioid. Hopefully, anesthesiologists who treat patients on methadone will appreciate the unique properties of this analgesic, and understand how to deal best with the perioperative needs of these patients.

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