Methadone is an old drug, first introduced in the U.S. in 1947 by Eli Lilly & Company as an analgesic.\(^1\) It works by occupying the brain receptor sites affected by heroin and other opioids.\(^2\) In the early 1960s, methadone was developed as an alternative to heroin in so-called methadone maintenance treatment (MMT) programs.\(^3\) Today, there has been renewed interest in pain management associated with various chronic disorders, especially cancer, and end-of-life care. This column explores clinical risk-management and P&T committee considerations regarding methadone analgesia and presents two real-world scenarios that illustrate these topics.

**METHADONE IN THE TREATMENT OF CHRONIC PAIN**

Methadone is a potent, long-acting opioid analgesic.\(^4\) Its use was once limited almost exclusively to the treatment of narcotic addicts who had voluntarily submitted to detoxification. This restriction was removed in 1976; physicians with appropriate Drug Enforcement Agency registration may now prescribe methadone for analgesia.\(^3\)

The unique pharmacokinetic and pharmacodynamic characteristics of methadone make it a valuable option for the management of chronic pain both as a first-line agent and as a replacement opioid.\(^1,4\) Even though methadone may be administered by several routes—oral, rectal, intravenous, intramuscular, subcutaneous, epidural, and intrathecal—it is most commonly given orally in either tablets or solution.\(^1,5\)

Numerous evaluations of methadone, including placebo-controlled clinical trials, have shown that it is an effective analgesic in cancer pain and in chronic non-cancer pain.\(^1\) Its pharmacological properties, however, demand greater precautions than are necessary with other opioids.\(^5\)

Methadone has a long-elimination half-life (8–59 hours),\(^7,8,9\) which might not correlate with its duration of analgesic efficacy (typically 8–12 hours with repeated dosing).\(^1\) This pharmacokinetic property necessitates careful management and titration of effective dosing schedules, because the mismatch of half-life and duration of analgesia is potentially life-threatening.\(^10\)

Day-to-day monitoring is essential when chronic methadone therapy is initiated or when patients are switching from another opioid to methadone for pain relief.\(^1\)

**METHADONE AS A THERAPY FOR OPIOID DEPENDENCE**

Methadone is the most commonly used medication for substitution therapy of opioid addiction (morphine or morphine-like drugs).\(^5\) Substitution therapy has been defined as “the administration under medical supervision of a prescribed psychoactive substance, pharmacologically related to the one producing dependence, to people with substance dependence, for achieving defined treatment aims.”\(^6,5\) Substitution maintenance therapy with methadone (MMT) has been shown to reduce illicit drug use, mortality rates and criminality associated with drug use, and the risk of the spread of human immuno deficiency virus (HIV) infection associated with opiate injection.\(^2,3,5\) MMT also improves physical and mental health as well as social functioning in patients with opioid addiction.\(^2,3,5\)

Methadone is useful in substitution therapy for the following reasons; namely, it: \(^2\)

- blocks the euphoric and sedating effects of opiates.
- relieves the cravings for opiates that is a major factor in relapse.
- relieves symptoms that are associated with withdrawal from opiates.
- does not cause euphoria or intoxication at stable doses.

In the U.S., methadone products may be dispensed only by opioid treatment programs that have been certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) and approved by the designated state authority.\(^8,9\) Medical practitioners who do not have this special license are prohibited from treating a patient with methadone to maintain an addiction to any controlled substance.

An exception is a patient who requires acute medical care, for whom the interruption of opiate maintenance treatment would create a medical complication (i.e., withdrawal). This is a common situation in acute-care hospitals, which admit addicted patients and must treat these individuals both for pain and for the prevention of withdrawal.
CLINICAL–LEGAL RISK MANAGEMENT
Respiratory Depression

All mu-opiate receptor agonists, including methadone, carry the risk of potentially fatal respiratory depression.\[^7,11,12\] Methadone carries an exceptionally high risk because of its unique kinetics (i.e., a long elimination half-life but a substantially shorter duration of analgesic action). After administration, methadone can remain in the liver and in other tissues, including fat cells, from which it is slowly released back into the circulation.\[^7\] If this slow release from tissues occurs while the patient is taking additional doses of methadone, the drug may reach toxic levels and may have a depressive effect on neurons in the brain’s respiratory center, located in the medulla.\[^11\] Importantly, methadone reabsorption from the tissues may continue for weeks after drug administration has ceased.\[^4\]

Because methadone’s half-life is much longer than its duration of action, the drug’s peak respiratory-depressant effects typically occur later and persist longer than its peak analgesic effects, particularly in the early dosing period.\[^1,7\]

The titration of methadone dosing must be performed by individuals with experience using this agent, and it is best monitored in chronic-pain clinics with multidisciplinary observation.

Equianalgesia

As mentioned, it is possible to underestimate the potency of methadone when patients are undergoing a transition from another opioid, such as controlled-release morphine (e.g., MS-Contin, Purdue Pharma) or oxycodone (OxyContin, Purdue Pharma). The available equianalgesic dosing tables provide only general guidelines.\[^1,13–15\] The previous use of high-dose morphine may lead clinicians to overestimate the correct replacement dose when patients are switching to methadone.\[^1\] In addition, the metabolism of methadone can vary considerably among patients;\[^16\] therefore, each patient must be evaluated individually.

The transition to methadone is further complicated by the fact that patients who are tolerant to other mu-opioid agonists may not be tolerant to methadone. It is critical that clinicians understand the pharmacokinetics of methadone when converting patients from other opioids. A high degree of opioid tolerance does not eliminate the possibility of a methadone overdose, iatrogenic or otherwise.\[^8,9\]

Methadone dosing should be conservative, in accordance with the adage “start low and go slow.”\[^1\] Incremental changes in dosing should be made infrequently, and the dosing interval should not be too short. Until a stable pattern of effective dosing has been established, frequent monitoring is vitally important for all patients undergoing the transition to methadone therapy.

Drug Interactions

Methadone is metabolized almost exclusively by the liver;\[^17\] the main step consists of N-demethylation of methadone by cytochrome P450 (CYP) enzymes (principally CYP3A4, CYP2B6, and CYP2D6) to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), an inactive metabolite.\[^8,9\] Interindividual differences in the activity of the various CYP enzymes may explain some of the variation in methadone metabolism observed among patients. For example, the amount of the CYP3A4 enzyme in the intestine can vary up to 11-fold, which may account for individual differences in the breakdown and absorption of methadone.\[^18\]

During methadone therapy, treatment with other agents may be necessary because of the comorbidities that are frequently encountered in drug addicts and in patients with chronic pain. These additional treatments (e.g., psychotropic drugs, antibiotics, anticonvulsants, and antiretroviral drugs) can precipitate a wide range of pharmaco kinetic interactions. Some drugs, such as verapamil (e.g., Calan, Pfizer) and quinidine, may alter the absorption of methadone; others, such as propranolol (e.g., Inderal, Akrimax) and tricyclic antidepressants, may influence the protein binding of methadone.\[^19\]

Several agents displace methadone from mu-opioid receptors, thereby blocking the effects of methadone. These drugs include buprenorphine (Subutex, Reckitt Benckiser), pentazocine (Talwin, Hospira), nalbuphine (Nubain, Endo), and butorphanol (Stadol, Bristol-Myers Squibb).\[^1,5\] Of particular concern are agents that potentiate the respiratory depression associated with opiates, such as alcohol and benzodiazepines.\[^20\]

In drug addicts undergoing MMT, the known drug–drug interactions associated with methadone do not have life-threatening consequences, but they usually result in decreased concentrations of the drug, which in turn can cause symptoms of withdrawal and increase the risk of relapse into heroin abuse.\[^21\]

Cardiac Effects

It has been well established, through both animal and human studies, that methadone has the potential to cause cardiac arrhythmias—specifically, QT prolongation and torsades des pointes.\[^22,23\] Therefore, the coadministration of other medications that increase the risk of QT prolongation and torsades des pointes, such as the antibiotics clarithromycin (Biaxin, Abbott) and erythromycin and the antidepressants fluoxetine (Prozac, Eli Lilly) and venlafaxine (Effexor, Wyeth/Pfizer), may result in additive effects and an increased risk of ventricular arrhythmias and sudden cardiac death.

Patients receiving methadone should be advised to seek medical attention if they experience symptoms that indicate the occurrence of torsades des pointes, such as dizziness, palpitations, or syncope. If patients are taking drugs that also cause central nervous system (CNS) or hypertensive effects (e.g., psychotropic agents, such as tricyclic antidepressants, pheno thiazines, and neuroleptic drugs), they should be made aware of the possibility of additive effects with methadone and should be counseled to avoid activities that require mental alertness until they know how these agents will affect them. High-dose methadone monotherapy has been associated with QT prolongation and torsades des pointes in drug addicts undergoing MMT.\[^24\] High doses of methadone are also used to treat chronic pain at pain-management centers. Patients with chronic pain, therefore, are at risk of QT prolongation and torsades des pointes from methadone treatment even in the absence of coadministered drugs.

UNINTENTIONAL METHADONE-RELATED DEATHS

In July 2007, a conference on methadone mortality rates, sponsored by the SAMHSA, concluded that the distribution of all forms of methadone (tablets, continued on page 821
patients who are not accustomed to the caution when prescribing methadone to pharmacies. At the same time, the number of methadone-related deaths has increased substantially.

A review of data from the National Vital Statistics System found that poisoning deaths attributed to methadone rose from 786 in 1999 to 4,462 in 2005, for an increase of 468% (Figure 1). Of these deaths, between 73% and 80% were classified as unintentional (3,701 such deaths in 2005). Of all narcotic drugs mentioned in reports of poisoning deaths, methadone showed the largest relative increases.

In November 2006, a public health advisory issued by the FDA included the following statement:

... the FDA has received reports of death and life-threatening side effects in patients taking methadone. These deaths and life-threatening side effects have occurred in patients newly starting methadone for pain control and in patients who have switched to methadone after being treated for pain with other strong narcotic pain relievers. Methadone can cause slow or shallow breathing and dangerous changes in heartbeat that may not be felt by the patient.

The advisory urged physicians to use caution when prescribing methadone to patients who are not accustomed to the drug, and it emphasized that patients should take the drug exactly as directed. As with any medication that can be fatal in large doses, methadone must be taken properly and with due care. As discussed previously, accumulation of the drug in tissues can reach toxic levels if the dose is too high or if the user’s metabolism of the drug is too slow. In such situations, a patient who fared well after the first few doses of methadone could experience high levels of the drug without taking more than was prescribed. For this reason, it is important that patients and their families be made aware of the symptoms that are characteristic of an opiate overdose.

LEGAL CASE SCENARIOS

The following scenarios provide examples of cases that have been brought against practitioners and their practices for deaths related to the use of methadone. These cases were settled out of court under seal, which is commonly done to avoid a costly and public trial.

Case #1

A 35-year-old mother of two was being treated by a pain-management physician in a midwestern state. She had a long history of low back pain and had undergone a laminectomy a few years earlier, which did not improve her condition. She was being maintained on oxycodone 20 mg every 12 hours for pain. She informed her physician that her husband had recently lost his job and that they no longer had health insurance. Her physician prescribed methadone 10 to 15 mg every 8 hours. The more expensive oxycodone was discontinued.

The woman and her husband went to a local chain pharmacy to fill the prescription for methadone. She took three 15-mg tablets that night, two tablets in the morning, two tablets at mid-day, and three tablets at bedtime. The husband found her unresponsive on the floor the following morning. An ambulance was called, and Emergency Medical Services (EMS) technicians declared her dead at the scene.

Case #2

A 35-year-old male school teacher and wrestling coach in a southwestern state was seen by a sports-medicine specialist. The patient was taking hydrocodone/acetaminophen (e.g., Vicodin, Abbott) for chronic low back pain. The sports specialist was concerned about potential acetaminophen toxicity. He prescribed “low-dose” methadone, 10 mg twice daily, and discontinued the hydrocodone/acetaminophen combination.

The next day, the patient stayed at his parent’s home. He was very drowsy, sleeping on and off most of the day, and went to bed early. On the morning of the third day, his mother was unable to awaken him. He was declared dead by EMS technicians.

In both cases, the medical examiner cited methadone intoxication as the cause of death. Both of the physicians, along with their practices (one a local hospital, the other a specialty group), were sued for wrongful death. Both physicians testified that the methadone dose was “equivalent” to that of previously used opiates. They considered their patients to be opiate-tolerant and considered the methadone prescriptions to be safe. Neither physician was aware of the unusual (and cumulative) kinetics of methadone, and neither of them recognized the need to start with a low dose, gradually discontinue existing opiates, and regularly reassess the patients’ tolerance to methadone.

DISCUSSION

Methadone is commonly used as a substitute for morphine or morphine-like...
CONCLUSION

The ubiquitous use of a drug like methadone illustrates the risk–benefit equation that applies to both old and new oral drugs. The real risk of patient harm along with legal exposure requires greater attention by P&T committees and the care delivery system itself.

REFERENCES


