CHAPTER 6

Methadone: A Complex and Challenging Analgesic, But It's Worth It!

INTRODUCTION

Ah methadone, magical, mystical, mischievous methadone! Dosing of no other opioid fuels controversy and heated debate as does methadone, yet one has to admire methadone's sheer cheekiness. Many are drawn to the cost-effectiveness of oral methadone, but methadone is clearly not for the uninitiated or uneducated practitioner. From an intellectual point of view, we could probably teach students in pharmacy school for 4 years just using methadone as the example drug. We have drama (the pharmacodynamics of methadone), we have intrigue (why DO we have so many conversion charts), excitement (wow—look at all those drug interactions), and we have danger (QT interval prolongation?). Despite, or in spite of, the good, the bad, and the ugly sides of methadone, its use is growing, particularly in serious illness. Despite the lack of well-designed clinical trials, evaluation of the available literature on using methadone for chronic noncancer pain shows that the majority of patients achieve effective pain control.[1] In this chapter, we will review the pharmacodynamics and pharmacokinetics of methadone, dosing of methadone in opioid-naïve patients, conversion calculations to and from methadone, and a look at the use of intravenous (IV) methadone. That should keep us out of trouble!

OBJECTIVES

After reading this chapter and completing all practice problems, the participant will be able to:

1. Describe the pharmacodynamics and pharmacokinetics of methadone.
2. Explain the mechanism of pharmacodynamic and pharmacokinetic drug interactions with methadone, list medications that commonly induce or inhibit methadone metabolism, and describe strategies for dealing with these interactions.
3. Describe appropriate and inappropriate candidates for methadone therapy.
4. List variables that increase the risk for methadone-induced QTc prolongation.
5. Determine a starting dose of methadone for an opioid-naïve patient, as well as a recommendation for rescue medication.
6. Calculate an appropriate dose of methadone for a patient converting to and from another opioid regimen.
7. Given an actual or simulated patient receiving methadone, describe a monitoring plan designed to detect methadone toxicity.
8. Describe the conversion process to and from oral to parenteral methadone and recommended dosing parameters for methadone delivered via patient-controlled analgesia.
9. Describe dosing strategies when using methadone as an adjunctive analgesic.

PHARMACODYNAMICS OF METHADONE

Methadone is a synthetic opioid agonist developed over 60 years ago, best known (sometimes to our disadvantage in pain management) for its use in treating opioid use disorder. Thanks to the long duration of action, efficacy, and low cost, methadone is enjoying increased popularity in the treatment of persistent pain.

Methadone is a mu-opioid receptor agonist (like morphine, oxycodone, and hydromorphone), and it also binds to the kappa- and delta-opioid receptors. Additional mechanisms of action include inhibiting the reuptake of serotonin and norepinephrine (which is how antidepressants act to treat pain). Additionally, methadone works as an antagonist at the N-methyl-D-aspartate (NMDA) receptor, thought to prevent central sensitization and reduce opioid tolerance, and possibly increase its effectiveness in treating neuropathic pain as compared to other opioids. Methadone is a racemic mixture of R- and S-methadone. R-methadone has a 10-fold affinity at the mu receptor, is up to 50 times more potent than S-methadone, and is responsible for most of its action.[2] S-methadone is responsible for serotonin and norepinephrine reuptake inhibition, and NMDA antagonism.[3]

PHARMACOKINETICS OF METHADONE

Absorption

Methadone may be given by a variety of routes of administration and dosage formulations. Routes of administration include oral, rectal, IV, intramuscular (IM? no, no, bad dog!), subcutaneous (sub-Q although it is quite irritating; see discussion later in chapter), epidural, and intrathecal (spinal administration is *not* Food and Drug Administration [FDA] approved).

Methadone is a basic and lipophilic drug that is detected in the blood 15 to 45 minutes after oral administration with peak plasma concentrations achieved in 2.5 to 4 hours.[4] Oral bioavailability is approximately 70% to 80% (range 36% to 100%), and absorption of oral methadone tablets and solution is equivalent.[5] Studies in healthy normal subjects who received methadone rectally, orally, and intravenously showed an absolute bioavailability of 76% (rectal) and 86% (oral), respectively.[6]

Distribution

Being highly lipophilic (fat-soluble), methadone is widely and quickly distributed throughout the body to the brain, gut, kidney, liver, muscle, and lung. Methadone is retained in these tissues and slowly released back into the plasma during redistribution and elimination. Due to these properties, methadone has a very long elimination half-life (time it takes for half the drug to be eliminated from the body). Methadone binds to alpha 1-acid glycoprotein, as well as albumin and globulin to a lesser degree. The portion of drug that is *free* or *unbound* is that which results in the pharmacologic actions of the drug; this portion varies fourfold among patients.[5] The range in protein binding could partially explain the extreme variability in patient responsiveness to methadone. For example, methadone 5 mg twice a day prescribed for me may result in a different response than methadone 5 mg twice a day prescribed for you (therapeutic or toxic).