CHAPTER **25**

USE OF OPIOID ANALGESICS FOR POSTOPERATIVE PAIN

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INTRODUCTION

In foot and ankle surgery, both bony and soft tissue structures are commonly encountered and are associated with a higher level of pain when compared with other types of procedures. Research has shown that the nociceptor concentration is highest within these periosteal and ligamentous tissues, which in comparison to other surgical specialties, creates a lower threshold for pain.[1] Proper management of this pain is of obvious importance and it is essential to recognize the many modalities and pharmacologic agents available. Opioid analgesics, proper surgical technique, and physical modalities including rest, ice, compression, and elevation allow the podiatric surgeon to effectively accomplish this goal

Opiates have been used as a treatment method for pain control since 3400 B.C.[2] Morphine, the most active constituent of opium, was first extracted in its pure form at the beginning of the 19th century. Following the introduction of synthetic compounds, along with the invention of the hypodermic needle, the widespread usage of opioids for pain management became accessible.[2]

PHARMACOLOGY OF OPIOIDS

Opioids can be divided into 4 chemical classes: Phenanthrenes (morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, butorphanol), Benzomorphans (pentazocine), Pheneylpiperidines (fentanyl, meperidine), Diphenylheptanes (propoxyphene and methadone), and Tramadol.[2] Each class can then be further broken down by either agonist/antagonist or partial agonist/antagonist, with most opioids acting as agonists.

Opioids function by binding to receptors within the 5 areas of the central nervous system. The receptors of interest are Mu (μ), Kappa (κ), Delta (δ), Sigma (σ) and Epsilon (ϵ), with the primary receptors being μ and κ. When an opioid binds to a presynaptic receptor of a nociceptive pain fiber, voltage-gated calcium channels are inactivated and the level of neurotransmitters responsible for pain (e.g. glutamate, substance P) is decreased, which in turn produces analgesia.[2] In addition, postsynaptic opiate binding decreases neuronal excitability via opening of potassium channels.[1] The end result of both of the above mentioned mechanisms is pain inhibition.

SPECIFIC OPIODS

Morphine, considered the gold standard of opioids, is derived from the Opium Poppy flower, *Papaver somniferum* and acts through μ receptor agonism. Isolated by Freidrich Serturner, it was named after Morpheus, the Greek god of dreams. It is indicated for moderate to severe pain and has an elimination half-life of 2 hours and duration of action of 4-7 hours. Given orally, the onset of action is 30 minutes, and 5-10 minutes if given IV. Morphine also exists in an extended release formula as well as within a D5W infusion. Usual dosage is 10-30 mg every 3-4 hours orally and 2-4 mg every 3-4 hours IV. The metabolism of morphine results in 2 metabolites, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). In a recent study, the former (M6G) has been shown to provide comparable analgesia to morphine with a reduction in incidence of nausea and vomiting.[3] The downside is that the potency is half that of morphine and it also exhibits a delayed analgesic effect due to the slow passage through the blood brain barrier.[3] However, researchers have found significantly less respiratory depression with M6G and promising studies are in progress to determine if M6G is a possible successor to morphine.

Codeine is a semisynthetic alkaloid synthesized from morphine in 1832. It is used for mild to moderate pain and is 60% bioavailable. A dosage of 120 mg subcutaneously is equivalent to 10 mg of morphine. The analgesic effect of codeine is believed to come from the metabolism of codeine to morphine.[2] Codeine is most often given in combination with acetaminophen, with varying doses of codeine (i.e., 15 mg, 30 mg, and 60 mg) given every 4 hours. It has an onset of action of 30 minutes and a half-life of 3 hours. The duration of action is 4-6 hours and sedation is unusual, causing little euphoria.

Hydromorphone is a ketone analogue of morphine and is thought to work by binding to μ receptors and to some degree on delta receptors.[2] Hydromorphone is significantly more potent than morphine, with some estimates stating a ratio of 7:1 up to 11:1.[2] The duration of

action of is 3-4 hours with an onset of approximately 30 minutes and an elimination half-life of 2 hours with oral dosing (2-8 mg every 4 hours). Hydromorphone is commonly used with patient controlled analgesia (PCA) for moderate to severe pain. Smith[4] warns that transient hyperglycemia may result with the use of hydromorphone and should be considered when treating diabetic patients.

Hydrocodone is a synthetic opioid analgesic that acts through μ receptor agonism, indicated for moderate to severe pain. While it is labeled as a weak μ receptor agonist, hydrocodone is converted to hydromorphone by demethylization, which has a much higher μ receptor binding capacity. It is the most commonly prescribed opioid with an elimination half-life of approximately 3 to 4 hours.[2] The duration of action is 4-8 hours and the onset of action is 10-20 minutes. Hydrocodone is orally given as 5-10 mg 4 times a day and is often in combination with acetaminophen. The maximum dose of hydrocodone is 60 mg/day but this may be limited by the maximum dose of acetaminophen, which is not to exceed 4 mg/day.

Oxycodone is derived from the opium alkaloid thebaine and works on multiple receptors.[2] It is two times as potent as morphine and has fewer hallucinogenic properties. Bioavailability is high through oral dosing and the elimination half-life is 2.5 hours. Oxycodone exists in immediate release, as well as controlled-release (CR) preparations. Dosage of immediate release oxycodone is 10-30 mg every 4 hours while the CR preparation is 10 mg and delivers oxycodone over a 12-hour period. The elimination half-life of the CR oxycodone is 4-5 hours. CR oxycodone is unique in that it possesses a biphasic absorption profile, with the first stage involving a rapid onset followed by a prolonged release phase.[4] Beer et al[5] compared standard therapy against CR oxycodone for postoperative pain management after knee and hip replacement in 194 patients in 2 separate studies. While CR oxycodone was just as effective in treating postoperative pain as standard therapy, the length of hospital stay was shorter and administration of analgesia was used less frequently.[5] Multiplication factors exist for most of the opioid analgesics when converting from parenteral to oral dosing of oxycodone, facilitating patient discharge. The equation is as follows:

Current opioid mg/day dose x factor =
Oxycodone mg/day dose

Common opioid factors: morphine oral factor of 0.5 and a parenteral factor of 3, hydromorphone oral factor of 4 with a parenteral factor of 20 and meperidine oral factor of 0.1 with a parenteral factor of 0.4.[4]

Meperidine was the first synthetic narcotic μ-agonist created. It is considered to be a weak μ-agonist, in that it is only 1/10 as potent as morphine. When dosed orally, it has an onset of approximately 30 minutes and a peak activity seen at 1 hour. The duration of action is approximately 3-5 hours and the elimination half-life is 3 hours. Dosing of meperidine is 50 mg every 4 hours and is often given in combination with promethazine. The metabolite of meperidine is normeperidine, which may cause epileptic activity and should not be given to patients on monoamine oxidase inhibitors (MAOIs), as it may potentiate severe respiratory depression, CNS excitation, and seizures.[2] Additionally, normeperidine is nonreversible with naloxone, so meperidine should not be used in renally impaired patients, as this may also potentiate epileptic activity.

Propoxyphene is a centrally acting opioid that acts by μ receptor binding. It is a mild opioid agonist indicated for mild to moderate pain. Propoxyphene is 66% as potent as codeine and has a peak of approximately 2 hours and an elimination half-life of 6-12 hours. Orally dosed, 65 mg is given every 4 hours, often in combination with aspirin and caffeine. The metabolite, norpropoxyphene, is created by degradation in the liver through N-demethylation, which has a half-life of 30 hours and has been shown to cause arrythmias.[6] It is for this reason that the use of propoxyphene is cautioned in the elderly.

Fentanyl, a μ-receptor agonist is related to meperidine in structure. The elimination half-life is 2-3 hours and it has 80 times the analgesic potency of morphine.[4] Fentanyl is more lipid soluble, therefore it is indicated for short duration and immediate postoperative pain. Fentanyl can be used as a transdermal system and is adequately maintained on 72-hour patch administration. In addition, fentanyl is often preferred for bronchospastic patients due to the absence of histamine release.

Methadone is a synthetic μ-receptor agonist with a structure unrelated to other opioids, allowing its use in true morphine allergic patients.[2] There are no active metabolites and the duration of action is 4 to 6 hours. However, it should be noted that due to the high lipid solubility of methadone, the half-life of methadone is extended to 8-59 hours.

Tramadol, an analogue of codeine, is an atypical opioid existing in 2 enantiomers. One form inhibits serotonin reuptake through μ-receptor agonism, while the other form inhibits norepinephrine reuptake.[2] The elimination half-life is 6-8 hours with an onset of 1 hour and duration of action of 9 hours. Tramadol may be an option for patients reluctant to take mainstream opioids and has been well tolerated in the elderly population.[7]

PATIENT CONTROLLED ANALGESIA

Hospital administration of IV medication in an overnight setting may be the optimal course of treatment for more involved cases, such as in reconstructive procedures. The advent of patient controlled analgesia (PCA) in 1973 has greatly revolutionized hospital administration of pain medicine.[8] In PCA, the goal is to maintain an adequate plasma concentration of medication, avoiding any significant peaks or troughs.[8] Therefore, it is important for the patient to understand the concept of dosing and the lockout interval that occurs with frequent dosing. Morphine, meperidine, hydromorphone, and fentanyl are commonly administered through PCA, with morphine most often prescribed and meperidine strongly discouraged due to the neurotoxic metabolite, normeperidine. Adjuvants, such as acetaminophen and ketorolac, have also been used in the treatment with PCA with satisfactory results.[8]

SIDE EFFECTS

Constipation is the most common side effect occurring with opioid use.[9] The activation of μ receptors in the gut is responsible for the decrease in gastric motility and reduction in secretions.[9] While the trend is to treat with stool softeners and laxatives, methylnatrexone may be another consideration in the future. Methylnatrexone is a μ receptor antagonist that is currently under clinical investigation and is unique in the fact that it has peripheral antagonistic affinity while sparing the central analgesic effects.[9]

Adverse side effects encountered with opioid usage are constipation and nausea but also include sedation, respiratory depression, urinary retention and pruritis. Although common, they can usually be reversed with the naloxone. Naloxone is an opioid antagonist and can reverse opioid induced sedation, hypotension and respiratory depression.[10] It is administered IV with an initial dosage of 0.2-0.4 mg. If no response is seen after 2-3 minutes, then an additional 1-2 mg IV is administered up to a total dosage of 10 mg.[10] While the duration of action of naloxone is approximately 45-90 minutes, the respiratory depression seen with opioid overdose may last 4-5 hours and subsequent dosing of naloxone may be required.[10]

SUMMARY

Elleby et al[6] performed a survey of over 50 podiatric physicians and questioned their primary and secondary drug of choice for postoperative pain. Although the study was performed over a decade ago, it is the most recent account of what most podiatric physicians are prescribing across the country. Tylenol with codeine was the primary drug of choice for 32% of all soft tissue procedures and 42% of bony procedures in the case of mild to moderate pain. When asked about moderate to severe pain, the primary drugs of choice were oxycodone (36%) and hydrocodone (26%). Specific to procedures, meperidine was the first choice for bunion surgery (32%) and was most often prescribed with promethazine. In 45% of the digital surgery cases, Tylenol with codeine was prescribed. Whether these trends have changed in the last decade has yet to be studied, but according to the Drug Enforcement Administration, hydrocodone is now the most prescribed opioid analgesic.[11]

Of all available analgesics, opioids prove to be the most reliable and effective method for pain relief.[12] While no "superior" opioid exists, there are multiple pain control regimens that are available and standardization should be greatly discouraged. The choice of opioid should be tailored to the individual patient and the side effect profile of each drug. In addition, the route of administration that is most convenient and least expensive (i.e., oral) should be implemented as soon as it is appropriate.[5]

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