EPIDURAL MORPHINE AND PRURITUS: A REVIEW OF TREATMENT OPTIONS

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ABSTRACT

The purpose of this literature review was to examine the effectiveness of existing antipruritic interventions, including droperidol, ondansetron, dolasetron, nalbuphine, naloxone, and nalmefene, for epidural morphine-induced pruritus.

Due to differences in study design, amount of morphine and antipruritic administered, and timing of medications, patients receiving the same medications can have varying effects. Epidural droperidol may produce a dose-related reduction in pruritus and may be more effective when epidural morphine is at a lower dosage. Ondansetron and dolasetron appear to be effective in treating intrathecal morphine-induced pruritus. Nalbuphine may decrease epidural morphine-induced pruritus but antipruritic effect using naloxone is inconsistent between studies and there is a suggestion of analgesic reversal. Nalmefene and diphenhydramine do not appear to be effective for epidural-induced pruritus. Finding a solution to preserve analgesic effect and minimize pruritus would enhance the care given to patients receiving epidural morphine.
CHAPTER 1
INTRODUCTION

Morphine has long been the drug of choice for pain relief, although it was not until the 1900s that it was used intrathecally (Matsuki, 1983). Since then, it has afforded many people pain relief that they were not able to obtain from other methods of pain treatment.

Epidural analgesia is the "administration of opioids and/or dilute anesthetic solutions into the epidural space in the spinal column" (Roman & Cabaj, 2005) (figure 1). Spencer, Carpenter, and Neal (1995) differentiated between epidural anesthesia, "the intraoperative use of local anesthetics" and epidural analgesia, "the postoperative use of local anesthetics or opioids." When pain medications are administered intramuscularly or intravenously (IV), the client has less pain control, as they have peaks and valleys in their level of pain. In contrast, patients receiving spinal anesthesia/analgesia have less postoperative pain and are less fatigued, leading to increased ambulation and oral intake sooner than those patients receiving medications by conventional routes (Carli, Phil, Mayo, Klubien, Schricker, Trudel, & Belliveau, 2002).

History of Intraspinal Morphine Use

The term intraspinal refers to "the spaces or potential spaces surrounding the spinal cord into which medications can be administered" (McCaffery & Pasero, 1999). The intrathecal space (figure 2), also referred to as the subarachnoid space, surrounds the spinal cord and is filled with clear, colorless, cerebrospinal fluid (CSF). This CSF acts as a
protective cushion, transporting dissolved gasses, nutrients, wastes, and other materials (Martini, 2001).

The epidural space is a potential space containing vasculature, a network of nerve extensions, and a protective padding of adipose tissue (Pasero, 2003). Since there is no fluid in this space, an epidural catheter can be left in place without concern that it will become occluded if an infusion is stopped for several hours.

Morphine was the first medication to receive approval for epidural and intrathecal use from the Food and Drug Administration (Sinatra, 1998). In 1984, Duramorph, a preservative-free morphine sulfate, was approved for epidural and intrathecal administration (Gradert, Baze, Satterfield, Hildebrand, Johansen, & Hassenbusch, 2003). Morphine continues to be the most extensively investigated and widely used spinal opioid.

Intrathecal morphine was first administered by a Japanese physician in 1901 for the treatment of vertebral inflammation (Matsuki). In 1979, two independent studies were conducted in an attempt to eliminate either intractable pain or pain associated with trauma or surgery.

Wang, Nauss, and Thomas (1979) conducted a double-blind study and studied the effect on pain control using intrathecal morphine in eight patients suffering with leg and back pain associated with lumbosacral plexus involvement from genitourinary tract malignancies. Each patient received a random dose of physiologic saline solution intrathecally with or without morphine, 0.5 to 1.0 mg. Using a visual pain scale from 0 to 10, patients were asked to rate their pain at 15-minute intervals for one hour. After initial relief of pain, patients made hourly notations of their pain level. Two of the patients re-
ported complete relief after injections of both morphine and physiologic saline, while the other six reported complete relief after the morphine.

Ten patients were chosen by Behar, Magora, Olshwang, and Davidson (1979) to determine if epidural injections of morphine would relieve acute or chronic pain. All patients received morphine 2 mg in 10 ml of 5% glucose or normal saline, injected into the lumbar or thoracic epidural space. Each patient also received a placebo drug of either 10 ml normal saline or 10 ml marcaine 0.5% to compare the effect of epidural morphine with other injections. All patients had 50-100% relief of pain with the morphine injections within two to three minutes, with a peak action of 10-15 minutes. Although the marcaine provided effective relief, patients found it not as acceptable as morphine due to concomitant muscle weakness. The normal saline injections offered some relief, but only while the patients were at rest.

The use of intrathecal morphine for relieving labor pain began in 1980 (Bragg, 1989). Although sufficient relief of pain was not obtained during delivery, contractual pain was alleviated. Intrathecal narcotics are most effective against visceral pain, which includes uterine contractions (Manning, 1996).

Besides the above mentioned patient types, epidural anesthesia is also used to manage pain associated with surgical procedures, such as "thoracic, intra-abdominal, orthopedic, and vascular surgery" (Roman & Cabaj).
CHAPTER 2

INTRASPINAL ANESTHESIA

Delivery of Intraspinal Anesthesia/Analgesia

Drug Receptors

Drugs affect the body by interacting with drug receptors, "specialized macro-molecular components in cells" (McCaffery & Pasero). These drug receptors are usually cellular proteins, but can also be enzymes, carbohydrate residues, and lipids. When drug molecules bind to their specific receptor molecules, they fit together similarly as a lock and key (figure 3).

Receptors have two functions: chemical recognition and physiologic action (Ferrante, 1996). The ability of opioids to bind to receptor sites is determined by their binding affinity, defined as the strength of their attachment. The biochemical properties and functions of the receptor molecule are changed when the configuration of the molecule is distorted by the electromagnetic forces produced by the bond between a drug and its receptor (McCaffery & Pasero).

Drugs bind to receptor sites as agonists, to produce analgesia, or antagonists, so as not to produce analgesia. Three major classes of opioid receptor sites involved in analgesia are mu, delta, and kappa. The mu receptor sites are the most frequently used sites for opioid analgesics. Some of the mu agonist opioid analgesics are morphine, hydromorphone, fentanyl, oxycodone, codeine, and meperidine (McCaffery & Pasero).
Epidural Opioids

Opioids are delivered close to opioid receptors when they are administered by the epidural route. One of the most important factors with epidural medications is the drug solubility, which refers to "the amount of a substance that will dissolve in a given amount of another substance" (Medical Desk Dictionary, 2002). Hydrophilic opioids spread rostrally (toward the brain) more readily than lipophilic opioids, resulting in analgesia across many dermatomes (Pasero). Hydrophilic opioids, such as morphine and hydromorphone, are slow to traverse the fatty dura mater to reach the aqueous CSF, although once in the CSF, they tend to remain there. They eventually move into the spinal cord to the opioid receptors, where they can last as long as 24 hours.

Dosing

Epidural analgesia can be delivered by bolus dosing, continuous infusion, and patient-controlled epidural analgesia (Pasero). The dosing factor is determined by the probable duration of a patient's pain.

Side Effects

The most common adverse reactions to epidural opioids are urinary retention, pruritus, hypotension, and nausea and vomiting (McCaffery & Pasero; Ready, 1990; Manning). A less common side effect, respiratory depression, may occur, so apnea monitors and pulse oximetry are recommended as standards of care (Gianino, York, & Paice, 1996). Of the adverse reactions, pruritus, defined as "the sensation that provokes the desire to scratch" (Iatrou et al., 2005) is one of the most elusive and most difficult to control. Studies by Fuller et al. (1990) and Manning found pruritus to be 58% and 89% in
patients receiving epidural morphine. According to Ready (1990), pruritus is most bothersome to obstetric patients and the face is the most common site. Until recently, the mechanism of action of this effect has been poorly understood, and this has hindered the development of adequate therapies (Schmelz, 2001).

Schwörer and Ramadori (1993) participated in a study of three patients with primary sclerosing cholangitis, chronic renal insufficiency and severe three-vessel coronary disease and chronic left-sided heart failure, and an amelanotic malignant melanoma with pulmonary, hepatic, adrenal, and osseous metastases. The patients received random doses of intravenous physiological sodium chloride and ondansetron 8mg added to 10ml physiological sodium chloride solution. These patients were then asked to rate the intensity of pruritus at 15, 30, 60, and 120 minutes and at regular intervals, up to 24 hours after initial injection. Ondansetron decreased the pruritus in all patients, but was most effective in the patient with cholestatic itching. Ondansetron, a serotonin type 3 (5-HT₃) receptor antagonist, appears to demonstrate that serotonin is involved in the sensation and/or generation of pruritus.

Purpose Statement

The purpose of this paper is to evaluate the effectiveness of existing antipruritic treatments for patients receiving epidural morphine.

This subject of epidural morphine-induced pruritus is of interest, since Gwirtz (1990) reported that "pain may be perceived as itching". The intensity theory suggested that minor activation of nociceptors by weak noxious stimuli presented as pruritus and stronger noxious stimuli induced pain (Ikoma, Rukwied, Ständer, Steinhoff, Miyachi, &
Schmelz, 2005). Identifying a causal agent of epidural morphine-induced pruritus may provide investigators with another step in identifying a solution.
CHAPTER 3

STUDIES OF TREATMENT FOR PRURITUS

Numerous studies have been done using various antipruritic agents in an attempt to diminish the discomfort caused by pruritus (Choi, Lee, Choi, & Bishop, 2000; Cohen, Ratner, & Kreitzman, 1992; Iatrou, Dragoumanis, Vogiatzaki, Vretzakis, Simopoulos, & Dimitriou, 2005; Kendrick, Woods, Daly, Birch, & DiFazio, 1996; Naji, Farschtschian, OH Wilder-Smith, & CH Wilder-Smith, 1990; Pelliegrini, Bailey, Graves, Paice, Shott, Faut-Callahan, 2001; Sanansilp, Areewatana, & Tonsukchae, 1998; Schwörer, & Ramadori, 1993; Wang, Ho, & Tzeng, 1998; Yeh, Chen, Lin, Chan, Chen, Lin, Sun, Wang, & Tsai, 2000). Although some medications relieve itching, not all medications relieve pruritus equally for all study participants.

Methods

All studies investigated received approval of an institutional and ethical committee and all patients gave informed consent. Patients met criteria of the American Society of Anesthesiologists (ASA) physical status I, II, or III (Table 3). Class I is referred to as a normal healthy patient. Class II is used when a patient has a mild systemic disease, such as mild diabetes mellitus, and Class III is used when a patient has a severe systemic disease that limits activity but is not incapacitating, such as severe or complicated diabetes or a combination of heart disease and respiratory disease (Sakland, 1941). The ASA classification, originally developed in 1941 and used by a group of American anesthesiologists to collect and compare statistical data (Sakland), is used by anesthesia providers
worldwide as an assessment of the preoperative physical health of patients (Aronson, McAuliffe, & Miller, 2003).

Medications

_Droperidol_

Droperidol is a neuroleptic drug useful in the treatment of chemotherapy-induced vomiting (Mycek, Harvey, & Champe, 2000) by blocking dopamine stimulation of the chemoreceptor trigger zone (Turkoski, Lance, & Bonfiglio, 2004). It has no known antipruritic effect, but has been used as an investigative medication for this purpose.

In a study by Horta et al. (1996), the inhibitory effect on pruritus of IV droperidol disappeared when the dosage was increased to 5mg. Horta, Ramos, & Goncalves (2000) studied four groups of women, 35 women in each group, undergoing cesarean sections to determine if epidural droperidol would have the same effect as IV droperidol, inhibiting epidural morphine-induced pruritus at 2.5mg but having that effect disappear when increased to 5.0mg. Pruritus was classified as absent, mild (restricted to one area and not bothersome), moderate (affected a larger area, but not troublesome), and severe (distributed extensively and often disturbing enough to require treatment of 50mg intramuscular [IM] promethazine). Using a double-blind design, each woman received 150mg (30mL) of 0.5% bupivacaine with 1:200,000 epinephrine and 2mg of morphine sulfate plus either 0.0, 1.25, 2.5, or 5.0mg of droperidol. Results from this study showed that treating pruritus with epidural droperidol can cause a dose-related reduction in itching (p < 0.001), but there is also an increase in somnolence with 5mg of droperidol (p < 0.05). These results
differed from the study of IV droperidol, where 5mg reversed the effect on pruritus but did not cause somnolence.

Naji, Farschtschian, Wilder-Smith, and Wilder-Smith (1990) conducted a study on 40 patients aged 30 to 80 years old undergoing elective hip-replacement surgery to assess the reduction of side effects and the potentiation of analgesia of epidural morphine by epidural droperidol. Two groups of 20 patients each received either epidural 4mg morphine with 0.9% Sodium Chloride (placebo) or with 2.5mg droperidol. There were more side effects of urinary retention, pruritus, nausea and vomiting, and hypotension with the morphine/placebo group and this group was also more sedated than the group with morphine/droperidol. The incidence of pruritus reduction in the morphine/droperidol group was more significant at the 4-hour point (p < 0.01) than at 24-hour postoperatively (p < 0.05).

Sanansilp, Areewatana, & Tonsukchai (1998) also studied the effect of IV and epidural droperidol on the incidence, duration, and severity of pruritus, nausea, and vomiting caused by epidural morphine in 97 women, ranging in age from 19 – 40 years old, undergoing cesarean section. After delivery, each patient received either 5mg of epidural morphine alone, 5mg of epidural morphine followed by 2.5mg of droperidol, or 5mg of morphine plus 2.5mg of droperidol IV after shown the baby. Although the incidence of nausea and vomiting in the group who received droperidol IV was lower than those in the group who received morphine alone, the incidence of pruritus in all three groups was no different. The investigators believed this finding was different than the study by Naji, Farschtschian, Wilder-Smith, & Wilder-Smith (1990) because in the present study, they
studied a different population (women undergoing a cesarean section as compared to patients with a wide range of age undergoing hip surgery) and used a larger dose of morphine (5mg as compared to 4mg). Also, since droperidol is a potent antagonist at the dopamine D₂ receptor, it has anti-emetic actions but has no known effect on pruritus.

In summary, based on the above limited studies, the antipruritic effect from epidural and IV droperidol is inconsistent and may be effective when morphine is at a lower dosage of 4mg.

**Ondansetron and Dolasetron**

Ondansetron and dolasetron selectively antagonize serotonin 5-HT₃ receptors. They are primarily used as preventative strategy for nausea and vomiting associated with emetogenic cancer chemotherapy (Semla, Beizer, & Higbee, 2003) and prevention and treatment of postoperative nausea and vomiting (Turkoski et al.). These medications have no known antipruritic effect.

Yeh and colleagues (2000) studied the effectiveness of ondansetron in preventing intrathecal morphine-induced pruritus in 60 non-breastfeeding women who were scheduled for cesarean deliveries. These subjects were injected with intrathecal bupivacaine 8-10mg for spinal anesthesia and morphine 0.15mg for control of postoperative pain. Immediately after delivery, Group 1 received a placebo injection of IV normal saline, Group 2 diphenhydramine 30mg IV, and Group 3 ondansetron 0.1mg/kg IV. The patients were evaluated for the next 28 hours by an anesthesia research fellow who was blinded to the study groups. The incidence of pruritus was significantly lower in the ondansetron group
(25%) compared to those patients in the placebo group (85%) or in the diphenhydramine group (80%).

Iatrou et al. conducted a study in 105 men and women undergoing elective urologic, orthopedic, or vascular surgery to determine the effectiveness of dolasetron and ondansetron for the prevention of pruritus after spinal anesthesia performed with bupivacaine and morphine. They found that there was a statistical significance in the effectiveness of managing pruritus in those receiving a placebo of 5ml normal saline (group P) versus those receiving 12.5mg dolasetron IV (group D) or 4mg ondansetron IV (group O). Each patient received the study medication 30 minutes prior to administration of spinal anesthesia of 10 to 17.5mg of 0.5% hyperbaric bupivacaine and 0.25mg of morphine. Severe pruritus was observed only in Group P, and 4 patients (11%) in this group required rescue medication of 3mg nalbuphine IV for pruritus. This study showed a reduction in pruritus by ondansetron (48%) and dolasetron (70%), but no effect when patients received placebo injections. There was no significant difference in pruritus among genders.

In summary, ondansetron and dolasetron appear to be effective in treating intrathecal morphine-induced pruritus in women undergoing cesarean deliveries and patients undergoing elective urologic, orthopedic, or vascular surgery.

Naloxone

Naloxone, an opioid antagonist, is the most commonly administered antagonist (Pellegrini, Bailey, Graves, Paice, Shott, Faut-Callahan, 2001) and binds with high affin-
ity to opioid receptors, particularly mu receptors (Mycek, Harvey, & Champe). Receptor-bound opioid molecules are rapidly displaced, reversing the effects of morphine.

Choi, Lee, Choi, and Bishop (2000) studied a group of 80 women scheduled for abdominal hysterectomies. Each group of 20 women received 5ml bupivacaine 0.33% via the epidural catheter and an additional 3-5ml bupivacaine 10 minutes after initial induction. Each patient then received 1/2 and 1/3 of the initial dose at one hour intervals during the remainder of the surgery. Each patient was given morphine 2mg through the epidural catheter as the surgeon was closing the abdominal cavity. The women, using a Two-day Infusor (Baxter, USA), were randomly divided into four groups, and each group received a different medication mixture. Group 1 received 80μg of morphine in 2ml bupivacaine 0.125% per hour; group 2 received the same mixture, but with the addition of 0.083μg·kg⁻¹·hr⁻¹ of naloxone; groups 3 and 4 were identical to group 2, except that group 3 received the naloxone infusion at a rate of 0.125μg·kg⁻¹·hr⁻¹ and group 4 received a rate of 0.167μg·kg⁻¹·hr⁻¹. Groups 3 and 4 had less itching than Groups 1 and 2 (p < 0.05 at 8, 16, and 32 hours for Groups 3 and 4 versus Group 1), although even Group 2 had some benefit from the naloxone (p < 0.05 at 32 hours versus Group 1). All patients experienced good pain control and there were no instances of analgesia reversal. This study found a dose-related reduction of epidural-induced pruritus with the addition of naloxone to a postoperative epidural infusion of bupivacaine and morphine.

*Naloxone versus Nalbuphine*

Nalbuphine, also known as Nubain, is an opioid agonist-antagonist, which binds to various opiate receptors in the central nervous system (CNS), altering perception of
and emotional responses to pain (Nursing 2004 Drug Handbook, 2004). It is used for moderate to severe pain and is an adjunct to balanced anesthesia.

Three studies examined the efficacy of IV administration of naloxone versus nalbuphine in the prevention of epidural morphine-related side effects (Cohen, Ratner, Kreitzman, Archer, & Mignano, 1992; Kendrick, Woods, Daly, Birch, & DiFazio, 1996; Wang, Ho, & Tzeng, 1998).

Cohen and colleagues (1992) compared naloxone and nalbuphine when administered for treatment of side effects, such as nausea and vomiting, pruritus, sedation, and pain, after epidural morphine 5mg for postcesarean analgesia. Immediately after delivery, all patients received epidural preservative-free epidural morphine 5mg. Women in Group 1 received IV naloxone 0.2mg and those in Group 2 received IV nalbuphine 5mg. Patients were assessed for presence and severity of nausea or pruritus, presence of vomiting, and the degrees of sedation and pain. In Group 2, there was a 25% reduction in pruritus but there was no change in Group 1. However, Group 1 did have an increase in pain scores (p < 0.01). There was also an increase in sedation following the administration of nalbuphine (Group 2), but not with those receiving naloxone (Group 1). This study suggests that nalbuphine may decrease epidural morphine-induced pruritus, but there is no antipruritic effect with naloxone. Furthermore, there is a suggestion of morphine reversal with naloxone.

Kendrick et al. (1996) compared the clinical efficacy of continuous infusions of mu-receptor antagonists (nalbuphine versus naloxone) in the prevention, rather than ex post facto treatment, of pruritus associated with epidural morphine analgesia in postce-
sarean section patients. Patients used a patient self-administration device for pain control to supplement the basal infusion with additional medication, permitting a determination of potency ratio for naloxone and nalbuphine. These devices allow a patient to push a button and receive medication only when needed. The subjects were divided into three groups, each receiving epidural, preservative-free morphine 5mg after delivery. Group A received IV nalbuphine at a rate of 2.5mg/h and were allowed to self administer nalbuphine 1mg every 5 minutes. Group B received IV naloxone at a rate of 50μg/h and were allowed to activate the PSA pump, which delivered normal saline. Group C was given IV naloxone 50μg/h with the addition of the ability to receive 40μg of naloxone every 5 minutes via the PSA pump. Patients were assessed for pruritus and other adverse reactions when the infusions began and every 8 hours for 24 hours. There were no differences in pruritus among the three groups except for the 16th and 24th hours, when patients in Group B, who received naloxone infusions and PSA saline, reported higher pruritus scores. However, these were not statistically significant (p = 0.14).

Kendrick and colleagues did not find the same evidence of analgesia reversal with the use of naloxone as Cohen et al. There was no consistent increase report of pain by those patients who frequently self-administered antipruritic medications. One patient in Group C used 0.4mg, 0.16mg, and 0.04mg of naloxone over the measurement periods, and her pain scores were 8.2, 4.8, and 8.1 respectively. Her pruritus scores over the same intervals were 1.7, 0.6, and 0. These numbers indicate she may have had analgesia reversal, since her pain score increased as she decreased her pruritus scores by self-administration of naloxone. Another patient in the same group had pain scores of 0, 5.0, 2.6, and
9.0 with corresponding pruritus scores of 0, 9.0, 7.3, and 8.0 respectively. This may be
due to a shortened duration of analgesia after increased use of the PSA.

Wang et al. compared the efficacy and side effects of intravenous infusion of nal-
buphine or naloxone in the prevention of epidural morphine-related side effects in pa-
tients who had received a total hysterectomy. Seventy-five patients were administered
3mg of preservative-free morphine in 10ml of normal saline via the epidural catheter at
the end of surgery, with the dose repeated in 12 hours. Group 1 patients received IV nal-
buphine 60μg/kg/h, group 2 received an IV infusion of naloxone 2μg/kg/h, and group 3
received IV normal saline 0.3ml/kg/h. Intramuscular diphenhydramine 20mg was avail-
able to the patients every 4 hours if necessary for unrelieved pruritus. They also were
able to receive meperidine 50 mg IM every 4 hours as needed for uncontrolled pain. No
patients in groups 1 or 2 requested treatment for pruritus, but a higher number of patients
in group 2 required rescue analgesia. Although the pruritus was controlled with both nal-
buphine and naloxone, the use of naloxone may cause reversal of analgesia.

In summary, data from the above studies showed that nalbuphine may reduce epi-
dural morphine-related pruritus. However, the antipruritic effect of naloxone is not con-
sistent and use of naloxone may also cause reversal of analgesia.

Nalmefene

Naltrexone, a long-acting opioid antagonist has been used previously for relief
from opioid induced side effects (Mok, Shuai, Lee, & Lippmann, 1986). However, this
medication must be given orally and patients experience a reduction in analgesia when
doses exceed 6mg. In 1986, nalmefene, a long-acting, pure opioid antagonist form of naltrexone, was introduced for parenteral administration.

In a randomized double blind study, Pellegrini et al. analyzed the effect of the administration of a prophylactic dose of nalmefene on opioid-induced side effects, such as nausea and vomiting, pain, pruritus, and level of sedation on 60 women (42 Caucasian, 16 African American, 1 Hispanic, and 1 Asian) scheduled for a nonemergent, nonurgent cesarean section. All patients were given spinal anesthesia of 11.25 to 15mg of bupivacaine, 0.25mg of preservative-free morphine, and 12.5μg of fentanyl. Patients were randomly assigned to Group A, receiving 20μg/ml of IV nalmefene, or Group B, receiving a placebo consisting of 30ml of IV bacteriostatic water. Postoperative assessments were performed every hour for the first 12 hours and every 2 hours for the next 12 hours.

When evaluated for pruritus, there was no statistically significant difference between the two groups except at the 10th (p = 0.008) and 11th (p = 0.018) hours. Those patients receiving nalmefene had statistically significant increases in pain more than those receiving the placebo (median times for patients to request additional analgesia was 6 hours in the nalmefene group and 14 hours in the placebo group). Since the nalmefene was given prior to surgery, it may have occupied the opioid receptor sites and not allowed the intrathecal morphine to assess these sites. This study indicates that Nalmefene is not a good prophylactic medication for epidural-induced pruritus because it reduced the pruritus at only the 10th and 11th hours but increased the need for supplemental pain medication.
Diphenhydramine

Diphenhydramine (Benadryl), an antihistamine, is used to relieve allergy symptoms. It competes with H1-receptor sites on effector cells and prevents histamine binding and action (Turkoski, Lance, & Bonfiglio). In a study conducted by Yeh et al. to investigate ondansetron in preventing intrathecal morphine-induced pruritus in women scheduled for cesarean deliveries, the investigators administered diphenhydramine 30mg IV to one group of women. They found the incidence of pruritus was 80%, not significantly different from the 85% in the placebo group who received normal saline. Therefore, the investigators suggested that diphenhydramine is not effective in reducing epidural morphine-induced pruritus in women undergoing cesarean section. Although diphenhydramine is sometimes used in attempts to relieve itching, it is not a drug of choice since itching caused by epidural morphine is not thought to be an allergic reaction.
CHAPTER 4
DISCUSSION

Several medications have been used in an attempt to alleviate the pruritus associated with epidural morphine. However, no specific medication is effective for all patients (Table 1). Depending on study design, amount of morphine and antipruritic administered, and time of medications, patients receiving the same medicines can have varying effects.

The effect of droperidol on epidural morphine-induced pruritus was investigated by Horta et al., Naji et al., and Sanansilp et al. The findings in the studies were inconsistent to recommend droperidol as an effective treatment for morphine-induced pruritus. These results may have been due to the difference in populations (women undergoing cesarean section versus patients of both genders undergoing hip surgery) or the dosage of medication administered (1.25mg versus 5mg). The study by Naji et al. also found that there was a more significant reduction of pruritus at the 4-hour point than at the 24-hour point. At the 24-hour point, the effect of the morphine was probably gone, so there would not have been a significant amount of pruritus. Droperidol may cause QT prolongation and torsade de pointes, so caution should be used in patients with bradycardia (< 50 bpm), cardiac disease, concurrent monoamine oxidase inhibitor therapy, Class I and Class III antiarrhythmics or other drugs known to prolong QT interval (Turkoski et al.).

Ondansetron and dolasetron were effective in reducing pruritus in both studies investigated, including women undergoing cesarean section and men and women undergoing elective surgery. Although labeled for use in the prevention of nausea and vomit-
ing associated with emetogenic cancer chemotherapy (Turkoski et al.), the use as an anti-
pruritic could provide relief for patients.

Naloxone, an opioid antagonist, and nalbuphine, an opioid agonist-antagonist, were found to have varying results. The analgesia reversal of naloxone noted by Cohen and colleagues is an expected finding, since this medication is given for respiratory de-
pression associated with overdosing (Turkoski et al.). The increased somnolence experi-
enced by those patients receiving nalbuphine could have been an additive effect of the
medication plus the morphine, since both medications cause CNS depression (Turkoski et
al.).

Pellegrini et al., in their study of IV nalmefene in women undergoing cesarean
sections, found there was no significant reduction in pruritus. Nalmefene is a competitive
antagonist at opioid receptor sites (Turkoski et al.), so the increase in pain noted by pa-
tients receiving this medication would be an expected finding. However, the medication
did not reverse the pruritic effects of epidural morphine, so it would not be a drug of
choice for this adverse reaction.

Diphenhydramine, used to relieve allergic symptoms caused by histamine release
(Turkoski et al.), was not extensively investigated in this review because of it is not a
medication of interest for this review. A study by Yeh and colleagues included diphen-
hydramine in their investigation comparing ondansetron, a medication of interest to this
review, but they found that diphenhydramine did not significantly reduce epidural-
induced pruritus in women undergoing cesarean section. An extensive review needs to
be conducted before the effectiveness of diphenhydramine in managing epidural-induced pruritus can be concluded.

Limitations with Existing Studies

Although medications for pruritus are sometimes helpful, there does not appear to be one that is effective for all patients. Because epidural morphine-induced pruritus is most bothersome to women having cesarean sections, most of the studies reviewed for this research were adult women. Naji et al. and Iatrou et al., in their study of IV ondansetron and dolasetron, found there was no significant difference in gender when experiencing epidural morphine-induced pruritus. Since only two studies reviewed included men, the results from this literature review may not be applicable to the male gender. There also were no studies reviewed including children. The frequency of epidural morphine-induced pruritus in children is unknown in this review. Whether these medications would have similar results in pediatric populations are unexplored.

Many studies have been done to identify how different ethnic groups respond to pain (Bates, 1987; Greenwald, 1991). However, the study by Pellegrini et al. was the only one that reported ethnicity among the participants in those receiving antipruritic medication for morphine-induced pruritus. In a study by Cepeda and colleagues (2001), Caucasians were found to be more resistant to the effects of morphine than Hispanics or native Indians. If this is true, the results of the above studies may not be reliable for populations other than Caucasians. This population may have increased epidural morphine-induced pruritus due to a need for more medication. This area of ethnicity should
be pursued, since there may be an ethnicity-specific genetic link between morphine, pruritus, and antipruritic medications.

Since the majority of patients in the reviewed studies met criteria of the ASA physical status I, II, and III, there is no indication that these medications would be effective for patients with more serious or chronic illnesses. Studies on effectiveness of antipruritic treatment in patients with category IV of the ASA physical status classification has not been done and should be investigated in the future. However, patients with ASA physical status class V are not expected to live without immediate intervention so studying effectiveness of antipruritic treatment in this population may not be a priority.

Alternative Medications

Ziconotide, a selective antagonist which acts as an antinociceptive agent, has been studied as an intrathecal pain medication (Gevirtz, 2005). Although it is several times more potent in pain management than morphine and does not have the tolerance or addictive characteristics as morphine, the adverse side effects preclude it being used as an alternative. Besides common side effects, such as nausea and vomiting, patients also experienced ataxia, nystagmus, dysmetria, agitation, and disorientation (Penn & Paice, 2000). After the medication was stopped, patients often continued to have adverse effects for days or weeks.

Clinical Significance

These studies identify medications that have been used in an attempt to reduce the incidence of epidural morphine-induced pruritus. The mechanisms of pruritus are not well understood. However, the adverse reaction of morphine-induced pruritus is proba-
bly not an allergic reaction but an effect of the route used to administer the medication. The study by Schwörer and Ramadori identifying the possibility of serotonin being involved in the sensation and/or generation of pruritus is encouraging. More studies should be conducted using serotonin type 3 (5-HT₃) receptor antagonists to investigate the effectiveness of these medications on epidural morphine-induced pruritus.

Conclusion

Epidural morphine is an effective anesthesia/analgesic medication, so it will continue to be a drug of choice of physicians, anesthetists, and patients. However, the associated pruritus experienced by many patients has long been a difficult reaction to treat. Finding a solution would enhance the care given to patients experiencing this adverse reaction. Until morphine-induced pruritus is better understood, it may be difficult to find one antipruritic medication that is useful for all populations.
FIGURE 1

Spinal Anatomy

FIGURE 2

Epidural Needle and Catheter Placement

FIGURE 3

Drug and Receptor Interaction

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Types &amp; Age</th>
<th>Sample Size</th>
<th>Design</th>
<th>Interventions</th>
<th>Significant decrease in pruritus</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horts et al 2000</td>
<td>C-section</td>
<td>Not specified</td>
<td>Total: 140</td>
<td>Double-blind</td>
<td>All groups received IV droperidol Group 1: 0.6mg Group 2: 1.25mg Group 3: 2.5mg Group 4: 5.0mg</td>
<td>Yes</td>
</tr>
<tr>
<td>Najj et al/1990</td>
<td>Elective hip replacement 30-60 years</td>
<td>Not specified</td>
<td>Total: 40</td>
<td>Randomized</td>
<td>Group 1: epidural morphine/placebo Group 2: epidural morphine/droperidol</td>
<td>Yes</td>
</tr>
<tr>
<td>Saraospit et al/1998</td>
<td>C-section</td>
<td>Not specified</td>
<td>Total: 97</td>
<td>Double-blind randomized, controlled</td>
<td>All groups received epidural morphine Group A: only morphine Group B: epidural droperidol 2.5mg immediately Group C: epidural droperidol 2.5mg after shown infant</td>
<td>No</td>
</tr>
<tr>
<td>Yoh et al/2000</td>
<td>C-section 18-46 years</td>
<td>Not specified</td>
<td>Total: 60</td>
<td>Double-blind randomized, placebo-controlled</td>
<td>Group 1: IV NS Group 2: IV diphenhydramine 30mg Group 3: IV ondansetron 0.1mg/kg</td>
<td>Yes</td>
</tr>
<tr>
<td>Istrou et al/2005</td>
<td>Elective urological, orthopedic, or vascular surgery</td>
<td>Not specified</td>
<td>Total: 105</td>
<td>Double-blind randomized, placebo-controlled</td>
<td>Group D: IV doxastason 12.5mg Group E: IV ondansetron 4mg Group P: IV NS 5ml</td>
<td>Yes</td>
</tr>
<tr>
<td>Cohen et al/1992</td>
<td>C-section</td>
<td>Not specified</td>
<td>Total: 40</td>
<td>Double-blind randomized</td>
<td>Group 1: IV naloxone 0.2mg Group 2: IV nalbuphine 5mg</td>
<td>Nalbuphine: Yes Naloxone: No</td>
</tr>
<tr>
<td>Kendrik et al/1996</td>
<td>C-section</td>
<td>Not specified</td>
<td>Total: 51</td>
<td>Double-blind randomized</td>
<td>Group A: IV nalbuphine 2.3mg/h + PMA nalbuphine 1mg q 5 min. prn Group B: IV naloxone 50microg/h + PMA NS prn Group C: naloxone 50microg/h + PMA naloxone 40microg q 5</td>
<td>No</td>
</tr>
<tr>
<td>Choi et al/2000</td>
<td>Total Abdominal Hysterectomy</td>
<td>Net specified</td>
<td>Total: 80</td>
<td>Double-blind</td>
<td>min. prn</td>
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<tr>
<td></td>
<td>Group 1: 35.7</td>
<td></td>
<td>Group 1: 20</td>
<td>All groups received 80μg morphine</td>
<td>Yes</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td></td>
<td>+/- 9.3</td>
<td></td>
<td>Group 2: 20</td>
<td>Group 1: above solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 2: 40.3</td>
<td></td>
<td>Group 3: 20</td>
<td>Group 2: + 0.083μg·kg⁻¹·hr⁻¹ naloxone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/- 9.8</td>
<td></td>
<td>Group 4: 20</td>
<td>Group 3: + 0.123μg·kg⁻¹·hr⁻¹ naloxone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 3: 38.3</td>
<td></td>
<td>Group 4: 20</td>
<td>Group 4: + 0.167μg·kg⁻¹·hr⁻¹ naloxone</td>
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<tr>
<td></td>
<td>+/- 7.8</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Group 4: 42.4</td>
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<tr>
<td></td>
<td>+/- 8.6</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pellegrini et al/2001</td>
<td>C-section</td>
<td>Caucasian: 42</td>
<td>Total: 60</td>
<td>Double-blind randomized, placebo-controlled</td>
<td>Only at specific hours</td>
<td>$P = 0.068$ (19th hour) $P = 0.018$ (11th hour)</td>
</tr>
<tr>
<td></td>
<td>African American: 16</td>
<td>Group A: 30</td>
<td>Group A: IV nalbuphene</td>
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<tr>
<td></td>
<td>Hispanic: 1</td>
<td>Group B: 30</td>
<td>Group B: IV 0.9% sodium chloride</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Asian 1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Classification</td>
<td>Criteria</td>
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</tr>
<tr>
<td>I</td>
<td>A normal healthy patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>A patient with mild systemic disease</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>III</td>
<td>A patient with severe systemic disease that limits activity, but is not incapacitating</td>
<td></td>
<td></td>
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<tr>
<td>IV</td>
<td>A patient with an incapacitating systemic disease that is a constant threat to life</td>
<td></td>
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<tr>
<td>V</td>
<td>A moribund patient not expected to survive 24 hours with or without operation</td>
<td></td>
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</tr>
<tr>
<td>E</td>
<td>In the event of an emergency operation, an E is placed after the Roman numeral</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

REFERENCES


