Meperidine (Demerol®) has local anesthetic properties separate from its opioid receptor agonist effect. Unlike morphine, meperidine is structurally similar to local anesthetics. Therefore, it is not surprising that it possesses some characteristics of local anesthetics. If meperidine acts like a local anesthetic, binding to the same receptor sites and inhibiting nerve conduction, then drugs that alter the action and duration of local anesthetics may have a similar effect on it.

This double-blinded investigation used low-dose meperidine as the sole intrathecal agent to determine the effect of epinephrine on the duration of sensory block. Thirty male ASA physical status I through III patients between the ages of 58-81 years who were scheduled for transurethral resection of the prostate or of bladder tumors were randomly assigned to receive meperidine with or without epinephrine. A continuous spinal technique was utilized, and meperidine 0.5 mg/kg was administered after ascertaining the proper position of the catheter.

Fourteen of the patients received epinephrine, and 16 patients did not. There were no statistically significant differences between the two groups in terms of age, height, weight, and ASA physical status. No statistically significant prolongation of the sensory blockade was observed with the addition of epinephrine. There were no statistically significant differences between the two groups with regard to onset time or the incidence of complications. The occurrence of a full motor block in the group that did not receive epinephrine was statistically significant.

Key words: Continuous spinal, local anesthetic, meperidine, transurethral resection of the prostate (TURP).

Introduction

Meperidine (Demerol®) is a synthetic phenylpiperidine-derivative opioid routinely utilized in anesthesia for pain management and sedation in the perioperative period. Among narcotics, meperidine is unique, because it alone possesses local anesthetic properties capable of producing regional anesthesia. Intrathecally, meperidine 0.5 mg/kg produces a sensory block with a mean duration of 77-100 minutes.

Epinephrine, an adrenergic agonist, is commonly used with local anesthetics to prolong their effects and raise the maximum dose. This investigation used low-dose meperidine as the sole agent during continuous spinal anesthesia for transurethral resection of the prostate and of bladder tumors to determine the effect of epinephrine on the duration of neural blockade.
Materials and methods

Thirty-two male ASA physical status I through III patients between the ages of 58 and 81 years who were scheduled for transurethral resection of the prostate or of bladder tumors were selected for this study. Those excluded were persons with severe cardiovascular disease requiring pulmonary artery catheters, persons with documented sensitivities to opioids, and those who were taking monoamine oxidase inhibitors. Adherence to the contraindications to spinal anesthesia (i.e., absolutes: lack of patient consent, local infection at the site of injection, increased intracranial pressure; relative: hypovolemia, coagulopathy, systemic sepsis, and progressive neurologic disease) were observed.4 Approval was received from the hospital Human Investigation Committee, and written informed consent was obtained from each patient.

In the operating room, the following monitors were utilized: an automatic blood pressure cuff, electrocardiogram, pulse oximeter, and a precordial stethoscope. A 14- or 16-gauge peripheral intravenous (IV) line was started, and an average preload of 500 mL of lactated Ringer’s solution was infused. Oxygen was administered by nasal cannula at a 2 L/min flow. Patients were initially sedated with midazolam 1-2 mg, as needed.

They were placed in the sitting position, and the skin was prepared with povidone-iodine solution. A continuous spinal technique, using a 20-gauge catheter, was selected to allow redosing if necessary. The midline approach was routinely used, with the exception of one patient in whom the paramedian technique was utilized due to midline calcifications. The L2-3 to L4-5 interspaces were identified.

An 18-gauge Tuohy needle, with the bevel oriented parallel to the dural fibers (sagittal plane), was advanced to the epidural space, as evidenced by the loss of resistance to air technique. The needle was then advanced through the dura to the subarachnoid space, as confirmed by the free flow of clear cerebrospinal fluid. The bevel was oriented cephalad, and a 20-gauge epidural catheter was inserted. If the patient complained of paresthesias or if the catheter did not thread easily, the bevel was reoriented to achieve a smooth insertion. The catheter was advanced 1-3 cm into the subarachnoid space and secured with a dressing, after checking for the free flow of cerebrospinal fluid.

A preservative-free, 10% meperidine solution (Wyeth, Philadelphia, Pennsylvania) was obtained from the pharmacy. The specific gravity of the 10% meperidine solution, as measured by a refractometer (National, Japan), was 1.050 at 22°C (baricity, 1.045). The following hyperbaric solution was prepared: 1 mL of 10% meperidine was added to 1 mL of 10% dextrose and 2 mL of normal saline to create a 2.5% meperidine solution. The attending anesthesiologist added 0.2 mL of either 1:1000 epinephrine or normal saline to the meperidine solution to maintain a constant volume and concentration of meperidine. The samples were coded, and researchers were blinded to the contents. The specific gravity and pH at 22°C were 1.025 and 5.4, respectively, in the meperidine solution with epinephrine added and 1.025 and 5.6, respectively, in the solution with no epinephrine. The specific gravity of the solutions at 37°C was 1.021, which also corresponds to a baricity of 1.021. A solution must have a baricity of at least 1.0015 at 37°C to be considered hyperbaric.5,6

A 0.5 mg/kg dose of meperidine solution was administered with the patient in the sitting position.3 The spinal catheter, which had a 0.33 mL capacity, was flushed with 1 mL of normal saline after administration of the meperidine solution. The patients remained seated for 5 minutes before being placed in the supine position to ensure an adequate sensory block of the S2-S4 dermatomes with the hyperbaric solution. The patients were tested for sensory block to pinprick and to temperature with alcohol. They were assessed to determine the onset of sensory blockade to the T10 level.

Once the T10 level had been attained, the patient was placed in the lithotomy position. Four of 32 patients developed a block lower than the T10 level 10-15 minutes after the initial dose. These patients were redosed with one third of the initial dose while supine, and a sensory block to the T10 level occurred within 5-12 minutes. Therefore, onset was considered to be the sum of both time intervals. In addition, nine of 32 patients complained of discomfort an average of 64 minutes (range: 43-116 minutes) into the procedure. They were redosed with one third of the initial dose while in the lithotomy position. An arbitrary dose equal to one third of the initial dose was chosen for rebolusing to provide adequate analgesia with a margin of safety, because an initial dose of 1 mg/kg had been safely given.6

The duration of sensory block by pinprick was determined by regression to the S2 dermatome. Due to the instances of redosing, it was necessary to calculate the duration using two different methods. In those patients who were not redosed, the duration was determined by regression to the S2 dermatome. The patients who required intraoperative redosing with one third of the initial dose required the following calculation: The time

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(T1) from the T10 level to the onset of pain was added to the time (T2) from redosing, to the regression of the block to the S2 dermatome. These two times were averaged to calculate the duration of block (T1 + T2/2). The frequency of dermatome level assessments was every 3 minutes for the first 15 minutes, then every 5 minutes for up to 30 minutes, and finally every 10 minutes intraoperatively.

The motor blockade was determined according to the modified Bromage scale:
0 = No paralysis.
1 = Inability to raise the extended leg.
2 = Inability to flex the knee.
3 = Inability to flex the ankle joint.

The motor blockade was noted at the same time intervals used for sensory block assessment. Once the patient was secured in the lithotomy position, motor blockade was not assessed until the end of the procedure.

Blood pressure and heart rate were monitored every minute for 25 minutes and every 3 minutes thereafter. Decreases in systolic blood pressure of greater than 25% below each patient's established baseline level were treated with an infusion of 250 mL of crystalloid and, if necessary, with vasopressors, i.e., 5 mg of ephedrine or 50 mg of phenylephrine, if the heart rate was greater than 100. Respiratory depression, which was defined as a decrease in Sao2 below 90%, a respiratory rate of less than 10 or greater than 30, and/or changes in level of consciousness, was treated with an increase in oxygen delivery to 4 L/min. Nausea and vomiting associated with hypotension responded to intravenous fluids and small doses of a vasopressor.

Table I

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>A group1 (n = 14)</th>
<th>B group2 (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean (± sd)</td>
<td>Mean (± sd)</td>
</tr>
<tr>
<td></td>
<td>69.4 (± 7.4)</td>
<td>68.2 (± 4.4)</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>55-81</td>
<td>58-75</td>
</tr>
<tr>
<td><strong>Height (inches)</strong></td>
<td>Mean (± sd)</td>
<td>Mean (± sd)</td>
</tr>
<tr>
<td></td>
<td>68.9 (± 2.9)</td>
<td>69.8 (± 2.1)</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>64-76</td>
<td>67-74</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>Mean (± sd)</td>
<td>Mean (± sd)</td>
</tr>
<tr>
<td></td>
<td>86.5 (± 17.9)</td>
<td>85.9 (± 11.8)</td>
</tr>
<tr>
<td><strong>Range</strong></td>
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<td>61-105</td>
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<td><strong>ASA physical status</strong></td>
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<td>I</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

No significant differences between groups. (All P values > 0.05)
1. Epinephrine-containing group
2. No epinephrine group

As described above. Nausea that was not associated with hypotension was treated with metoclopramide 10 mg IV or droperidol 0.625 mg IV, as needed. Pruritus (both intraoperative and postoperative) varied from mild, requiring no treatment, to uncomfortable, and responded to either diphenhydramine 12.5-25 mg IV or naloxone 0.04 mg IV in incremental doses to a maximum dose of 0.16 mg. Postoperative interviews were conducted with all patients. Patients were followed for 3 days postoperatively or until discharge, and complications were recorded.

In the statistical analysis, age, height, weight, and time to onset were tested for significance by means of a unpaired Student's t-test. An adjusted t-test was performed to determine the significance of duration due to the unequal variance between the groups. The chi-square test was applied to the ASA physical status, the incidence of motor blockade, hypotension, pruritus, nausea, and vomiting. A value of P < .05 was considered significant.

Results

There were 14 patients in the epinephrine group (A group) and 16 patients who did not receive epinephrine (B group). No statistically significant difference existed between the two groups with regard to age, height, weight, and ASA physical status (Table I).

Sensory blockade

There was no statistically significant difference in the onset time of sensory blockade between group A (13.3 ± 13.3 minutes) and group B (11.9 ± 11.9 minutes). The mean duration in the A group was 94.4 minutes compared to 79.3 minutes in the B group. Although this demonstrates a 15.2-minute prolongation in the A group, the difference was not statistically significant (Table II). To determine if redosing influenced the duration, the data was analyzed as described in the methods section to obtain an “average” duration. This was compared to the time until S2 regression or a complaint of pain occurred, which excluded the time period after redosing. The results indicated no significant difference using either method of calculating the duration.

Motor blockade

Motor block was not detected in all 14 patients in the A group; however, 4 of the 16 patients in the B group had a full motor block, according to the modified Bromage scale (Table II). This was a statistically significant finding (P < .04). Because minimal muscle relaxation was needed for surgery, the lack of motor block did not cause any difficulties and was not monitored after initial assessment.
Intraoperative complications

Of the 14 patients in the A group, 3 (21.4%) showed a decrease in systolic blood pressure greater than 25% from each patient’s established baseline. In the B group, 7 of the 16 patients (43.7%) experienced a decrease of blood pressure greater than 25% from the established baseline. The incidence of hypotension between the two groups was not statistically significant.

There was one patient in each group who experienced respiratory depression; both responded to oxygen therapy via face mask with no further sequelae. The incidence of nausea and vomiting and of pruritus was similar for both groups (Table III). One patient in the B group complained of a postdural puncture headache and was successfully treated with an epidural blood patch.

Two patients, who were not included in the statistical analysis of this study, required general anesthesia. The first patient experienced an ineffective sensory (“spotty”) block, which was attributed to the fact that he had been dosed in the supine rather than the sitting position. The protocol was then altered to ensure that initial dosing was done when the patients were sitting. Catheter migration, with the inability to aspirate cerebrospinal fluid caused the second failed block.

Discussion

The ability of epinephrine to alter the quality and duration of spinal blockade resulting from local anesthetics has been attributed to several possibilities. Epinephrine apparently prolongs spinal anesthesia by decreasing vascular uptake of some local anesthetics, e.g., tetracaine, from the subarachnoid space, thereby exposing neural tissue to higher concentrations of local anesthetic for longer periods of time.

Controversy exists with respect to the addition of epinephrine prolonging bupivacaine and lidocaine. Chambers and colleagues were unable to demonstrate that vasoconstrictors added any “useful” prolongation of lidocaine or bupivacaine anesthesia.9, 10 In contrast, Leicht and Carlson reported that the time to regression of two segments and the time to total recovery of sensory and motor blockade were prolonged when epinephrine was added to lidocaine.11

Epinephrine has been suggested to alter the pH and therefore the binding and diffusion characteristics of the local anesthetics.12 However, no evidence was found to support this mechanism. The pH of the meperidine solution only changed from 5.6 to 5.4 with the addition of epinephrine. Finally, epinephrine itself may have direct anti-nociceptive properties; for example, alpha-agonists have been shown to interact with specific receptors in the spinal cord to produce analgesia.13

The results showed no statistically significant prolongation of sensory blockade with the addition of epinephrine to intrathecal meperidine. However, the mean duration in the epinephrine-containing group was 15.2 minutes longer than in the group without epinephrine. That this is not statistically significant may be explained by the small group numbers and the large variance in mean duration within these groups. Repetition of these experiments using different amounts of meperidine and/or epinephrine with solutions of varying baricity or increasing the sample size may demonstrate the ability of epinephrine to prolong sensory blockade.

The duration of spinal anesthesia depends upon two major factors: concentration of local anesthetic in the cerebrospinal fluid and vascular ab-
sorption of the local anesthetic. The greater the concentration, the greater the duration. Patients who were redosed initially exhibited a longer duration when compared with the mean duration of those patients who received only an initial dose of 0.5 mg/kg. Specifically, in those patients in the A group who received 0.5 mg/kg, the mean duration was 94.4 minutes, whereas in the B group it was 79.3 minutes. In those patients who received 0.65 mg/kg (due to redosing), the mean duration was prolonged to 121 minutes in the A group and 92 minutes in the B group. Therefore, epinephrine may significantly prolong the duration of intrathecal meperidine when a larger study sample and a greater initial dose are used.

Although segmental regression was not quantitatively measured, once the block began to regress, it did so very rapidly in both groups. This observation has not been reported in the literature, although it is known that regression occurs most rapidly with hyperbaric spinals.

A unique characteristic of meperidine at this concentration is its limited ability to produce motor blockade despite adequate sensory blockade. All 30 patients described varying degrees of heaviness of their lower extremities, while four patients had a complete motor block. Each patient could move himself from the operating table to the cart by the end of the procedure. This reduced recovery room stay and promoted early ambulation while continuing to provide analgesia; these characteristics are advantageous for outpatient surgery.

In a previous study by Acalovschi and associates, meperidine at 0.5 mg/kg was noted to be hemodynamically stable when used intrathecially. The mean age of their subjects was 37 years in a sample population of 111 patients. Only three patients experienced hypotension, with no decreases in systolic blood pressure greater than 20% of their baseline value. In this study, a greater incidence of hypotension may in part be attributed to the older age of its population (mean of 69 years) and the prevalence of cardiovascular disease.

Although it was not a statistical difference in this small study, the high incidence of hypotension in patients in the group that contained no epinephrine (twice that in the epinephrine-containing group) suggests some benefit for epinephrine. A larger study may clarify this observation. (Authors' note: In a retrospective study of 15 patients undergoing transurethral resection of the prostate or of bladder tumors at our institution who received "conventional" spinal anesthesia with tetracaine (10-12 mg), 3 (20%) developed hypotension by our criteria and 6 (40%) received either ephedrine or phenylephrine intraoperatively.)

A sensory blockade above the T4 level ("high block") was noted in 15 of 34 patients. Of these, only 2 patients met any of the criteria for respiratory depression, with a drop in $\text{O}_2$ saturation to less than 90%, and both responded to supplemental oxygen. Of the patients who experienced hypotension, the majority had blocks above the T4 level. Hypotension may be attributed to sympathetic blockade, volume status, and possible suppression of cardioaccelerator fibers (T1-T4). However, the incidence of hypotension was 53% overall. None of the patients who experienced hypotension had a change in heart rate, suggesting that alteration of cardioaccelerator fibers did not play a dominant role. (It should be noted that only 1 of the 15 patients with a high block was on a beta blocker.) If hypovolemia secondary to sympathetic blockade was the cause, a reflex tachycardia would be expected to occur. Probably, the hypotension was a combination of several factors, but it cannot be precisely determined by this study. Interestingly, one of the major advantages of spinal opioids is the "selective" blockade of presynaptic and postsynaptic nociceptors in the substantia gelatinosa of the dorsal horn, which avoids the sympathetic block frequently seen with local anesthetics.

Baricity, limited protein binding, and limited lipid solubility may contribute to these "high blocks." Because the patients are placed in the lithotomy position shortly after they have been placed supine, the natural lordotic curve of the lumbar spine was decreased, promoting a greater cephalad spread of unbound meperidine hyperbaric solution with time. In a study by Van Gessel and colleagues using bupivacaine during continuous spinal anesthesia, the cephalad spread produced by a hyperbaric solution was significantly greater than with an isobaric solution.

Documented side effects of spinal narcotics include respiratory depression, urinary retention, nausea, vomiting, and pruritus. In this study, there were 6 cases of nausea; 2 were associated with hypotension (due to the absorption of irrigation fluid at the prostatic venous sinuses), 2 with hypotension, and 2 were attributed to the meperidine.

Pruritus was the most common side effect, with complaints ranging from mild, requiring no treatment (5 patients), to uncomfortable requiring treatment (10 patients). The patients were treated with either intravenous diphenhydramine or naloxone, and symptoms were alleviated within 5-8 minutes. There was no reversal of the local anesthetic effects of meperidine in any of the patients who received naloxone. This observation was supported by the lack of regression of sensory block, and no
patient who received naloxone complained of pain. Late respiratory depression is not as great a concern with intrathecal meperidine as with morphine because its higher lipid solubility decreases the rostral spread within the cerebrospinal fluid. Meperidine apparently acts at spinal μ-receptors to provide prolonged postoperative pain relief. Other studies have used 1 mg/kg of meperidine with an increased incidence of side effects. It is possible that 0.65 mg/kg will provide therapeutic efficacy with fewer side effects than 1 mg/kg.

Conclusion
Intrathecal meperidine was used for spinal anesthesia. Based on the statistical analysis of the data, the presence of epinephrine does not prolong the duration of intrathecal meperidine. Limited motor blockade was observed with meperidine. It may be that meperidine is beneficial for certain orthopedic surgeries and in the outpatient setting. Obstetric anesthesia is another area where the lack of a motor block may be appreciated, because it preserves the mechanics of labor while providing anesthesia.

Prolonged analgesia is also advantageous for both inpatients and outpatients. Late respiratory depression is not associated with this opioid. Its major side effects—hypotension, pruritus, nausea, and vomiting—responded well to treatment. Future investigations with meperidine, such as varying the baricity of the solution, manipulating the dose, combining it with other local anesthetics to ensure a motor blockade, and its use for other types of regional anesthesia, will help define its role in anesthesia.

Finally, cost containment is currently an issue in all institutions, and the cost of meperidine is a fraction of that of other local anesthetics.

REFERENCES

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