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Muscular Spasm in the Lower Limbs of Laboring Patients after Intrathecal Administration of Epinephrine and Sufentanil

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THE use of intrathecal opioids for the management of labor pain has the advantage of providing analgesia for patients in labor without producing motor or autonomic blockade. In addition, intrathecal opioids produce no demonstrable deleterious fetal or neonatal ef-

fects.¹ Combinations of opioids such as fentanyl and morphine have been reported to give rapid-onset and prolonged analgesia for patients in labor.² Sufentanil provides an extremely rapid onset of analgesia and a duration comparable to that of the morphine-fentanyl combination.³ Additional work has demonstrated that intrathecal sufentanil produces more profound analgesia than does intrathecal fentanyl in the management of labor pain.⁴

Epinephrine has a long history of use as an adjuvant to intrathecal anesthesia in obstetrics. Recently, in our initial management of patients in labor, we have used 10 µg intrathecal sufentanil in a double-needle technique similar to that used for cesarean delivery.⁵ When the parturient patient requests additional analgesia, epidural analgesia is administered. Because it has been demonstrated that the addition of 300 µg epinephrine to 50 µg sufentanil, epidurally administered, prolongs analgesia,⁶ we thought that the addition of 200 µg epinephrine to 10 µg spinally administered sufentanil would prolong the action of the sufentanil and also

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enhance analgesia because of the α_2 -adrenergic actions of the epinephrine.⁷

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Thirteen patients received 10 μ g sufentanil, 200 μ g epinephrine, and 1 ml preservative-free normal saline. The epinephrine and normal saline used in individual patients had been produced by different manufacturers. The analgesia from the intrathecal administration of this mixture lasted 90–150 min, as evidenced by patients' requests for additional analgesia. All patients complained of generalized mild pruritus within minutes of the injection of the intrathecal medications. No patients requested treatment for the pruritus.

Of the first 13 patients given the combination of sufentanil, epinephrine, and saline, 7 evidenced a mild to profound contraction, of relatively brief duration, of the lower limb musculature with no evidence of residua. In addition to the complaints of the patients cited below, the events were witnessed by one or more of the authors in every case. In cases in which the duration of the phenomenon is noted, the duration began with the first complaint by the patient or the first observation by the anesthesia personnel and ended when the patient said that the "stiffness" was gone and that she could easily move the affected limb(s). Age is noted in parentheses.

- Case 1 (35 yr). Reported stiffness of both legs. It was not noted how long the "stiffness" lasted.
- Case 2 (29 yr). Reported a "curling of the feet, without pain, like a cramp." The spasm lasted 7 min.
- Case 3 (28 yr). Reported "stiff muscles but no pain." The spasm started within 2 min after injection and involved the entire right leg and the lower left leg. Five minutes after injection the right leg was "OK." The left leg was "OK" 7–8 min after injection.
- Case 4 (30 yr). Complained of stiffness without pain affecting both legs. The stiffness resolved 6.5 min after injection.
- Case 5 (23 yr). Reported stiffness of the left leg only and with no pain. It resolved in 6.5 min.
- Case 6 (22 yr). Reported stiffness beginning 2 min after injection and lasting 7 min. The left leg was more stiff than the right leg. There was no report of pain.
- Case 7 (19 yr). Reported that her left leg felt "very heavy" and that she "couldn't move." There was no pain. Onset was at 7 min after injection, and the phenomenon lasted 3.5 min.

We observed that at the time of a patient's complaint, 1–2 min after the injection of the combination of sufentanil and epinephrine, the muscles of the lower limb(s) were contracted. We could not move or bend affected limb because of rigidity in the foot and in the lower or entire leg. Within 6–7 min the stiffness and spasm had abated. After the spasm had abated, there was no discernible alteration in the sensation of cold to alcohol wipes in the lower limbs, abdomen, or thorax to the T4 level. In addition, there was no discernible change in sensation obtained with a needle from the lower limbs to the T4 level. The patients were not tested for sensory level during the phenomena. Of these seven patients, two reported the effect on one side only, whereas in the other five patients the phenomenon was bilateral.

During the spasm there was no decrease in maternal blood pressure or alteration in fetal heart rate. All neonates had 5-min Apgar scores of 9. One neonate had a 1-min Apgar score of less than 8 (Apgar score 6). One of the parturient women had a cesarean delivery because of persistent variable decelerations occurring hours after the

initiation of epidural anesthesia. The other patients had vaginal deliveries.

The patients reported no problems after delivery and have reported none in the interval since the births of their children. Some patients, in retrospect, have described the experience as similar to a painless "charley-horse."

Discussion

We have described seven patients who exhibited a painless contraction of the muscles of the lower extremity after the intrathecal administration of 10 μ g sufentanil and 200 μ g epinephrine. Opioid-induced muscular rigidity is an attractive explanation for this phenomenon. Opioid-induced muscular rigidity reported after the parenteral administration of large doses of opioids has involved the thoracic and abdominal musculature.^{8–10} A recent study demonstrated muscular rigidity in rodents most prominently in the gastrocnemius muscle compared to the rectus abdominis after intravenous administration of fentanyl.¹¹ This rigidity as well as myoclonic seizure activity can be elicited by intrathecal administration of a large dose of opioid.^{12–14} Muscular rigidity seen after spinal administration of opioids is mediated by a receptor-specific interaction in brainstem centers.¹⁵ It is believed that the phenomena observed in the current cases, however, cannot be attributed to the actions of intrathecally applied opioids on the brainstem centers. In our patients, a large dose of an opioid was not given. The muscular effect was present within 2 min after the administration of the sufentanil–epinephrine mixture, and thus not enough time had elapsed between the injection and the onset of the spasm for cephalad migration of a significant concentration of sufentanil.¹⁶ Finally, neither intrathecal^{4,17,18} nor epidural^{17,19} administration of clinical doses of sufentanil has been reported to produce any muscular effects.

Perhaps the mixture of epinephrine and sufentanil produced the observed muscular effects in the lower limbs. The addition of epinephrine to epidural sufentanil,⁶ hydromorphone,²⁰ or diacetylmorphine²¹ has not been reported to produce any evidence of muscular rigidity. It could be hypothesized that the observed phenomena were due to the enhancement of sufentanil-induced muscular rigidity by the addition of epinephrine. This seems unlikely, however, because the intraperitoneal administration of dexmedetomidine prevents the opiate-induced rigidity seen after systemic alfentanil administration.²² Dexmedetomidine is an α_2 agonist, and epinephrine also has α_2 agonist actions.

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Therefore, if any opioid-induced rigidity resulted from the use of sufentanil, it would be antagonized, not enhanced, by the addition of epinephrine.

The increased intensity and duration of the subarachnoid block produced by some local anesthetics has been attributed to the vasoconstrictor action of epinephrine, with 200–300 μg commonly used.²³ The addition of epinephrine may have increased the opioid concentration in the cerebrospinal fluid by decreasing its absorption. The effect observed may have been a toxic effect of the sufentanil. Rawal *et al.*¹² have reported the following results in sheep after intrathecal administration of sufentanil every 6 h for 3 days. After administration of 7.5 $\mu\text{g}/\text{kg}$ sufentanil, they saw initial whole-body muscular rigidity during the injection, lasting for as long as 90 s after the injection. A period of hindlimb motor weakness lasting 1.5–5 h followed the initial rigidity. The histopathologic changes seen were moderate to severe inflammatory changes (meningitis and arachnoiditis) as well as some neuronal chromatolysis and axonal swelling. The smaller dose of sufentanil (1.5 $\mu\text{g}/\text{kg}$) produced only mild histopathologic changes, and the motor effects were much less severe. The rigid extension of the forelimbs disappeared after the cessation of the injection, and the hindlimb weakness had abated within 30 min.

The dose of sufentanil used by Rawal *et al.*,¹² however, was about ten times the dose used in the current cases. In addition, the volume of the intrathecal space in sheep is much smaller than in humans.¹⁷ Therefore, the concentration of sufentanil in the sheep would be much greater than that we administered to our patients. Even with the possible increase in the intrathecal concentration of sufentanil as a result of the epinephrine addition, the concentration would not have been nearly as much as that used by Rawal *et al.* Furthermore, we saw only lower limb rigidity. There was no subsequent weakness or flaccidity of the lower limbs. Therefore, we believe that the neurotoxicity observed by Rawal *et al.* is not the same as the phenomenon reported here.

Finally, could the observed phenomenon be attributed solely to epinephrine? Wu *et al.*²⁴ reported that in rhesus monkeys “following small [intrathecal] doses of epinephrine (less than 0.3 mg/kg, 0.1 per cent solution) . . . excitation developed, which was characterized by hyperextension, rigidity and hyperactive tendon reflexes. Larger doses (0.6–1.0 mg/kg) . . . produced excitation followed by depression.”²⁴ This description sounds identical to that in the current reports, with the exception that we did not test the ten-

don reflexes. Wu *et al.* suggested that “the clinical picture and the neurological signs were similar to those of acute anoxia or hypoxia of the spinal cord.”²⁴ The doses used in the work by Wu *et al.* are far greater than those used clinically, and they provide no evidence for the occurrence of ischemia. In addition, in the work of Priddle and Andros,²⁵ a dose of 1 mg epinephrine was given intrathecally to three patients without any untoward effects, nor were any signs of excitation reported in these three patients or in seven others, who received 400 μg of epinephrine intrathecally. Like our seven patients, none of these ten patients had any symptoms or residua that could be attributed to spinal cord ischemia. It seems unlikely that what was observed in the current work was a result of transient ischemia of the spinal cord.

If the phenomena reported can be attributed to the effects of epinephrine, they probably are not mediated by the α_2 actions of epinephrine, because no motor effects have been reported to occur with intrathecal or epidurally applied clonidine.^{7,26} Data exist to support the hypothesis that the motor effects observed in the current work can be attributed to the α_1 actions of epinephrine. Intrathecal application of the α_1 agonist methoxamine in rats produced a motor disturbance that was “characterized by hyperreflexia, clonic flexion of the hindlimbs and rigidity and serpentine movements of the tail.”²⁷ A similar hindlimb rigidity or hyperextension has been seen in rats treated with yohimbine, an α_2 antagonist,²⁸ producing a predominance of α_1 effects. Therefore, if the initial effect of the intrathecally administered epinephrine was as an α_1 -agonist, an excitatory motor pattern could be expected. This excitation would be terminated by the “antagonism of the α_1 effects by α_2 effects”²⁷ or perhaps by the “local anesthetic effects of epinephrine.”²⁵

In summary, we present seven cases of transient lower limb rigidity after the administration of intrathecal sufentanil and epinephrine. We believe that the phenomenon is mediated by the α_1 -adrenoreceptor system and is neither a toxic manifestation of sufentanil nor a variant of opioid-induced rigidity. We have continued to use the mixture intermittently and have continued to observe the phenomenon, although not as frequently as described in this report. We currently are engaging in a formal study of the effects of intrathecal opioids with and without α -adrenergic agonists.

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