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Procaine Spinal Neurotoxicity

Michael E. Johnson, M.D., Ph.D., Jerry W. Swanson, M.D.†*

THE rare but devastating complication of cauda equina syndrome (CES) after spinal anesthesia has been reported with several local anesthetics, most frequently lidocaine.[1] A separate complication of spinal anesthesia, transient neurologic syndrome (TNS), consisting of potentially severe but transient lumbosacral pain, has also been reported and is also most frequent with lidocaine.[2] The mechanism of CES from local anesthesia is most likely necrotic or apoptotic neuronal death, depending on the intensity of the local anesthetic exposure.[3] The mechanism of TNS is unknown but seems to be distinct from that of CES.[4,5]

Lidocaine's pharmacokinetics are ideal for spinal anesthesia for short-duration, ambulatory surgery. The increased frequency of CES and TNS with lidocaine has encouraged the study of other local anesthetics to substitute for lidocaine, without complete success.[6–8] Procaine has been reported to be less likely to produce TNS than lidocaine, with a kinetic profile also suitable for short-duration surgery.[9,10] However, there has been no modern study of procaine and CES. We now report a case of permanent CES after procaine spinal anesthesia.

Case Report

A 52-yr-old, 89-kg female licensed practical nurse was healthy except for occasional migraine headaches, which were well controlled with 25 mg topiramate every morning and 50 mg every evening, and 80 mg long-acting propranolol every evening. She had asymptomatic, mild aortic regurgitation associated with a bicuspid aortic valve, and normal ventricular size and function. She was gravida 3, para 3, with two lacerations and one episiotomy during deliveries, and later had a total abdominal hysterectomy and bilateral salpingo-oophorectomy. She had also undergone a tonsillectomy and adenoidectomy, and had a euthyroid goiter and a history of resolved tennis elbow. She had a remote history of tingling upper and lower extremity paresthesias when she began taking topiramate, until her dose was appropriately adjusted. Otherwise, she had no history of anesthesia or paresthesia, parasacral or otherwise. She had normal bowel, bladder, and sexual function.

She experienced a right knee injury and was scheduled to undergo an elective right knee arthroscopy. She received a spinal anesthetic administered in the sitting position, after she received 2 mg midazolam and 100 μg fentanyl intravenously. After 60 mg lidocaine infiltration, the subarachnoid space was entered on the first pass with a 24-gauge Sprotte needle at the L3–L4 interspace. Free flow of clear fluid was obtained, with no paresthesia or bleeding, and 1.5 ml procaine, 10%, was injected. A sensory level of T10 was recorded. Oxygen saturation measured by pulse oximetry (Spo_2) immediately after the spinal anesthetic was administered was 90% on room air. Supplemental oxygen was added at 3 l/min by nasal cannula, with Spo_2 of 93–97%. No further sedation was given. Total anesthesia time was 35 min, with blood pressure 105–150/70–80 mmHg, heart rate 76–92 beats/min, and intravenous fluid 600 ml lactated Ringer's solution. A right partial medial meniscectomy was performed in 17 min, with 15 min tourniquet time at 350 mmHg, and negligible blood loss. After transfer to the postanesthesia care unit, the patient was nauseated and received 4 mg ondansetron and 0.25 mg droperidol, with improvement and no other apparent problems. Her sensory level decreased from T12 to L1 during her 30-min stay in the postanesthesia care unit.

After a further stay in the hospital's ambulatory surgery unit (exact time not documented), the patient was discharged home. She recalled no neurologic deficit at the time of discharge, although a detailed neurologic examination was not performed then, and her primary focus was her surgical site. However, at home, she was unable to urinate when desired, was intermittently incontinent of urine, and became aware of some pelvic numbness. The next day, she presented at her local emergency department and on examination had numbness of the right perineum extending back to the perianal area. Postvoid residual was measured at 375 ml. Magnetic resonance imaging of the lumbar spine showed mild degenerative disk disease with no significant central canal or nerve root compromise, no extra-arachnoid or epidural fluid collection, and no abnormal conus or cauda equina enhancement. She was discharged from the emergency department with instructions to catheterize her bladder intermittently. A week later, she noted a new pain of parasacral burning and throbbing, which she rated 10/10, together with an intermittent shooting right thigh pain, and a left heel paresthesia. She was unable to defecate for a week after surgery, until she was placed on bowel softener and laxative. She reported a total lack of vaginal sensation and inability to achieve orgasm, which was not present before the surgery. A follow-up magnetic resonance image without and with intravenous gadolinium 12 days after the first magnetic resonance image showed no change.

A detailed neurologic examination 18 days after her spinal anesthetic showed decreased superficial pain sensation over the right perineal and perianal region. Anal tone and voluntary contraction were normal. The remainder of the neurologic examination, including muscle strength testing, gait, and muscle stretch reflexes, was normal. Electromyography and nerve conduction studies of the right lower extremity were performed 32 days after the spinal anesthetic and were normal. In addition, needle electromyography activity of the anal sphincter was normal. Urodynamic studies were performed 33 days after the anesthesia and showed findings consistent with an acontractile bladder. When taken together, the symptoms and findings were consistent with a CES affecting predominantly lower sacral roots.

The patient was seen in follow-up 12 months after the spinal anesthetic. She continued to have perineal and left foot numbness as before. She was having relatively infrequent urinary incontinence but overall was managing well with a bladder training program. She was experiencing relatively frequent urinary tract infections. She continued to note significant constipation that required a bowel management program. There was no limb pain, but she had intermittent low back pain. There was also localized right knee pain with weight bearing. The neurologic examination was essentially unchanged from that of the previous year. A urodynamic study showed a poorly

* Assistant Professor, Anesthesiology Department, † Professor, Neurology Department, Mayo Clinic College of Medicine.

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Address correspondence to Dr. Johnson: Mayo Clinic, Anesthesiology Department, SMH 2-MB, 200 Southwest First Street, Rochester, Minnesota 55905. johnson.michael@mayo.edu.

contractile bladder with the patient voiding with low-amplitude detrusor contractions.

Discussion

This is the first report in modern indexed medical literature of irreversible CES associated with procaine spinal anesthesia, where factors other than procaine neurotoxicity can reasonably be excluded. Procaine was the first synthetic local anesthetic and was used extensively in the early 20th century. It has been displaced in modern anesthesia by other local anesthetics, likely related to its lesser stability in solution and higher incidence of allergic reactions and nausea.[11,12] The incidence of procaine use in spinal anesthesia in recent surveys ranges from 33% during 1987–1990 in the Midwest[13] to 0% during 1998–1999 in France,[14] the former mostly in combination with tetracaine.

Interest in procaine as a short-acting spinal local anesthetic has been revived with reports[9,10] that it does not cause TNS, an acute pain syndrome that can follow spinal anesthesia with lidocaine, the most common option for short-acting spinal anesthesia. Although the etiology of TNS is unclear, available evidence suggests that it is distinct from the irreversible spinal injury, usually CES, that can also follow lidocaine spinal anesthesia.[4,5] Therefore, a lesser incidence of TNS with procaine does not necessarily imply a lesser incidence of CES.[15]

The important question is whether the case reported here indicates a neurotoxicity for procaine similar to that of lidocaine. Unfortunately, although several studies *in vitro*[3,16] and *in vivo*[14,17–19] have provided estimates of the neurotoxicity of other local anesthetics commonly used in spinal anesthesia, there are few modern data available on procaine, except for a single study that used an assay of uncertain relevance to mature spinal cord neurotoxicity (growth cone collapse in growing invertebrate neurons) and did not account for differences in local anesthetic potency.[20] However, there is a surprising abundance of case reports and animal studies from the first half of the 20th century suggesting that procaine has a low therapeutic index.[15,21,22] Schildt's conclusions in 1947, summarizing from a database in which procaine was predominant, are presciently similar to the current view of local anesthetic neurotoxicity: "The probable cause of the injuries of the spinal cord is a chemotoxic effect. Animal experiments show that just the anesthetic and not other substances present in the solution is the cause. The effect on the myelon [*sic*] is also proportional to the strength of the anesthetic solution as well as to the injected volume. It is always observed that the damage to the myelon [*sic*] is most marked caudally where the concentration of the drug can be considered to have been the highest."[21]

Procaine is generally considered to be half as potent as lidocaine, and the total dose of 150 mg procaine was within the recommended maximum single dose of 200 mg procaine for spinal anesthesia.[23] The medical records available to us do not indicate the specific formulation of 10% procaine used in the case reported here. However, there is only one commercially available, Food and Drug Administration–approved formulation of 10% procaine hydrochloride in the United States, that of Hospira,‡ and 10% procaine hydrochloride is always hyperbaric.[24] Use of a small-bore needle, hyperbaric procaine, and the sitting position may have contributed to poor mixing of procaine with cerebrospinal fluid, resulting in high local concentrations.[25] It is interesting that a major regional anesthesia book from a period when procaine was used much more frequently recommends dilution of procaine to 5% or less before intrathecal injection, even though local anesthetic neurotoxicity was not considered a significant problem at that time.[26] To the extent that maldistribution of procaine contributed to the neurotoxicity seen in this case, the injection of 10% procaine was likely more neurotoxic than an equal dose given as 5% procaine would have been. We are not aware of recommendations to dilute 10% procaine to 5% before injection in more recent texts.

In summary, this case documents that procaine can cause irreversible CES after spinal anesthesia, similar to other local anesthetics. More study is required to establish the relative risk from procaine compared with other local anesthetics. Until those data are available, it is questionable whether minimizing TNS, a transient and self-limited pain syndrome, is a sufficient indication for selecting procaine to replace lidocaine as a short-acting spinal local anesthetic.

‡ See the Food and Drug Administration's searchable drug database, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name, where searching for procaine and 10% yields only the single Hospira formulation. Accessed May 1, 2008.

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