

$\pm 45.2$  and  $391.8 \pm 83.3$  s, respectively). The reason for this apparent difference between edrophonium and neostigmine is unknown. It is known that inhibition of the cholinesterase enzyme by edrophonium occurs by a different mechanism from that of neostigmine.<sup>16</sup> Although there is still some controversy concerning the mechanism of anticholinergic action of edrophonium and neostigmine,<sup>§,17,18</sup> cholinesterase inhibition appears to be a major factor.<sup>§</sup>

Three questions, however, have to be answered before recommending the routine clinical application of this maneuver. First, what is the optimal time interval between the first (priming) and the second dose of the acetylcholinesterase inhibitor? Secondly, what is the optimal priming dose? Lastly, what is the optimal size of the second dose?

We conclude that, compared with a single bolus, administration of edrophonium  $0.2 \text{ mg} \cdot \text{kg}^{-1}$  followed 3 min later by  $0.8 \text{ mg} \cdot \text{kg}^{-1}$  significantly accelerated the rate of reversal of residual atracurium-induced neuromuscular blockade. With this sequence of administration, about 4 min were necessary to obtain a TOP ratio of 0.75 when antagonism of atracurium paralysis was attempted at 90% depression of twitch height.

#### REFERENCES

1. Abdulatif M, Naguib M: Accelerated reversal of atracurium blockade with divided doses of neostigmine. *Can Anaesth Soc J* 33:723-728, 1986
2. Viby-Mogensen J: Clinical evaluation of neuromuscular transmission. *Br J Anaesth* 54:209-223, 1982
3. Ali HH, Kitz RJ: Evaluation of recovery from non-depolarizing neuromuscular block using digital neuromuscular transmission analyzer: Preliminary report. *Anesth Analg* 52:740-743, 1973
4. Armitage P: *Statistical Methods in Medical Research*. London, Blackwell Scientific Publications, 1971, pp 269-301
5. Barber HE, Calvey TN, Muir KT: The relationship between the pharmacokinetics, cholinesterase inhibition and facilitation of twitch tension of the quaternary ammonium anticholinesterase drugs, neostigmine, pyridostigmine, edrophonium and 3-hydroxyphenyl-trimethylammonium. *Br J Pharmacol* 66:525-530, 1979
6. Foldes FF, Deery A: Protein binding of atracurium and other short-acting neuromuscular blocking agents and their interaction with human cholinesterases. *Br J Anaesth* 55 (Suppl. 1): 31S-34S, 1983
7. Cronnelly R, Morris RB: Antagonism of neuromuscular blockade. *Br J Anaesth* 54:183-194, 1982
8. Paton WDM, Waud DR: The margin of safety of neuromuscular transmission. *J Physiol (Lond)* 191:59-90, 1967
9. Miller RD (Editorial). The priming principle. *ANESTHESIOLOGY* 62:381-382, 1985
10. Bowman WC: Prejunctional and post-junctional cholinergic receptors at the neuromuscular junction. *Anesth Analg* 59:935-943, 1980
11. Donati F, Ferguson A, Bevan DR: Twitch depression and train-of-four ratio after antagonism of pancuronium with edrophonium, neostigmine and pyridostigmine. *Anesth Analg* 63: 314-316, 1983
12. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. *Br J Anaesth* 56:453-457, 1984
13. Engbaek J, Ording H, Ostergaard D, Viby-Mogensen J: Edrophonium and neostigmine for reversal of the neuromuscular blocking effect of vecuronium. *Acta Anaesthesiol Scand* 29: 544-546, 1985
14. Rupp SM, McChristian JW, Miller RD: Neostigmine antagonizes a profound neuromuscular block more rapidly than edrophonium (Abstract). *ANESTHESIOLOGY* 61:A297, 1984
15. Casson WR, Jone RM, Skelly AM, Robinson PD, Adams AP: Reversal of profound atracurium induced paralysis. Anticholinesterases compared using train-of-four stimulation (Abstract). *ANESTHESIOLOGY* 63:A360, 1985
16. Kitz RJ: The chemistry of acetylcholinesterase activity. *Acta Anaesthesiol Scand* 8:197-218, 1964
17. Blaber LC, Bowman WC: A comparison between the effects of edrophonium and choline in skeletal muscles of the cat. *Br J Pharmacol* 14:456-466, 1959
18. Blaber LC: The mechanism of the facilitatory action of edrophonium in cat skeletal muscle. *Br J Pharmacol* 46:498-507, 1972

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## Intrathecal Morphine in Conjunction with a Combined Spinal and General Anesthetic in a Patient with Multiple Sclerosis

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Selecting an anesthetic management plan for patients with multiple sclerosis can be difficult. General anesthesia is usually recommended, while spinal anesthesia is dis-

couraged. In this report, spinal anesthesia supplemented with inhaled general anesthetics were used successfully in a patient with multiple sclerosis. In addition, we describe the first reported use of intrathecal morphine in a patient with this disease.

#### REPORT OF A CASE

A 53-yr-old male with impotence related to long-standing multiple sclerosis presented for elective insertion of an inflatable penile pro-

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thesis. The patient's medical history was significant for moderate ethanol consumption and hepatitis suffered 15 yr prior to this admission. He denied smoking, and all other medical problems were directly related to multiple sclerosis.

Multiple sclerosis was first diagnosed 13 yr prior to this admission. His disease has been very slowly progressive, with no major exacerbations noted. He suffered impotence and a neurogenic bladder. Although motor deficit was noted in all extremities, including problems with gait control, sensory capacity appeared intact, including the groin area. His visual acuity was also disturbed.

He had undergone a transurethral resection of the prostate 1 yr prior to this admission under spinal anesthesia with either intravenous sedation or general anesthesia. The patient was unable to recall the details, and his prior records were unavailable. He reported no untoward effects from that anesthetic combination. He denied history of epilepsy or seizure activity. He was not taking any medications and reported no allergies. Laboratory data were all normal, except for the ECG which showed abnormal "R" wave progression in the precordial leads, and small "q" waves in lead III, suggesting an inferior infarct in the past. However, the patient denied any history of angina, chest pain, or dyspnea.

After a detailed discussion with the patient of the available anesthetic options and risks, spinal anesthesia was selected as appropriate for the surgical procedure. Patient comfort was to be provided by general inhaled anesthesia, as opposed to iv sedation, which tends to produce greater respiratory depression. Although postoperative pain management is not a major problem with this surgical procedure, intrathecal morphine was selected, since access would be available during insertion of the spinal anesthetic.

The patient was brought to the operating room unpremedicated. He had received cefoxitin 2 gm and gentamicin 80 mg iv preoperatively. Hives appeared after the gentamicin. No other symptoms were noted, and no treatment was initiated. After applying appropriate monitors, the patient was placed in the left lateral decubitus position. The subarachnoid space was entered at the L3/4 interspace on the first attempt using a 25-G spinal needle. Clear CSF was noted to flow freely from the hub. Ten milligrams of tetracaine in 100 mg dextrose (10%) and 0.5 mg of preservative free morphine (Dura-morph®, 1 mg/cc) were injected. No epinephrine was used.

The patient was then placed in the supine position and 100% oxygen administered via a mask. Slow intravenous induction of general anesthesia was accomplished with divided doses of diazepam (total 10 mg) and thiopental (total 100 mg), and then inhalation of nitrous oxide, oxygen, and enflurane via a mask. Glycopyrolate 0.2 mg was also given iv. The patient continued to breathe spontaneously. The pulse oximeter registered 99% saturation throughout the 2-h surgical procedure. Nitrous oxide and oxygen were administered at a constant 2.5 l/min flow rate, and enflurane concentration varied from 0.5–1.0%. No other anesthetic or adjuvant agents were used. The arterial blood pressure decreased from base line 140/80 mmHg with a heart rate of 70 bpm to 105/60 mmHg with a heart rate of 62 bpm, and remained at this level throughout, until emergence, when both returned to baseline levels. Urine output was well sustained, and no hyperpyrexia was observed, as measured by a temperature "strip" placed on the forehead.

Emergence from general anesthesia was uneventful. The patient regained movement of his lower extremities in less than 3 h after insertion of the spinal. He was monitored on the regular ward for 24 h, applying a standard nursing protocol for patients who have received intrathecal or epidural morphine. He remained pain-free, and required no postoperative pain medications through discharge from the hospital the next day. No significant problems were noted. Rectal temperatures remained normal. He had some slight itching on his back, which required no treatment. On follow-up, the patient was noted to have some minor problems with micturition for 4–5 days post-surgery, which then resolved and returned to baseline without treatment. He remained

free of exacerbation of his multiple sclerosis at the 1-month and 6-month follow-ups.

## DISCUSSION

Multiple sclerosis (MS) is an acquired, demyelinating disease of the brain and spinal cord. There are strong indications for a viral etiology with genetic susceptibility factors.<sup>1</sup> Disease of the optic nerve causes visual disturbances, and optic neuritis leads to diminished visual acuity and defective pupillary reaction to light. Spinal cord lesions cause limb paresthesias, weakness, urinary incontinence, and sexual impotence. Involvement of the cerebellum leads to gait disturbances. This patient reported signs of all of the above.

In their review article, Jones and Healy present data implicating many different anesthetic agents in the exacerbation of symptoms.<sup>2</sup> Thiopental, and all muscle relaxants, have cautionary statements. Enflurane and methohexitone should be avoided if a history of epilepsy is given,<sup>2</sup> since they have been associated with producing seizures under anesthesia. Jones and Healy cite several references demonstrating an increased incidence of epilepsy in patients with multiple sclerosis.<sup>2</sup> Local anesthetics which cross the blood-brain barrier easily can lead to convulsions in multiple sclerosis patients, and should be used with caution,<sup>3–5</sup> in the presence of epilepsy.

Bamford *et al.*\* noted no increase in relapse rate after general anesthesia over the accepted rate in non-surgical MS patients, and the new symptoms which did present resolved within 10 days. However, pyrexia seems to be a greater danger than general anesthetics, because even a small increase of 1° C in body temperature can lead to deterioration of nerve tissue at sites of demyelination.<sup>1,6</sup> Pyrexia is almost a universal component of the postoperative surgical course.

The most controversial anesthetic appears to be spinal anesthesia. Several single cases implicate spinal anesthesia and, indeed, even lumbar puncture alone in the relapse or appearance of symptoms of multiple sclerosis.<sup>7,8,†</sup> Bamford *et al.*\* present data on eight multiple sclerosis patients who received a total of nine spinal and three caudal anesthetics. In one case, the patient experienced aggravation of the multiple sclerosis symptoms after the spinal anesthetic. More damaging are the data of Stenuit and Marchand,<sup>9</sup> who describe complications noted after spinal anesthesia during the period from 1961–1966 at their clinic. Twenty-nine cases of spinal anesthesia involving complications were noted. Of these 29 cases, 19

\* Bamford C, Sibley W, Laguna J: Anesthesia in multiple sclerosis. *Le Journal Canadien des Sciences Neurologiques* 5:41–44, 1978

† Critchely M: Discussion on the neurological sequelae of spinal anesthesia. *Proceedings of the Royal Society of Medicine* 30:1007–1015, 1937

patients had multiple sclerosis. However, only in 2 of these 19 patients did the complications involve aggravation of the symptoms of multiple sclerosis.<sup>9</sup>

Although exposure to almost all the anesthetics we use in general anesthesia have been implicated in aggravating or causing the new onset of symptoms of multiple sclerosis, including such agents as meperidine and fentanyl, these drugs are not neurotoxic, even when given intrathecally.<sup>10</sup> Morphine has not aggravated multiple sclerosis.\* It would, therefore, be the agent of choice for intrathecal administration.

We used hyperbaric spinal anesthesia, using a relatively low dose of tetracaine without the addition of epinephrine. The duration of the spinal anesthesia was not prolonged. The addition of general anesthesia in a spontaneously breathing patient did not prolong the duration of the spinal anesthetic. No untoward effects on the patient's condition were noted.

This case also appears to be the first reported use of intrathecal morphine in a patient with multiple sclerosis. The effectiveness of intrathecal morphine for postoperative pain control cannot be evaluated from this case, since postoperative pain in this surgical procedure is not a major therapeutic problem. However, intrathecal morphine did not appear to alter the time course of the spinal or general anesthetic in this patient, nor were any of the known side effects of intrathecal morphine exaggerated in this patient with multiple sclerosis. Only mild pruritis was noted. The bladder was catheterized for the first 24 h, and so urinary retention was not a problem that could be evaluated.

Regardless of the drugs or technique selected for use in anesthesia in patients with multiple sclerosis, postoperative exacerbation of symptoms of this disease remain a significant risk, especially if fever develops. Certainly, the changing neurologic picture in patients with multiple

sclerosis must be appreciated when considering the selection of regional anesthesia. The data implicating regional anesthesia in the aggravation of multiple sclerosis is based on relatively few reported cases. While our case represents only a single case report, it does demonstrate that a combination of spinal and general anesthesia may be appropriate, and can be administered safely to a patient with long-standing but relatively stable multiple sclerosis. In addition, if regional anesthesia is selected, the addition of intrathecal morphine does not increase risk.

## REFERENCES

1. Stoelting AK, Dierdorf SF: *Anesthesia and Co-Existing Disease*. New York, Churchill-Livingstone, 1983, pp 284-286
2. Jones RM, Healy TEJ: Anesthesia and demyelinating disease. *Anaesthesia* 35:879-884, 1980
3. Userbiaga JE, Wikinski J, Ferrero R, Userbiaga LE, Wikinski R: Local anesthetic-induced convulsions in man . . . an electroencephalographic study. *Anesth Analg* 45:611-20, 1966
4. Truant AP, Takman B: Differential physical-chemical and neuropharmacologic properties of local anesthetic agents. *Anesth Analg* 38:478-84, 1959
5. Acheson F, Bull AB, Glees P: Electroencephalogram of the cat after intravenous injection of lidocaine and succinylcholine. *ANESTHESIOLOGY* 17:802-808, 1956
6. Katz J, Benumoff J, Kadis L: *Anesthesia and Uncommon Diseases*, 2nd edition. Philadelphia, W.B. Saunders Comp., 1981, pp 495-496
7. Fleiss A: Multiple sclerosis appearing after spinal anesthesia. *NY State J Med* 49:1076, 1949
8. Hammes FM: Neurological complications associated with spinal anesthesia. *Minn Med* 36:339-45, 1943
9. Stenuit J, Marchand P: Les sequelles de rachi-anesthésie. *Acta Neurol Belg* 68:626-35, 1968
10. Lee A, Atkinson RS, Watt M: *Lumbar Puncture and Spinal Analgesia, Intradural and Extradural*. Edinburgh, Churchill-Livingstone, 1985, pp 315-316

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## Premedication Abolishes the Increase in Plasma Beta-endorphin Observed in the Immediate Preoperative Period

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Beta-endorphin (B-END) and adrenocorticotrophic hormone (ACTH) are released into the circulation from the pituitary gland in response to various stressful stimuli,

including surgery, in experimental animals and humans.<sup>1-7</sup> Increased levels of plasma B-END<sup>5,6</sup> and ACTH<sup>7</sup> have been observed in non-premedicated patients before

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