find an increasing number of uses for epidural cathethers in patients who have special conditions placing them at higher risk.

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Refractory Arterial and Intracranial Hypertension in the Intensive Care Unit: Successful Treatment with Isoflurane

LAWRENCE R. MILLER, M.D.,* JOHN C. DRUMMOND, M.D., F.R.C.P.C.,† RODERICK G. LAMOND, M.D.‡

We report a case of refractory arterial and intracranial hypertension in a patient with reduced intracranial compliance and suspected cerebral dysautoregulation after resection of an arteriovenous malformation (AVM). The patient was managed safely and effectively by the prolonged administration of isoflurane.

Case Report

The patient was a 40-yr-old, 70-kg male who was well until the occurrence of a grand mal seizure 30 days prior to the current admission. Neurologic evaluation, including cerebral angiography, revealed a large intraparenchymal AVM in the left posterior frontal region just anterior to the pre-Rolandic gyrus. Past medical history included mild controlled systemic arterial hypertension and cigarette smoking (40 cigarettes daily for many years). His medications at the time of admission were pindolol 5 mg twice daily and diphenylhydantoin 400 mg once daily. He had sustained an aspiration pneumonia at the time of his seizure. However, a recent x-ray of the chest revealed no persistent abnormality, and his lung fields were clear to auscultation. Preoperative blood pressure was 140/90 mmHg.

The patient underwent a craniotomy for excision of the AVM. Induction of anesthesia was accomplished with thiamylal, pancuronium, and fentanyl (10 $\mu g \cdot kg^{-1}$). Anesthesia was maintained with fentanyl by infusion (3 $\mu g \cdot kg^{-1} \cdot h^{-1}$), isoflurane (0.5% end-tidal), and 50% nitrous oxide. Blood gas analysis early in the procedure revealed *p*H 7.45, arterial carbon dioxide tension (Pa_{CO_2}) 40 mmHg, arterial oxygen tension (Pa_{O_2}) 143 mmHg (fractional inspired oxygen concentration [FI_{O_2}] 0.35). The patient was hemodynamically stable throughout the 12-h procedure. However, the anesthetic course was complicated by bronchospasm and decreasing lung compliance. These were attributed to cigarette use and to the residual effects of the aspiration pneumonitis. At the conclusion of the procedure, peak inspiratory pressure was 40 cmH2O, and Pa_{O_2} was 75 mmHg and FI_{O_2} 0.4. A decision was made to transfer the patient to the intensive care unit (ICU) for mechanical ventilation.

There was concern regarding the possibility of cerebral dysautoregulation (perfusion pressure breakthrough)[1,2] because of the size of the resected lesion. Accordingly, prior to departure from the operating room a Camino intracranial pressure (ICP) monitor (Camino Laboratories, San Diego, CA) was placed in the right frontal lobe, and it was decided to maintain systolic blood pressure at less than 100 mmHg. The choice of threshold was somewhat arbitrary, but represented a

* Resident in Anesthesiology, University of California, San Diego.
† Associate Professor of Anesthesiology, University of California, San Diego; Staff Anesthesiologist, VA Medical Center, San Diego.
‡ Assistant Professor of Surgery (Neurosurgery), University of California, San Diego.

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Address reprint requests to Dr. Drummond: University of California, San Diego, 0629, La Jolla, California 92093.

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"curbside consensus" among neurosurgeons and anesthesiologists as to a pressure that would avoid ischemic complications while minimizing the pressure head in those vessels surrounding the resected nidus of AVM that are believed to be at risk for the perfusion pressure breakthrough phenomenon. This "target" pressure has been used by others in the management of similar situations.[2] The initial ICP, with the patient in a 30° head-up posture, was 8 mmHg. The patient was transferred to the intensive care unit.

The initial postoperative chest x-ray revealed an infiltrate in the left lower lobe. Controlled ventilation with PEEP (5 cmH2O) was continued. Sedation was provided by infusion of morphine at 10 $mg \cdot h^{-1}$ and with intermittent doses of midazolam 1–2 mg. Paralysis was maintained with intermittent doses of vecuronium. Diphenylhydantoin, 100 mg was administered intravenously every 6 h. Pa_{CO_2} was maintained between 27–30 mmHg, and the patient was nursed in a 30° head-up posture. Over the course of the first 7 h ICP increased to 28 mmHg. ICP control was accomplished with a total of 100 g mannitol and 300 mg pentobarbital. A computed tomography (CT) scan revealed a region of moderately increased attenuation in the vicinity of the resection site compatible with hyperemia or the presence of intraparenchymal blood. There was some effacement of the ipsilateral ventricle and 2–3 mm of midline shift. A chest x-ray revealed left lower lobe consolidation with a left pleural effusion and a right lower lobe infiltrate. A culture of an endotracheal aspirate grew *Klebsiella oxytoca*.

During the first postoperative day, blood pressure became more difficult to control, and ICP increases were noted to correlate with increases of blood pressure. The morphine infusion was increased to 20 $mg \cdot h^{-1}$ and an infusion of sodium nitroprusside (SNP) was started at 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The response of both blood pressure and ICP was initially satisfactory. However, the improvement was short-lived, and during the ensuing 2.5 days, ICP ranged between 18 and 29 mmHg. During that time numerous pharmacologic agents were used singly and in combinations in attempts to control blood pressure and ICP. Mannitol was administered on eight occasions in doses of 12.5–50 g. Esmolol at rates up to 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ had no significant impact on blood pressure. Trimethaphan was effective initially, but tachyphylaxis occurred rapidly and it was ultimately without effect at an infusion rate of 6 $mg \cdot min^{-1}$. Intravenous hydralazine in 5–10-mg boluses (total 30 mg), sublingual nifedipine (total 20 mg), and clonidine 0.3 mg per nasogastric tube were administered without effect on blood pressure. By the evening of the 3rd postoperative day the patient was receiving infusions of morphine 30 $mg \cdot h^{-1}$, midazolam 4 $mg \cdot h^{-1}$, SNP 3.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, nitroglycerin (NTG) 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and phentolamine 0.7 $mg \cdot kg^{-1} \cdot h^{-1}$. Systolic blood pressure remained increased at 130–140 mmHg. ICP was 24 mmHg. Arterial blood gas analysis (FI_{O_2} 0.5) revealed *p*H 7.41, Pa_{CO_2} 30 mmHg, Pa_{O_2} 101 mmHg, and a base excess of 0 mEq/l. The thiocyanate concentration was 1.5 $mg \cdot dl^{-1}$ (nontoxic).

The anesthesia service was consulted. The attending neurosurgical staff were unwilling to submit the patient to a period of barbiturate-induced EEG isoelectricity on the basis of their clinical impression that pulmonary complications (pneumonias and adult respiratory distress syndrome) are common concomitants of this therapy. They viewed the ongoing *Klebsiella* pneumonia as a contraindication to barbiturate coma. A Drager Narkomed 3 anesthesia machine (North American Drager, Telford, PA) was brought to the bedside. The scavenging apparatus was connected to a wall vacuum. Isoflurane was introduced in increments of 0.25% during continuous observation of the ICP. Blood pressure decreased, and inspired concentrations of 1–1.5% isoflurane were required to maintain systolic blood pressure at 100 mmHg.

Within 1 h the infusions of NTG, SNP, and phentolamine were discontinued. ICP decreased from 24–26 to 15–18 mmHg in parallel with the reduction of systolic blood pressure from 130–140 to 90–100 mmHg. Other hemodynamic parameters were well maintained; cardiac output and pulmonary artery occlusion pressure decreased from 11 $l \cdot min^{-1}$ and 16 mmHg respectively to 10 $l \cdot min^{-1}$ and 14 mmHg; heart rate increased from 95 to 110 beats per min. Arterial blood gas analysis after discontinuation of the infusions of NTG, SNP, and phentolamine revealed *p*H 7.45, Pa_{CO_2} 37 mmHg, Pa_{O_2} 89 mmHg (FI_{O_2} 0.4) with a base excess of 3 mEq/l. Isoflurane administration was continued for 24 h with anesthesia personnel in constant attendance. The concentration requirement increased slightly. An inspired concentration of 1.5–2% isoflurane provided control of blood pressure. No other hypotensive agents were administered. ICP remained between 16 and 20 mmHg.

Beginning on the evening of the 4th postoperative day, the isoflurane concentration was reduced gradually over 6 h. At the same time an infusion of verapamil (10 $mg \cdot h^{-1}$) was instituted as an adjunct to blood pressure control. ICP remained between 18 and 20 mmHg despite an increase in systolic blood pressure to 130–140 mmHg. Accordingly, the blood pressure limits were relaxed. At the time of discontinuation of isoflurane, systolic blood pressure was 140 mmHg and ICP was 18–20 mmHg.

The pneumonia responded gradually to antibiotic therapy and frequent bronchoscopy. The trachea was extubated uneventfully on the 14th postoperative day. At follow-up 6 months later, he was neurologically intact and blood pressure was well controlled on enalapril 10 mg once daily.

Discussion

Isoflurane controlled blood pressure rapidly and effectively in a patient in whom numerous other agents had been ineffective. Isoflurane administration was undertaken cautiously because the patient's ICP initially was increased. However, administration of isoflurane was associated with improvement rather than deterioration in ICP.

All of the volatile anesthetics are cerebral vasodilators,[3–6] and in certain patients these agents can produce substantial increases in ICP.[7,8] The available experimental data suggest that isoflurane has the least effect on cerebral blood flow.[3,5,9] It is, nonetheless, a cerebral vasodilator, and significant increases in ICP have been observed in patients with intracranial mass lesions.[7] However, there are data and substantial clinical experience to suggest that isoflurane can be administered safely to the majority of neurosurgical patients. In two separate studies, it has been demonstrated in patients with intracranial pathology that increases in cerebral spinal fluid pressure in response to 1.0 MAC isoflurane can be blunted or prevented by either simultaneous or prior establishment of hypocapnia.[8,10] Campkin and Flinn[8] also demonstrated that established isoflurane-related cerebrospinal fluid pressure increases could be reversed by subsequent hyperventilation. Nonetheless, isoflurane-related ICP increases have been observed despite the institution of hypocapnia, both in humans and in experimental animals.[7,11] In the current patient, there was an additional concern about the likely efficacy of hypocapnia. Hypocapnia had been maintained for 3 days prior to the introduction of isoflurane. Since CBF gradually returns to normal levels over 8–12 h during sustained hypocapnia,[12] there was concern that use

of isoflurane in this instance was essentially equivalent to administering the drug to a normocapnic patient with reduced brain compliance. Accordingly, isoflurane was introduced cautiously during continuous observation ICP.

Despite the theoretical concerns, isoflurane resulted in a reduction of ICP. There are several possibilities as to why isoflurane was well tolerated. The first is that the elevated blood pressure, which was effectively controlled by isoflurane, had been contributing significantly to the ICP elevation. The patient had under gone resection of a large AVM, and cerebral dysautoregulation was suspected. In this setting, a portion of the brain is believed to be "pressure-passive," such that increases in arterial pressure can result in vascular engorgement and, perhaps, increased edema formation. The second is that the administration of isoflurane and the concomitant control of blood pressure allowed the discontinuation of other potent cerebral vasodilators (SNP[13] and NTG) that were being administered in high concentrations. The third possibility is that since the effect of isoflurane on CBF is dose-dependent,[3,14] the concentrations of isoflurane given (1.0–2.0% inspired) may have been less than those needed to produce significant cerebral vasodilation in this patient. The ICP effects might have been less beneficial or perhaps deleterious had higher concentrations been required.

Experience with the prolonged administration of isoflurane in the intensive care setting is limited. Its use has been reported in the treatment of status asthmaticus[15] and status epilepticus.[16] The use of isoflurane entails certain practical limitations, including the need for appropriate scavenging systems and the continuous presence of an anesthesia care provider. Of greater concern is that the potential hazards of prolonged administration, including the development of fluoride nephrotoxicity,[17] physical dependence (as suggested by Kofke *et al.*[18]), and immune suppression, have not been completely explored. With respect to immune suppression, there is evidence that prolonged exposure to halothane retards lymphocyte proliferation and may thereby have an inhibitory effect on immune function.[19,20] It is not known whether prolonged exposure to isoflurane has a similar effect on the immune system. Accordingly, further investigation to confirm the safety of prolonged isoflurane exposure should be performed before its use can be considered routine. However, in a patient who is refractory to conventional drug therapy, isoflurane provides an alternative treatment. The use of isoflurane in these circumstances may permit a "drug holiday" that may serve to decrease tachyphylaxis to other agents or to allow an opportunity for reduction of the rising cyanide levels associated with SNP administration. Isoflurane therapy also has the advantage that it can be withdrawn rapidly at physician discretion.

Nevertheless, the current report is not intended as advocacy of the casual application of isoflurane in these or other intensive care unit circumstances. In particular, it is to be noted that in the current patient, administration of a barbiturate to the point of EEG isoelectricity might have served the same purposes equally well. Ordinarily, barbiturates are our first recourse in these circumstances. However, as noted above, the attending surgeon was reluctant to resort to barbiturate coma because of concerns regarding the immunologic effects of sustained barbiturate administration[21] to a patient with a *Klebsiella* pneumonia. This concern has not been systematically validated but was nonetheless a prevailing constraint in our management of the current patient. As noted above, the immunologic implications of prolonged isoflurane administration have not been evaluated.

In summary, our experience suggests that isoflurane may be useful in the treatment of refractory systemic arterial hypertension in patients unresponsive to conventional agents. In addition, our experience demonstrates that despite theoretical concerns, isoflurane can be administered safely in some situations in which ICP is elevated.

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Neuropathic Pain Can Be Relieved by Drugs That Are Use-dependent Sodium Channel Blockers: Lidocaine, Carbamazepine, and Mexiletine

DARRELL L. TANELIAN, M.D., PH.D.,* WILLIAM G. BROSE, M.D.†

Pain due to acute or chronic nerve injury is difficult to treat and is often resistant to conventional analgesics.[1,2] Common pain syndromes attributed to peripheral nerve injury include posttraumatic neuralgia, diabetic peripheral neuropathy, postherpetic neuralgia, phantom limb pain, ischemic neuropathy, and postirradiation neuropathy.[3–7] The use of agents known to block sodium channels in a use-dependent fashion (lidocaine, mexiletine, and carbamazepine) is a relatively new therapeutic intervention that is achieving success in the management of neuropathic pain.[1–2,8–11] We report four cases of chronic neuropathic pain that were responsive to the use-dependent sodium channel blockers, lidocaine, mexiletine, and carbamazepine.

CASE REPORTS

Case 1. The patient was a 72-yr-old woman with a 2-yr history of left lower extremity phantom limb pain following amputation below the knee secondary to diabetes. The patient reported four types of pain contributing to an overall constant pain level of 8–9 of 10 on a visual analog scale (VAS). She described her pain as originating in the nonexistent left lower leg and characterized the sensations as: a sharp, "cutting" pain lasting about 1 min each day; an ice-cold sensation; numbness over her missing left foot and toes; and a constant electric shock sensation over the entire missing lower limb. Nonsteroidal antiinflammatory drugs (NSAIDs), Elavil, and Vicodin (hydrocodone 50 mg/day) did not improve the pain or abnormal sensations. The patient received carbamazepine (100 mg orally every hour) and was instructed to increase the dose by 100 mg every 3 days until pain control was achieved (maximum of 1,200 mg/day). Upon returning to the pain clinic 1 week later, taking 100 mg carbamazepine orally three times per day, the patient reported significant pain relief, such that the VAS was now 2–3 of 10. The patient continues to receive this dose of carbamazepine and has continued to have good pain control for the past 11 months.

Case 2. A 74-yr-old woman with a 5-yr history of metastatic breast carcinoma developed severe left hand and arm pain 6 weeks prior to presenting to the pain clinic. As part of her therapy she had received irradiation to her left supraclavicular and axillary region 18 months previously. A magnetic resonance imaging (MRI) scan of her left neck, axilla, and arm revealed no evidence neither of tumor nor of abnormality of the left arm innervation. Physical examination revealed an edematous left arm and hand. There was total absence of motor function in all muscle groups of the patient's left hand, as well as 2/5 motor strength of the upper arm musculature. The patient described chronic unremitting pain of her left arm and hand, characterized as tingling, burning, and intermittently sharp pain, especially with movement. Sensory examination revealed a loss of sensation of vibration, light touch, and cold in the left hand. The skin on the forearm region was hypersensitive to stroking. Aspirin, acetaminophen, ibuprofen, and codeine (300 mg/day) had all failed to control the pain. Pain therapy with carbamazepine was started at 100 mg orally every hour, and at a dosage of 200 mg orally three times per day (serum concentration 7.1

* Assistant Professor of Anesthesia.
† Assistant Professor of Anesthesia.

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Address reprint requests to Dr. Tanelian: Department of Anesthesia, Room S-268, Stanford University School of Medicine, Stanford, California 94305.