

Prolonged Low Flow Isoflurane Anesthesia for Status Epilepticus

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When continuous seizures are refractory to conventional iv anticonvulsant drugs, some neurologists suggest that an inhaled anesthetic be employed.^{1,2} We describe the effectiveness of isoflurane in the management of status epilepticus and illustrate many of the problems that may be encountered when isoflurane is administered for prolonged periods outside the operating room.

REPORT OF A CASE

A 10-year-old, previously well, 36-kg girl developed symptoms of an upper respiratory tract infection. Two days later, she developed an erythematous rash over her face, neck, and trunk, with left upper quadrant pain and emesis. Subsequently, she became febrile (38.5°C) and was treated with aspirin. Her symptoms resolved. Four days after onset, however, she developed tonic-clonic seizures refractory to phenobarbital, phenytoin, diazepam, and paraldehyde therapy and was transferred to our hospital. On the fourth hospital day, following endotracheal intubation, a pentobarbital infusion was initiated and maintained for 3 days, resulting in control of seizures with electrographic suppression.³ However, with discontinuance of this first infusion and two subsequent one-week pentobarbital infusions, seizures returned. The average daily dose of pentobarbital required during each of these infusions was 2.2, 4.0, and then 4.1 g. On the 27th hospital day, seizures again returned. After we obtained informed parental consent, isoflurane anesthesia was instituted (fig. 1) according to a protocol previously approved by our Clinical Investigation Committee.

The etiology of her seizures was unclear. Encephalitis was felt to be likely, although viral studies and multiple cerebrospinal fluid analyses were nondiagnostic. Liver function tests and cranial computed tomograms were normal.

At the onset of isoflurane anesthesia ventilation was controlled. Arterial blood gases, blood glucose, serum electrolytes, and platelet count were normal. Serum anticonvulsant levels were as follows: phenobarbital 35 mg/ml (15-40), phenytoin 17 mg/ml (5-25), pentobarbital 20 mg/ml (3-7). Arterial blood pressure was 130/80 mmHg, heart rate 122 bpm, pulmonary artery pressure 25/13

mmHg, pulmonary capillary wedge pressure 8 mmHg, and central venous pressure 13 mmHg. Cardiac output was 6.5 l/min.

Anticonvulsant agents used and her response throughout her complicated hospital course are diagrammatically summarized in figure 1.

Apparatus. An Ohio Heidbrink® anesthesia machine, an Ohio® temperature and flow compensated calibrated vaporizer, low-flow rotameters, and an Air Shields® upright-bellows ventilator were used. Oxygen concentration was varied with a Bird® air-oxygen blender. Inspired and expired O₂, CO₂, and isoflurane concentrations were measured with an in-line mass spectrometer (Perkin-Elmer 1100A®). EEG activity was monitored continuously until electrographic suppression occurred, thereafter being monitored every 30-60 min. A Boehringer® scavenging system was used (model numbers 4844 and 5300), and a Bodai® flexible bronchoscopy endotracheal tube adaptor (Sontek Medical) was utilized to facilitate endotracheal suctioning with minimal gas leak.

Anesthetic Technique. Isoflurane was administered in O₂-N₂ at an FE_{O₂} of 0.5. Total gas flow initially was 6 l/min. Isoflurane was increased in 0.25-0.5% increments to suppress EEG seizure activity while maintaining blood pressure. After 4 h, flows were decreased to about 700 ml/min, subsequently being maintained at about 350-700 ml/min.⁴ During induction of anesthesia, emergence, and endotracheal suctioning, 6 l/min flows were used. One 1.13 kg soda lime cannister (Sodasorb Pre Pak® W. R. Grace and Co.) was depleted after each 24-h period, inspired CO₂ concentration remained below 1 mmHg. Liquid isoflurane, 420 ml, was used for the 48 h of the anesthetic. An anesthetist was always present.

Neurologic Effects. Twenty-four hours after starting to taper the third pentobarbital infusion (initially 110 mg/hr), seizure activity recurred (fig. 1) and isoflurane was begun. Twenty-two minutes after the start of isoflurane, seizures stopped and the EEG showed a burst suppression pattern. End-tidal isoflurane concentration was 0.8%. Isoflurane then was discontinued briefly, resulting in recurrence of seizures. Subsequently, isoflurane administration was resumed, titrated to maintain a burst suppression pattern with suppression intervals up to a minute or more (fig. 2). After 24 h of anesthesia, isoflurane was stopped. During emergence, as the end-tidal isoflurane concentration decreased to 0.4%, her tongue began to tremor as spike and wave discharges appeared on the EEG. The inspired isoflurane concentration then was increased, and the EEG again was suppressed. After 48 h of anesthesia, isoflurane was stopped again. As end-tidal concentration decreased from 2%, electrographic seizures developed at an end-tidal concentration of 1.1% but without motor activity. As end-tidal isoflurane concentration further decreased to 0.3%, disorganized delta activity predominated without clinically stereotyped seizures (fig. 2). This was associated with diffuse myoclonic activity, which was treated with iv medications (fig. 1). She remained unconscious.

Hemodynamics. With institution of isoflurane, mean arterial pressure decreased but responded to fluid and phenylephrine infusion. Subsequent hemodynamic changes are summarized in figure 3.

Laboratory Data. After anesthesia, SGOT rose to 84 and 122 U/l 2 and 9 days postanesthesia but subsequently returned to normal (5-40 U/l). Urine fluoride excretions for the 6 days after anesthesia

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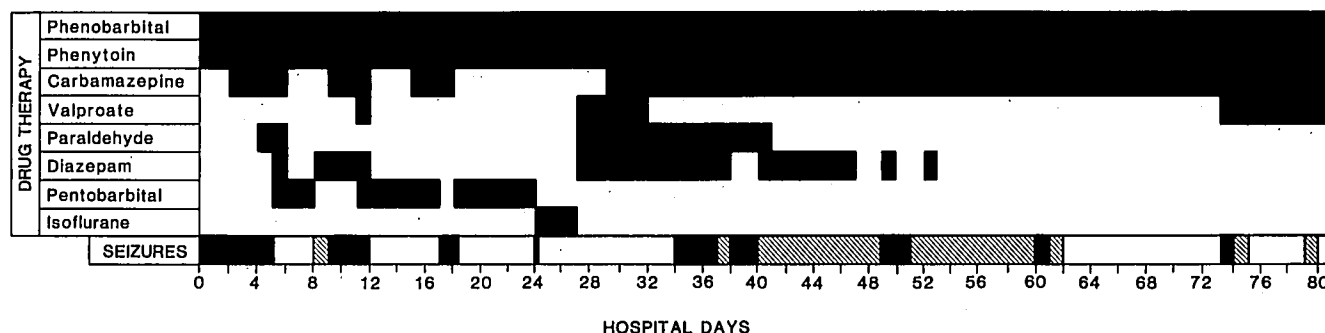


FIG. 1. Qualitative summary of drug therapy and seizure activity for entire hospital course. Seizure activity per 24-h period: □ = no seizures; ▨ = focal seizures; ■ = generalized seizures.

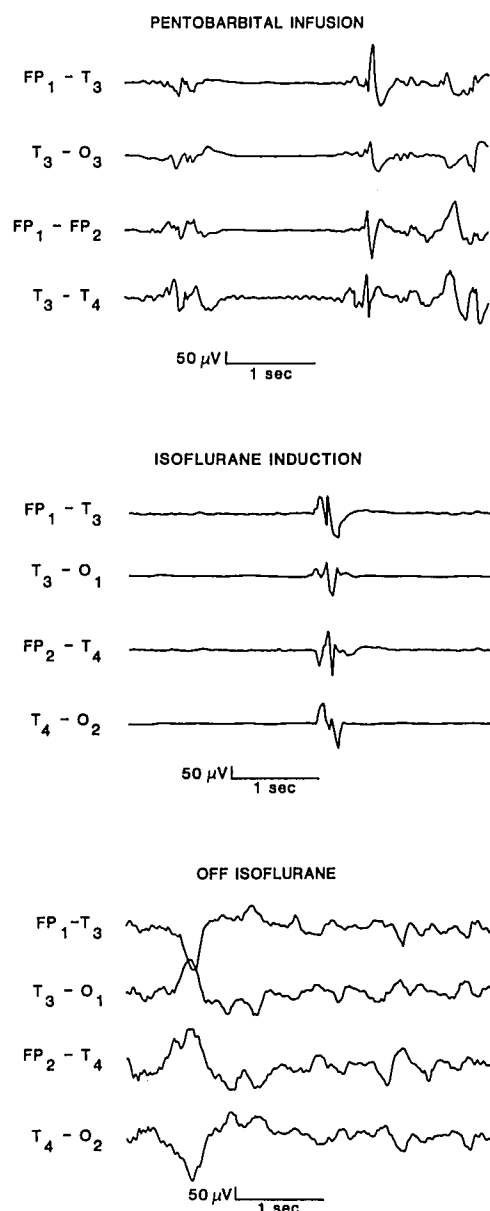


FIG. 2. Electroencephalogram of seizure activity with decreasing rate of pentobarbital infusion, electrographic suppression by isoflurane, and disorganized electrographic activity with discontinuance of isoflurane.

were 63, 81, 64, 42, 40, and 54 $\mu\text{M}/\text{day}$. Urine specific gravity was 1.009 at the start of anesthesia, varied between 1.005 and 1.015 for the first 24 h, and rose to between 1.017 and 1.028 for the second 24 h, despite a 4-l positive fluid balance. With discontinuation of anesthesia, urine specific gravity decreased to 1.002 with diuresis. For the 6 days postanesthesia urine specific gravity varied between 1.006 and 1.027.

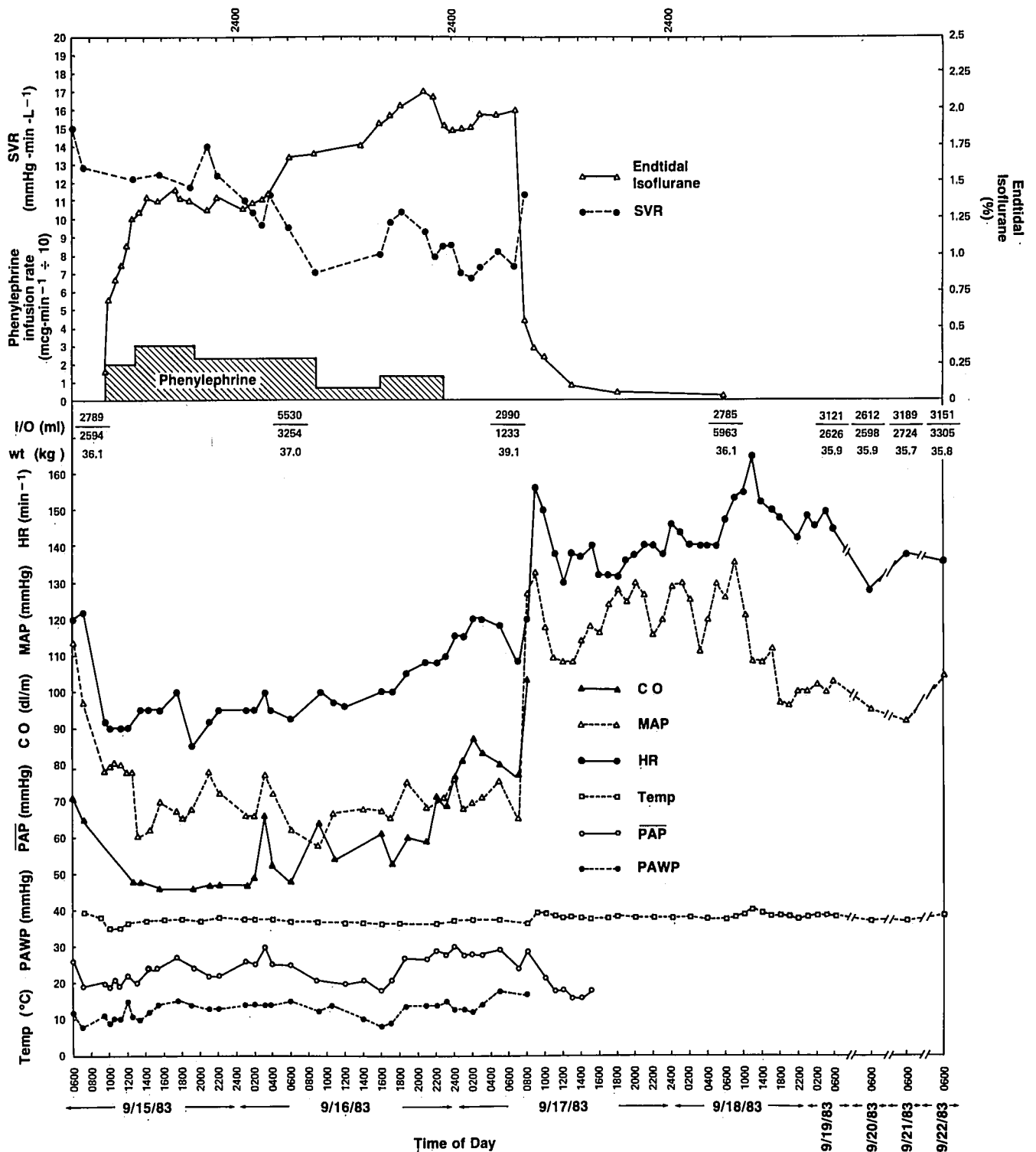
Postanesthetic Course. In-hospital postanesthesia course is summarized in Figure 1. At discharge 2 months later, she was having occasional facial seizures. Thereafter, she sustained gradual improvement and presently has partial return of cognitive and motor function.

DISCUSSION

The anesthesiologist asked to control status epilepticus has a variety of options. High-dose barbiturates can cause hypotension^{3,5} and, given for a prolonged period, theoretically may induce seizures on withdrawal.⁶ Halothane has been recommended for inhaled anesthesia^{1,2} but totally can suppress seizure activity only at concentrations that cause significant hemodynamic depression.^{7,8} Enflurane, although an isomer of isoflurane, can cause seizure activity.⁹ Nitrous oxide can increase seizure threshold¹⁰ but given long term can cause bone marrow suppression.¹¹ Isoflurane produces an isoelectric EEG at a hemodynamically well-tolerated concentration and has minimal organotoxicity.^{8,12-14} In addition, isoflurane and other inhaled anesthetics may inhibit viral replication.¹⁵ The potential of the inhalation anesthetics for physical dependence is not known. Possibly in our patient, isoflurane allowed a seizure-free withdrawal from the pentobarbital infusion.

Fluid and phenylephrine iv infusions initially were required (Fig. 3). Phenylephrine was used to offset the vasodilation produced by isoflurane and was increased for hypotension while ensuring adequate intravascular volume as indicated by the CVP, urine output, and acid-base status. The infusion of phenylephrine was decreased as the cardiac output, mean arterial blood pressure, and heart rate increased with decreasing systemic vascular resistance. On emergence from anesthesia, a hyperdynamic state was apparent to which a declining pentobarbital level may have contributed.

There may be problems associated with administering



expensive, and costs were not recouped from third-party payers. We believe it was warranted because of the frequent changes that were needed in anesthetic concentration, iv fluids, and phenylephrine infusion rate (fig. 3).

In addition to these considerations with prolonged anesthesia, there were problems with administration of an inhaled anesthetic outside the operating room. The pediatric physicians and nurses had no experience with inhalation anesthesia and were given information detailing the physiologic effects and occupational risks of isoflurane. To keep trace levels of anesthetic low,¹⁸ we used a scavenging system, a Bodai® flexible bronchoscopy adapter to allow suctioning without ventilator disconnection, and a low-flow technique. In addition, an isolation room was used to avoid contamination of the environment of other patients and staff. Finally, equipment was arranged around the bed to facilitate nursing care and patient monitoring.

This is the longest low-flow/closed-circuit case described. Such a low-flow technique was advantageous in this patient because it enabled us to monitor for small leaks, to maintain circuit humidity without the risks of overheating or water accumulation, and to save isoflurane. When the trachea was suctioned through the bronchoscopy adapter, flows did have to be increased briefly. This acted, however, to prevent accumulation of other physiologic gases in the circuit.

When is general anesthesia indicated for status epilepticus? Delgado-Escueta *et al.*¹ suggest that when phenobarbital, phenytoin, and low-dose diazepam are ineffective, high-dose diazepam or paraldehyde should be administered. Young *et al.*³ also have administered pentobarbital effectively in this setting, as was done in our patient. These measures severely obtund respiratory reflexes, require endotracheal intubation, and constitute general anesthesia. Isoflurane administration, therefore, simply could be considered another available general anesthetic that offers the advantages of titratability, quantitation of seizure threshold (by noting the end-tidal concentration producing electrographic burst suppression), minimal negative inotropic effects, and ability to effect rapid elimination. However, these advantages are offset by the cardiovascular effects of isoflurane, logistic problems with its use, lack of substantiation of its use in seizing animals, and lack of widespread clinical experience. Thus, until more information is available addressing these issues, it is our opinion that isoflurane administration only should be considered seriously when intravenous general anesthetics are ineffective or are producing adverse cardiovascular effects. In the future isoflurane may have a role in the earlier management of refractory status epilepticus.

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