Delayed Seizure Activity Following Enflurane Anesthesia

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Although electroencephalographic and seizure-like abnormalities in man during enflurane anesthesia, particularly in the presence of respiratory alkalosis, have been reported,[1] delayed postoperative seizure activity has not, to our knowledge, been documented. This report describes two patients who developed postoperative generalized seizures that may have been related to the administration of enflurane.

REPORT OF TWO CASES

Case 1. A 30-year-old woman was hospitalized for evaluation of low back pain associated with hypalgesia and motor weakness in the right leg. Her past medical history included symptoms of chronic cholecystitis, frequent urinary tract infections, hepatitis as a child, and occasional frontal headaches, aggravated by a car accident three years prior to admission. Her maternal grandparents, her mother, and two of her children had a seizure disorder. Physical examination disclosed a slightly enlarged liver, hypalgesia in the right leg, and a left-sided hearing loss. All laboratory test results were within normal limits. A myelogram revealed a L5–S1 root sleve amputation, and excision of a herniated nucleus pulposus was planned. The patient was premedicated with morphine, 10 mg, and scopolamine, 0.3 mg. Anesthesia was induced with thiopental, 275 mg, intubation of the trachea was facilitated with succinylcholine, 60 mg, and anesthesia was maintained with nitrous oxide, 3 l/min, oxygen, 2 l/min, and enflurane, 1.5–3 per cent, inspired from a semiclosed circle system. The operation was performed with the patient in the prone position. Additional muscle relaxation was obtained with gallamine, 60 mg. Ventilation was mechanically controlled at a tidal volume of 650 ml and a rate of 10/min. Total anesthesia time was 140 minutes. At no time was seizure activity apparent. Blood pressure ranged from 85/50 to 115/70 mm Hg; heart rate ranged from 60 to 80/min; estimated blood loss was 30 ml, and 700 ml of lactated Ringer's solution were administered during the operation. The patient awoke immediately after operation and was soon feeling well and ambulatory. On the fourth postoperative day she had a spiking fever; a urinary tract infection was diagnosed and treated with ampicillin. On the sixth postoperative day the patient experienced a seizure that lasted 30 seconds and was characterized by tonic–clonic movements starting in the left leg, progressing to the left arm and left face, and then descending to the right side. Her eyes deviated to the left. The patient did not completely lose consciousness, but she did have retrograde amnesia for the event. That patient's temperature was 38.5 C at the time of her first seizure; it increased to 40.0 C three hours later, and was normal thereafter. Despite treatment with diazepam, phenobarbital, and diphenylhydantoin, the patient had six to 12 seizures per day for the next three days. Her last seizure was observed on the ninth postoperative day. The patient was emotionally unstable and had difficulty concentrating. Neurologic examination disclosed no abnormality. A lumbar puncture showed a normal opening pressure, and laboratory examination of the cerebrospinal fluid was negative. A brain scan was normal. The EEG revealed marked generalized abnormalities, with a preponderance over the left posterior regions. Electrical seizure activity without marked laterlization was evident. Results of all blood studies performed during the period of seizure activity were normal. Urinalysis revealed signs of infection. On the eleventh postoperative day the patient was afebrile and free of seizure activity. She was discharged with advice to continue dipheylhydantoin and phenobarbital medication. When seen in the clinic four weeks later, the patient was feeling well, her back pain had been alleviated, and she had no sign of seizure activity or emotional problems. Medication with deipheylhydantoin and phenobarbital was discontinued.

Case 2. A 38-year-old woman was hospitalized for granulomatous colitis involving the colon and rectum, with associated low-grade fever, diarrhea, weight loss and anemia. Her medical history was otherwise unremarkable. Her only medications were birth control pills. There was no family history of neurologic disorders. A grade 3/6 systolic murmur was audible, but the physical examination was otherwise unremarkable. Abnormal laboratory values included an erythrocyte sedimentation rate 25 mm/hr, hemoglobin 10.7 g/100 ml, and calcium 8.6 mg/100 ml. A total colectomy, anterior and posterior lymph-node dissection, and fractional dilatation and curettage were performed. The patient was premedicated with morphine, 10 mg, and pentobarbital, 100 mg. Anesthesia was induced with thiopental, 200 mg, intubation of the

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trachea was facilitated with succinylcholine, 60 mg, and additional muscle relaxation was obtained with pancuronium, 4 mg. Anesthesia was initially maintained with nitrous oxide, 3 l/min, oxygen 2 l/min, and 2 to 5 per cent enflurane, inspired from a semiclosed circle system. After one hour of anesthesia, the anesthesia system was closed and enflurane vapor, 12–24 ml/min, was administered with nitrous oxide and oxygen. The oxygen concentration in the efferent limb of the anesthetic circuit was monitored continuously and was never less than 30 per cent. Ventilation was mechanically controlled at a tidal volume of 550 ml and a rate of 10/min. Total anesthesia time was six hours. No seizure activity was observed. Blood pressure ranged from 96/55 to 120/70 mm Hg; pulse rate ranged from 90 to 130/min. The blood loss of 1,000 ml was replaced with 500 ml whole blood and 2,500 ml 5 per cent dextrose in lactated Ringer's solution. Urinary output totalled 750 ml after administration of 20 mg furosemide. The patient awoke immediately following operation; within two days she was afebrile and ambulatory. Six days after operation the patient complained of multiple bilateral visual scotomata and a severe headache. On the eighth day she had diplopia, intermittent visual aura, and one generalized motor seizure. The seizure was treated with phenobarbital and diphenylhydantoin. Ophthalmologic examination showed bilateral inferior field defects, but the remainder of the neurologic examination was normal. A brain scan was normal. The EEG revealed marked disturbances over the left parieto-occipital area, and epileptiform discharges were found over both temporal regions. The patient had no further seizures, but for two days she appeared to have personality changes. She was discharged free of symptoms on the sixteenth day, with advice to continue taking diphenylhydantoin and phenobarbital. The patient was again hospitalized five months later, and at that time she reported no further seizure activity or visual disturbance. There was no indication of a permanent change in personality. Neurologic examination and EEG disclosed no abnormality. She underwent surgical excision of a rectovaginal fistula under caudal anesthesia, and her postoperative course was uneventful.

In summary, we report two patients who developed seizure activity six and eight days after enflurane anesthesia. Neither patient had seizures prior to or during anesthesia. One patient had a strong family history of seizure disorders and a history of headache. Both patients manifested personality changes for several days. Follow-up neurologic examinations disclosed no abnormality.

Abnormal EEG recordings, characterized by high-amplitude spikes or spike–wave complexes, and overt tonic–clonic motor activity have been found during enflurane anesthesia in man[1] and in animals.[2] A recent study in cats anesthetized with enflurane, 5 per cent, showed abnormal EEG activity for as long as 16 days after anesthesia.[3] Although the EEG was normal for two to four hours after anesthesia, abnormalities became apparent on the second day, reached a maximum on the fourth or fifth day, and persisted for as long as 16 days. The abnormal EEG pattern was accompanied by behavioral changes, but no overt seizure activity was observed. Similar experiments with other halogenated ether and hydrocarbon anesthetics showed none of these findings.

It is unlikely that enflurane *per se* would still be present a week after anesthesia. Chase *et al.*,[4] however, demonstrated in man that approximately 2 to 4 per cent of administered enflurane is biotransformed into fluorinated metabolites (0.5 per cent inorganic fluoride ion and 1.9 per cent organic fluorine metabolites). Unidentified organic fluorine metabolites were excreted in the urine for 17 days. Although purely speculative, delayed EEG changes and behavioral abnormalities in the two patients and experimental animals could result from one of the metabolic byproducts of enflurane. There was no evidence to suggest cerebral hypoxia or enflurane-induced CNS damage during anesthesia. It is also possible that enflurane could create an irritabie focus that produces overt seizures several days after anesthesia. Postoperative ischemic or embolic processes also cannot be ruled out.

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