Diagnostic Activation of Epileptogenic Foci by Enflurane

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Enflurane anesthesia is associated with epileptiform cortical and motor activity,1–3 enhanced by hyperventilation.4–6 We used this drug in two cases to activate silent epileptogenic foci intraoperatively, in order to delineate them prior to discrete surgical excision.

REPORT OF TWO CASES

Patient 1. A 19-year-old youth had sustained a severe head injury, resulting in coma of three months' duration, at the age of 6 years. Permanent sequelae included slight mental retardation, moderate left hemiplegia, intractable partial complex seizures, and hydrocephalus, treated by ventriculoperitoneal shunt.

The seizures manifested aggressive prodromal symptoms lasting as long as a day, culminating in pantoclastic activity (destructive to everything) with or without the subsequent accompaniment of generalized motor seizures. Automatisms and visceral responses such as pallor, sweating, and bradycardia were frequently associated with the seizures, which were thought to emanate from a frontotemporal focus, documented by electroencephalography.

Medical attempts to control the seizures had included administration of diphenhydantoin, primidone, carbamazepine, dipropyacetate, and phenobarbital. Despite this therapy, the incidence and severity of the seizures and associated aggressive behavior increased to the point where the patient posed a severe management problem. He was referred to the University of Wisconsin Clinical Science Center for consideration of temporal lobectomy.

Preoperative evaluation revealed that the patient was normotensive, slightly mentally retarded, and well developed physically. Computed axial tomography and cerebral angiography demonstrated an area of cortical atrophy involving the right temporal lobe and anterior inferior part of the parietal lobe. The Wada test* demonstrated that amobarbital injection into the right internal carotid artery did not impair memory or any other cognitive function. Longitudinal EEG studies confirmed the presence of a fairly active focus of epileptogenic activity in the anterior and midtemporal areas, while serum levels of antiepileptic drugs were considered to be stable and within a therapeutic range. The history and findings, in our opinion, justified restricted temporal lobectomy, guided by intraoperative electrocorticography.

Anesthesia was induced with thiopental, 6 mg/kg, after premedication with atropine. Orotracheal intubation was facilitated by pancuronium and anesthesia was maintained with nitrous oxide.

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in 30 per cent oxygen. The arterial blood carbon dioxide tension was reduced and maintained by hyperventilation to 28 mm Hg. Morphine, 0.2 mg/kg, did not reduce blood pressure, which remained elevated: 160/90 mm Hg during the early part of the procedure.

A corticographic recording was attempted after the brain had been exposed to define the exact position of the epileptic focus. A high-amplitude periodic baseline shift was seen to coincide with the cerebrovascular pulse wave, which was attenuated by reduction of mean arterial blood pressure to 80 mm Hg with sodium nitroprusside. In addition, brain bulk was reduced by the intravenous administration of urea, 0.75 g/kg.³ Definite seizure activity was not observed in the corticographic recording at that time; therefore, pharmacologic activation of the focus was deemed necessary. Three per cent enflurane was administered from a calibrated vaporizer (Enflurac 110° Cyprane, Ltd.) at a flow rate of 5 l/min into the circle absorber circuit. After 2.0 min, epileptiform spikes appeared from the temporopolar electrode, spreading in 10 sec to involve nearby areas and becoming continuous (fig. 1). After 6 min the enflurane was discontinued. During the subsequent 40 sec, the epileptiform spikes diminished in frequency and ceased. During the administration of enflurane, mean arterial pressure was maintained at about 80 mm Hg by appropriate reduction of the sodium nitroprusside infusion. (Subsequent inspection of the record revealed rare but definite spikes emanating from the same electrodes that were vigorously active after enflurane administration.)

The temporal lobe was incised to the temporal horn, thus exposing the hippocampus, onto which were placed five of the recording electrodes. Forty-five minutes after the initial recording, 3 per cent enflurane was again administered, and within 2.4 min, high-voltage spikes were observed from three of these electrodes. The pre-existing corticographic pattern returned within 3.5 min of discontinuance of enflurane.

Only tissue demonstrated by corticography to be epileptogenic was excised after which the wound was closed. Recovery from anesthesia and operation was uneventful. During the three postoperative months, the patient was free of behavioral or grand mal seizures, and the EEG demonstrated delta activity over the right fronotemporal region, with no evidence of an epileptogenic focus.

Patient 2. A 22-year-old man had had idiopathic partial complex seizures since the age of 7 years. During the past three years he had had two or three seizures weekly, with frequent periods of status epilepticus of the partial complex type that had not responded to adequate blood levels of combinations of phenobarbital, diphenhydantoin, primidone, carbamazepine, and valproic acid. The electroencephalogram during this period demonstrated a right mid-temporal spiking focus that showed phase reversal in the right nasopharyngeal leads. The Wada Test demonstrated left hemispheral dominance with no memory or other high intellectual functional impairment after injection of amobarbital into the right carotid artery. He was admitted for right temporal lobectomy, guided by intraoperative electrocorticography.

The anesthetic management was substantially similar to that of the previous case except that moderate hyperventilation in the early
The corticographic recording revealed very rare spiking from the anterior mid-temporal region, with extension into the inferior frontal convolution. Enflurane, 3 per cent at a flow rate of 6 l/min, was added to the anesthetic circuit in an attempt to increase the incidence of spiking for more accurate delineation of the focus. Within 45 sec the amplitude and frequency of the spikes increased markedly, but they remained localized to those parts of the cortex described above. Enflurane administration was discontinued and the spiking diminished to the pre-enflurane level of activity.

As in the first case, the hippocampus was exposed, and five of the recording electrodes were placed on it. After 40 sec of enflurane administration, infrequent spiking from a localized area of the hippocampus was again brought to vigorous yet localized activity, which diminished after cessation of the administration of enflurane.

Areas of the temporal lobe and hippocampus associated with spiking activity were excised, but the frontal lobe, was left intact.

A month after the procedure, the patient was free of seizures; however, the EEG demonstrated spiking from the frontal region. He is still being treated with valproic acid and carbamezepine, 1 g of each daily.

**DISCUSSION**

The need to activate a silent epileptic focus for localization by encephalography is a common diagnostic problem. There are many techniques and drugs available to achieve this end, but none is ideal. The activity of intravenous analeptics is not easily terminated, and activity may be triggered in locations that are normal, becoming generalized, masking the focus and progressing to grand mal seizure. Some, for example, pentylenetetrazol and Megimide®, are circulatory stimulants, while methohexital, which is also used to activate such foci, induces high-voltage fast EEG activity, which may mask interictal spikes. Methohexital, in addition, induces general anesthesia, and is associated with laryngospasm, hiccup, loss of the airway, and respiratory and circulatory depression. Electrical stimulation only demonstrates the after-discharge threshold, rather than localizing the site of interictal focal spiking. Enflurane requires the attention of one skilled in anesthesia to manage administration and withdrawal, because concentrations above those required to maintain anesthesia are usually necessary to induce seizure activity reliably. Furthermore, intubation of the trachea and hyperventilation may be needed because the incidence of spiking is increased and the concentration of enflurane necessary to induce peak activity may be reduced with hypocarbic media. In common with other inhalational anesthetics, enflurane may increase cerebral blood flow and intracranial pres-
sure (ICP)^11,17 independent of seizure activity, which presents a relative contraindication to its use in those who have a variety of illnesses in which ICP is raised.

We chose enflurane as the epileptogen in these instances for several reasons: the trachea was already intubated and Pao2 reduced as part of a routine neurosurgical anesthetic. The drug was readily available, and could be given to effect by personnel competent in its administration and then promptly withdrawn. Last, the side effects of enflurane, arterial hypotension and increases in brain bulk, were being directly monitored, were unlikely to cause morbidity, and could be easily managed had they occurred.

We are confident that enflurane induced the epileptiform activity because on four occasions, administrations and withdrawals of the drug were closely related to its onset and disappearance.

We believe that the epileptogenic foci rather than unrelated sites generated the electrical activity: first, the activity arose within the areas under consideration. Second, not all exploring electrodes detected spikes, suggesting that damaged areas had lower seizure thresholds than normal brain tissue. Third, postoperative scrutiny of the corticographic recording revealed rare but definite spikes that were not detected prior to the administration of enflurane. These emanated from the same electrodes that were vigorously active during the administration of enflurane (fig. 1).

We suggest that enflurane may be used to provoke a quiescent epileptic focus into activity during the investigation of seizure disorders. When the patient is already anesthetized, it may be the drug of choice for this purpose. Hyperventilation will increase the likelihood of the focus becoming active and reduce the concentration of enflurane needed to induce spiking activity. Caution will be necessary when the patient has a disorder involving abnormally low intracranial compliance. The possibility that electrical activity may arise in regions of the brain that are not abnormal or spread from epileptogenic foci into normal brain tissue must be considered.

REFERENCES