Anesthetic Barbiturates in Refractory Status Epilepticus

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SUMMARY: *Two patients with previous cerebral damage and seizures and three patients with acute inflammatory cerebral lesions developed status epilepticus. They were unresponsive to standard anticonvulsants, but anesthetic barbiturates (thiopental and pentobarbital) stopped the seizures promptly.*

RÉSUMÉ: *Deux patients souffrant préalablement de lésion cérébrale et d'épilepsie et trois patients avec lésions cérébrales de nature inflammatoire aiguë développent un status epilepticus. Les patients ne répondent pas à la médication anticonvulsive standard mais l'emploi de barbituriques anesthésiques (thiopental et pentobarbital) s'avéra d'un secours rapide.*

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INTRODUCTION

Generalized status epilepticus is a medical emergency requiring prompt treatment to prevent cerebral damage or death. Rapidly acting anticonvulsants such as diazepam, phenytoin or paraldehyde are usually effective. Neurology texts, review articles and monographs on epilepsy occasionally mention anesthesia for resistant cases. Anesthetic barbiturates are less commonly specified and their effectiveness is not well documented. We present five cases successfully treated with anesthetic barbiturates after conventional anticonvulsants failed.

CLINICAL MATERIAL

Case 1. A 19 year old girl with a congenital right hemiplegia and previous left hemispherectomy had a seizure disorder since age two years. A flurry of seizures occurred while she was toxic on phenytoin (serum level 50 mcg/ml. She had frequent grand mal seizures for five days becoming continuous for three hours. They failed to respond to repeated intravenous doses of diazepam and phenobarbital, a reduced maintenance dose of phenytoin or rectal paraldehyde.

Artificial ventilation was used while she received pentobarbital 100-140 mgm/hr. intravenously. Seizures stopped instantly, but when pentobarbital was discontinued two days later grand mal seizures returned. Three more days of pentobarbital anesthesia were required. She recovered consciousness two days later and returning to her previous state, was discharged home.

Case 2. A 62 year old man had meningitis twenty years ago with resulting mild aphasia and recurrent right-sided and generalized convulsions. Continuous convulsions occurred four days prior to transfer to our unit, when serum phenytoin was 16.2 ugm/ml. Seizures did not respond to intravenous phenobarbital (500 mgm. in 12 hours), diazepam (repeated 10 to 20 mgm. bolus doses) or rectal paraldehyde (10 cc's with 10 cc's of mineral oil every four hours). With intubation and respiratory support an intravenous bolus of 250 mgms. thiopental was given, followed by 80-120 mgm/hr. as a continuous infusion for four days. The seizures stopped promptly. A right-sided hemiparesis resolved over the next week and he returned home without additional neurological deficit.

Case 3. A 41 year old woman developed measles a week prior to the onset of delirium and convulsions. Multi-focal clonic or grand mal seizures continued for two days. These were refractory to intravenous phenytoin (a loading dose of 1000 mgm intravenously followed by 200 mgm every twelve hours), phenobarbital (200 mgm intravenous bolus and 60 mgm every 6 hours), intravenous diazepam and rectal paraldehyde. Under respiratory support intravenous pentobarbital infused at 100-150 mgms/hr. promptly stopped the seizures. Reduced dosage was associated with recurrence of seizures and overall nine days of pentobarbital were required. She recovered consciousness two days after stopping the drug but showed a memory deficit. This resolved completely over six weeks but she has sporadic grand mal seizures.

Case 4. A 24 year old male developed a febrile illness with generalized and multifocal seizures. Herpes zoster was isolated from a left temporal lobe biopsy. Seizures persisted for six days without intervening consciousness. They were uncontrolled by intravenous phenytoin, phenobarbital, diazepam and clonazepam; valproic acid via nasogastric tube and rectal paraldehyde. With ventilatory assistance thiopental anesthesia controlled the attacks. Thirteen days of anesthesia were required. He recovered completely and had no neurological deficits.

Case 5. A 21 year old woman developed general malaise and fever followed one week later by multi-focal and generalized convulsions. Cerebrospinal fluid (CSF) contained lymphocytic pleocytosis with normal protein and glucose. A specific viral or other agent was not identified serologically or by CSF culture. Phenytoin and phenobarbital intravenously and valproic acid by nasogastric tube failed to

control the seizures. Intravenous thiopental (30 mgm/kg bolus doses) controlled the seizures for the twelve days of its administration. She was left with impaired intellect, ataxia and left hemiparesis.

The depth of anesthesia was assessed electroencephalographically, clinically, and by serum barbiturate levels. A burst-suppression electroencephalographic (EEG) pattern with a two to seven second interburst interval stopped clinical and electrographic seizures. The interburst interval was measured hourly in two patients using a single channel (C_z - O_2 derivation) at the bedside. Other patients had standard recordings. The four patients treated with pentobarbital had twice daily serum levels measured to help maintain a serum barbiturate level of 2-4 mgm/dl as suggested by Conn et al (1978) and Marshall et al (1975) in treating raised intracranial pressure. We found this level corresponded to a burst-suppression EEG pattern. Pupillary size was also helpful; in stages 3 and 4 of barbiturate anesthesia it returns to normal after constriction at lighter stages. (Atkinson, et al, 1977).

Drugs given prior to anesthesia were continued in maintenance doses by naso-gastric tube during anesthesia. Case 3, 4 and 5 also received dexamethazone. Rectal temperature dropped as low as 35.5° C. but controlled hypothermia was not instituted. All patients had ventilatory support but none required skeletal muscle relaxants. Muscle tone was flaccid, possibly because of a depressant effect of anesthetic barbiturates on spinal motor neurons (Macdonald and Barber, 1979).

DISCUSSION

Our five cases with status epilepticus were refractory to full doses of anticonvulsants. They responded abruptly to intravenous administration of pentobarbital or thiopental. These had to be continued from four to thirteen days. Cases 1 and 2 with longstanding cerebral lesions returned to their previous states. Only one of the three patients with inflammatory lesions recovered completely. A seizure disorder was the only obvious residiuum in case 4 while case 5 was more severely impaired. These two patients may have sustained cerebral insults from the inflammatory processes rather than the status epilepticus, but both may have contributed.

Experimental work by Meldrum et al (1973) indicates that prolonged seizures may damage multiple cerebral structures, even if the animals are paralyzed and adequately oxygenated. When status epilepticus is resistant to usually effective anticonvulsants we feel this risk outweighs the difficulties of anesthetic barbiturate administration. Early use of such drugs without intubation and ventilatory support was sometimes disastrous (Dundee and Gray, 1967). With respiratory support available in modern intensive care units, hazards are minimized. Neurological evaluation is difficult with anesthesia but continued seizures confuse interpretation of clinical signs in the non-anesthetized patient.

The anesthetic barbiturate pentobarbital directly depresses neuronal excitability by a gamma-amino butyric acid (GABA) mimetic action, an effect not shown by phenobarbital, an anticonvulsant, non-anesthetic barbiturate. Moreover, pentobarbital is more potent in augmenting GABA and decreasing glutamate responses (Macdonald and Barber, 1979). These properties of anesthetic barbiturates likely account for their anesthetic action and also possibly for their potency against seizures.

Blennow et al (1978) suggest that brain damage due to seizures may be caused by the production of free radicals with resultant lipid peroxidation and cell membrane or mitochondrial damage. Barbiturates may decrease the suspectibility of these membranes to peroxidation (Demopoulous et al, 1977; Majewska et al, 1978), thus preventing brain damage.

During experimental status epilepticus with pentylenetetrazol the cerebral metabolic rate of oxygen ($CMRO_2$) is increased by 60% (Siesjö, 1978). Barbiturates can lower the $CMRO_2$ to 50% of normal during anesthesia (Siesjö, 1978). Barbiturates may also lower lactate content, increase glycogen and glucose content of the brain and decrease utilization of high energy phosphate compounds as well as certain amino acids and neurotransmitters (Siesjö, 1978). Increased intracranial pressure which accompanies convulsions may be reduced. These are additional theoretical benefits of barbiturates in status epilepticus.

CONCLUSIONS

High dose anesthetic barbiturates are effective in stopping generalized status epilepticus refractory to other methods. Standard anticonvulsants should be tried first, in view of the necessity of ventilatory support and the impairment of consciousness which occur with barbiturate anesthesia. The treatment may have to be continued for several days to prevent status epilepticus from returning when the drug is stopped. This may apply especially to seizures due to inflammatory cerebral lesions. Skeletal muscle relaxants are not necessary when this treatment is used.

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