The author reviews the potential risks and anesthetic considerations encountered with epileptic and mentally retarded patients, including drug toxicity and anticonvulsant drug interactions with anesthetic agents.

Mental deficiency among patients with epilepsy is less frequently reported at present than in the past, but the percentage of retardates in any large population of epileptics, especially if it includes children, is still found to be three to four times higher than in a nonepileptic population of the same age.

Consequently, epilepsy with mental deficiency is likely to be encountered in preoperative evaluations at some time during any anesthetist's practice. This article provides a review and investigation into the potential problems and risks that may be encountered when anesthetizing such patients. Emphasis is on anticonvulsant drug interactions with anesthetic agents.

Epidemiology

Epilepsy is defined as "a symptom of excessive temporary neuronal discharges due to intracranial or extracranial causes; it is characterized clinically by discreet episodes, which tend to be recurrent, in which there is a disturbance of movement, sensation, behavior, perception and/or consciousness."  

Mental deficiency, when associated with epilepsy, is usually due to antecedent brain damage or to the combined effects of brain damage and epilepsy. The nature of the attacks depends upon the area of the brain being affected. The fact is that relationships exist between certain types of retardation and certain types of epilepsy. Infantile spasms and hypsarrhythmia are highly associated with mental retardation, as is the petit mal variant. These most infantile forms of epilepsy are most likely to be complicated by intellectual impairment.

Considerations for anesthetic management

Epileptic, mentally subnormal patients often present to the operating room in a state that is unamenable to reason; they are frequently frightened, uncooperative, and even belligerent. They may have anatomical abnormalities such as large heads or tongues that endanger control of the airway. They frequently show either spasticity or involuntary movements, thus rendering it difficult for the anesthetist to start an intravenous line.

In addition to having a predisposition to convulsions, many of these patients have received long-term treatment with drugs which can have toxic side effects and are capable of participating in drug interactions with anesthetic agents. Such patients often require extensive dental treatment and because they may be uncooperative due to associated personality disorders, they are more likely to have this treatment under general anesthesia.

Mentally retarded patients also cause concern...
because they may eat immediately before surgery without informing the medical staff. In such instances, regurgitation and aspiration are most likely to occur during induction of or emergence from anesthesia.

The majority of epileptics receive long-term therapy with either phenobarbital, phenytoin, (Dilantin®) or primidone (Mysoline®), or a combination of these three anticonvulsant drugs. Toxic effects that may occur with these drugs include gingival hypertrophy, folate deficiency, osteomalacia, and blood dyscrasias. Neurological side effects and clues of ensuing toxicity are drowsiness, dizziness, ataxia, confusion and coma.\(^5\)

The metabolism of these common anticonvulsants is mainly effected by parahydroxylation in the liver and about 10% of the preparation is excreted unchanged in the bile. Parahydroxylation is a common pathway for the metabolism of many other drugs and important interactions may result, namely, enzyme induction and enzyme inhibition.\(^4\)

Both phenobarbital and phenytoin are capable of accelerating their own metabolisms by microsomal induction, and both possess the ability to increase the rate of metabolism of digoxin and anticoagulants, which use the same pathway for metabolism. This mechanism has been shown to accelerate the metabolism of certain volatile anesthetic agents, and to increase the body uptake of the anesthetic agent and its metabolites.\(^3\)

Since it is thought that anesthetic metabolites may be responsible for occasional organ toxicity from halogenated anesthetic agents, it appears that anesthesia for the epileptic patient could be dangerous.\(^5\) "In our society one in every 200 persons suffers to a certain degree from epilepsy and is treated with anti-epileptic drugs.\(^2\)

Certain drugs may compete with phenytoin for a common metabolite degradation pathway or inhibit phenytoin metabolism, thus resulting in increased plasma phenytoin levels. Drugs that can produce this enzyme inhibition include diazepam, chlorpromazine and chloridiazepoxide, which are commonly used as premedicants. This must be taken into consideration when prescribing the preoperative medication for the epileptic patient.\(^5\)

The anticonvulsant primidone (Mysoline®) has been reported to render the patient abnormally sensitive to the action of barbiturates by greatly prolonging recovery time and depressing respiration.\(^6\) If intravenous induction of anesthesia with a barbiturate is considered to be essential in such cases, dosage should be reduced to the minimum necessary to suppress consciousness. In known epileptics, where the exact nature of previous drug therapy cannot be established, the anesthetist should proceed on the assumption that primidone has been employed.

A considerable amount of primidone is converted to phenobarbital in man. The addition of phenytoin to primidone therapy increases the phenobarbital levels found, probably by stimulating the conversion of primidone to phenobarbital. A contributing effect might be phenytoin-induced competitive inhibition of phenobarbital metabolism.\(^5\)

**Anesthetic effects**

Several cases of epileptiform seizures have been reported in association with the administration of methohexital. Methohexital, although a barbiturate, is potentially a convulsant because it is a methylated compound. It is used to activate the EEG in order to facilitate the diagnosis of epilepsy.\(^7\) Thus, if possible, it would seem advisable to avoid the usage of methohexital in epileptic patients during surgery.

Methoxyflurane can produce high frequency EEG activity, but it does not appear to cause seizures. However Ethrane\(^6\) (enflurane), which is structurally similar to methoxyflurane, does have stimulant properties. There are reports of convulsive behavior in patients under enflurane anesthesia.\(^8\)

Enflurane package inserts state, "Increasing depth with Ethrane\(^6\) may produce a change in the EEG characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity, which may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or jerks of various muscle groups. It is self limiting and can be terminated by lowering the anesthetic concentration. This EEG pattern associated with deep anesthesia is exacerbated by low arterial CO\(_2\) tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity."\(^9\)

Halothane may produce hepatotoxicity with resultant impairment of hepatic metabolism of phenytoin, thus leading to elevated phenytoin plasma levels or toxicity. Halothane and other hepatotoxic drugs should be given cautiously to patients receiving phenytoin.\(^5\)

Ketamine hydrochloride produces excitation of the central nervous system (CNS) and EEG changes similar to epilepsy. One of the problems following the administration of ketamine is the
frequent occurrence of spontaneous muscular movement. This may consist of mouth and tongue movements, and random movements of the extremities. Although early reports suggested that ketamine hydrochloride may induce seizures and therefore may not be preferred for epileptics, other studies indicated that ketamine may actually suppress seizures. This latter finding has been verified in a recently published study disclosing that ketamine has been used without untoward effects in a large number of mentally retarded patients, many of whom had seizure disorders.9

Long-term anticonvulsant treatment for epilepsy can cause an accumulation in the body, and if intake of the drug exceeds its rate of destruction and excretion, signs of toxicity can occur. Anesthesia for patients on anticonvulsants may be predisposed to drug toxicity and the phenytoin neurological overdose symptoms are evident. There are two causes for this. The general depression caused by anesthetic itself may retard hepatic degradation to the extent that phenytoin levels build up to toxic levels. Another cause may be the inhibition of microsomal enzymes in the metabolism of phenytoin which may occur in the presence of another drug using the same metabolic pathway.

Considering the possibility of precipitating anticonvulsant drug toxicity, it may seem advisable to withhold all anticonvulsant therapy immediately preoperatively. However, withdrawing all medication involves the risk of convulsions. Therefore, epileptic patients should be kept on anticonvulsants before and after the surgery.10

A study investigating the interaction between phenytoin and d-tubocurarine with cats showed that cats receiving phenytoin had a greater and more prolonged response to d-tubocurarine than did control cats. It is proposed that the site of action of phenytoin is prejunctional and thus additive to the effect of the relaxant at the neuromuscular junction. This evidence suggests that there may be increased sensitivity to d-tubocurarine and other non-depolarizing muscle relaxants in patients receiving phenytoin for epilepsy.11

Conclusion

The possible risks and anesthetic considerations that must be taken into account when anesthetizing the epileptic and mentally retarded patient, namely, drug toxicity, convulsions, and drug interactions have been reviewed. It is important for the anesthetist to recognize and understand these primary factors so that he/she can be better prepared for selecting acceptable anesthetic agents and techniques.

REFERENCES


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