British Journal of Anaesthesia **108** (4): 562–71 (2012)
Advance Access publication 8 March 2012 · doi:10.1093/bja/aes027

BJA

REVIEW ARTICLES

Anaesthesia and epilepsy

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Editor's key points

- The authors have reviewed the mechanism of action of old and new antiepileptic drugs.
- Awareness is required regarding seizure-provoking properties of certain anaesthetic drugs.
- Status epilepticus, refractory to two antiepileptic drugs carries a high morbidity and requires general anaesthesia.
- For uncontrolled seizures, treatment with midazolam, thiopental, or propofol is acceptable; opioids should be avoided.

Summary. Epilepsy is the most common serious neurological disorder, with a prevalence of 0.5–1% of the population. While the traditional antiepileptic drugs (AEDs) still play a significant role in treatment of seizures, there has been an influx of newer agents over the last 20 yr, which are now in common usage. Anaesthetists are frequently faced with patients with epilepsy undergoing emergency or elective surgery and patients suffering seizures and status epilepticus in the intensive care unit (ICU). This review examines perioperative epilepsy management, the mode of action of AEDs and their interaction with anaesthetic agents, potential adverse effects of anaesthetic agents, and the acute management of seizures and refractory status epilepticus on the ICU. Relevant literature was identified by a Pubmed search of epilepsy and status epilepticus in conjunction with individual anaesthetic agents.

Keywords: anaesthesia; anticonvulsants; epilepsy; status epilepticus

Epilepsy is a tendency to have recurrent unprovoked seizures. It is the most common serious neurological disorder with a prevalence of 0.5–1% of the population. The highest incidence is at the extremes of age and in those with structural or developmental brain abnormalities. The International League against Epilepsy (ILAE) has classified seizures into focal (or partial) seizures which arise from one hemisphere and generalized seizures which show electrographic seizure onset over both hemispheres.[1 2] Lamotrigine and carbamazepine are considered drugs of choice in focal epilepsies, while valproate is probably the most effective drug for primary generalized seizures.[3 4] If the initial antiepileptic drug (AED) results in adverse effects, an alternative AED is tried as monotherapy. If, on the other hand, seizures continue in spite of adequate doses, combination therapy is often necessary.

In the last 20 yr, there has been an influx of a new generation of AEDs.[5] Many of these are the products of rational drug development programmes, while others are modifications of previously existing molecules that result in improved pharmacokinetic properties. The newer AEDs are generally associated with fewer adverse effects and drug interactions. Many anaesthetic agents affect the propensity to seizures, both in patients with epilepsy and in those with no prior history of seizures. In patients taking AEDs, drug interactions and maintenance dosing of AEDs during periods of starvation are important considerations in the perioperative period.

Patients with epilepsy often require anaesthesia for elective and emergency surgery. Appropriate perioperative management of AED therapy is vital in maintaining seizure control in these patients. Anaesthetists need to be aware of the pharmacological properties of commonly used AEDs. Patients with epilepsy may also require anaesthetic care during treatment of status epilepticus, either for airway management or induction of general anaesthesia for refractory status epilepticus. This article aims to examine the current treatment of epilepsy, the mode of action of antiepileptics, the effect of AEDs on anaesthesia, and the effect of anaesthesia on epilepsy in adults. The use of anaesthetic agents in the management of refractory status epilepticus is also discussed.

Mechanisms of action of AEDs

In simple terms, a seizure can be seen as the result of imbalance between excitatory and inhibitory neuronal activity. This leads to the generation of hyper-synchronous firing of a large number of cortical neurones. Traditional AEDs exert antiseizure activity by the following mechanisms:

- reduce the inward voltage-gated positive currents (Na^+, Ca^{2+}),
- increase inhibitory neurotransmitter activity (GABA),
- decrease excitatory neurotransmitter activity (glutamate, aspartate).

The effects are summarized in Table 1. In addition, many new AEDs possess novel mechanisms of action. Novel sites of drug binding include synaptic vesicle (SV2) protein (levetiracetam), steroid binding sites on $GABA_A$ receptors (ganaxolone), and voltage-gated potassium channel (retigabine).[6 7]

Effect of antiepileptics on anaesthesia

There are important pharmacokinetic and pharmacodynamic interactions between AEDs and drugs commonly used in anaesthesia. These affect both drug efficacy and the risk of seizure activity intraoperatively.[8]

Induction and inhibition of the cytochrome P450 isoenzymes in hepatic metabolism constitutes the most significant mechanism of drug interactions involving AEDs. Many of the older-generation AEDs, such as carbamazepine, phenytoin, phenobarbital, and primidone, have potent enzyme-inducing properties. This leads to a decreased plasma concentration of many medications including immunosuppressants, antibacterials, and cardiovascular drugs, particularly amiodarone, β-blockers (propranolol, metoprolol), and calcium channel antagonists (nifedipine, felodipine, nimodipine, and verapamil).[9] In patients taking warfarin, introduction or withdrawal of enzyme-inducing AEDs requires close monitoring of the international normalized ratio. Oxcarbazepine and eslicarbazepine are weaker inducers of hepatic microsomal enzymes compared with carbamazepine, but the effects may be clinically significant.[10] Topiramate also induces hepatic microsomal enzymes in a dose-dependent manner. Valproate is an inhibitor of hepatic microsomal enzyme systems and may reduce the clearance of many concurrently administered medications, including other AEDs. Gabapentin, lamotrigine, levetiracetam, tiagabine, and vigabatrin do not induce hepatic enzymes.[11]

Macrolide antibiotics, particularly erythromycin, are potent inhibitors of CYP3A4, which is involved in carbamazepine metabolism and can lead to carbamazepine toxicity. Concomitant use of carbapenem antibiotics can lead to a significant decrease in serum valproate concentrations.[12 13]

Effect of anaesthetic agents on epilepsy

Many of the agents used possess both pro-convulsant and anticonvulsant properties, which could impact on the choice of anaesthetic.[14]

Inhalational anaesthetics

Nitrous oxide (N_2O) provokes seizures in animal models (cats), but this has not been replicated in humans. In mice, withdrawal seizures have been seen after short exposures to N_2O.[15] During a case of electrocorticographic monitoring for epilepsy surgery, N_2O visibly suppressed epileptiform activity, which manifested again on N_2O withdrawal.[16] Myoclonus has been observed in volunteers exposed to hyperbaric (1.5 atm) N_2O[17] and when used in combination with isoflurane or halothane.[18]

There are multiple case reports of sevoflurane-provoking seizure-like activity, particularly in children[19] and where high concentrations are used in conjunction with hypocapnea.[20] In high concentration, enflurane exhibits periods of suppression with paroxysmal epileptiform discharges in cats and rats.[21] There have been multiple reports of seizure activity in humans after enflurane anaesthesia.[18 22] Isoflurane has well-characterized anticonvulsant properties. Both isoflurane and desflurane can be used in refractory status epilepticus, described in a later section.[23]

Opioids

Meperidine is the opioid with the strongest association with myoclonus and tonic-clonic seizure activity.[24] However, fentanyl, alfentanil, sufentanil, and morphine have been reported to cause generalized seizure patients after low-to-moderate dose,[25 26] particularly after intrathecal use.[27–29] Fentanyl and its analogues have not been shown to possess any anticonvulsant properties.

Opioid anaesthetic agents are used to enhance EEG activity in patients with focal epilepsy. Both remifentanil and alfentanil have been used to induce spike activity in localizing epileptogenic zones intraoperatively during epilepsy surgery,[30] although alfentanil appears to be the more potent activator.[31] The addition of alfentanil to propofol anaesthesia for electroconvulsive therapy (ECT) also increases seizure duration.[32]

I.V. anaesthetic agents

The barbiturates (thiopental, methohexital, and pentobarbital) and propofol are well established as agents for the treatment of refractory status epilepticus.[33–35] All agents have been reported to produce excitatory activity, such as

Table 1 Main modes of action of commonly used AEDs.[6 7] *From the evidence, it is not clear which of the actions of valproate is responsible for its actions. Lamotrigine is primarily a sodium channel blocker with some effects on T-type calcium channels

Mode of action	Antiepileptic drug
Increase GABA activity	
Increased frequency of Cl channel opening	Benzodiazepines (binds to BZ_2 receptors); tiagabine (prevents reuptake); gabapentin (prevents reuptake)
Increased mean Cl channel opening duration	Barbiturates
Blocks GABA transaminase (blocking GABA catabolism within the neurone)	Vigabatrin
Glutamate antagonist	Topiramate (at AMPA receptor)
Reduction of inward voltage-gated positive currents	Phenytoin (Na^+ channel); carbamazepine (Na^+ channel); ethosuximide (Ca^{2+} channel)
Increased outward voltage-gated positive currents	Sodium valproate (K^+ channel)
Pleotropic sites of action	Sodium valproate (1, 2, 3 and 4)*; lamotrigine (2 and 3)*; topiramate (1, 2, and 3)