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Adult epilepsy and anaesthesia

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Key points

- Epilepsy is a common neurological disorder affecting 600 000 people in the UK.
- The standard treatment for adults with epilepsy is antiepileptic drug (AED) therapy, but resective surgery may be considered in those patients in whom seizure control is not achieved.
- AEDs have multiple drug interactions, which need to be considered in the perioperative period.
- Perioperative care of patients with epilepsy should focus on minimization of interference in normal AED regimes and avoiding physiological or pharmacological disturbances that may lower the seizure threshold.
- Status epilepticus is a common medical emergency with significant morbidity and mortality.

Epilepsy is a disorder of the brain characterized by a predisposition to generate abnormal synchronous neuronal activity. This results in recurrent and unpredictable interruptions of normal brain function, observed clinically as epileptic seizures.[1] Epilepsy is common; 50 million people worldwide are affected and the estimated prevalence of active epilepsy [continuing seizures or the need for antiepileptic drug (AED) treatment] is 4–10 per 1000 people.[2] Within the UK, ~600 000 people have a diagnosis of epilepsy and take antiepileptic medication.[3] All anaesthetists will regularly encounter patients with epilepsy in their practice and should be aware of the special considerations when managing patients with this disorder. Planned and thoughtful care of these patients can minimize the risk of seizure occurrence in the perioperative period.

Epileptic seizures and epilepsy

Diagnosis of epilepsy

Epilepsy is conventionally diagnosed after two unprovoked seizures occurring at least 24 h apart. This reflects the fact that after two non-febrile seizures, more than 70% of people will have another seizure within 4 yr,[4] whereas only 40–50% of people will go on to develop epilepsy after a single unprovoked seizure.[5] The diagnosis of epilepsy depends on a convincing history, witnessed seizures, or both in combination with investigations including EEG to detect abnormal neuronal discharges and computed tomography (CT) or magnetic resonance imaging (MRI) to detect underlying structural brain abnormalities.[6] More than 60% of patients with epilepsy may have normal investigations (idiopathic epilepsy) and diagnosis is often difficult. As a result, it is believed that 5–30% of people diagnosed with epilepsy in the UK may have an incorrect diagnosis.[7]

Classification of epilepsy

Epilepsy is not a single condition. There are more than 40 different types of epilepsy consisting of at least 29 syndromes and a further 12 or so clinically distinct groups defined by the specific cause.[8] Classification systems typically focus on underlying aetiology or descriptions of clinical features such as seizure type.[8] Common causes of epilepsy include congenital neurological or metabolic conditions, traumatic brain injury, stroke, brain tumours, and central nervous system (CNS) infections. Underlying genetic susceptibility and environmental factors may also contribute to this condition. The precise aetiology of epilepsy is often not important in the perioperative environment, but anaesthetists should note if epilepsy is part of a multisystem syndrome or disease process.

Epileptic seizures are subdivided into focal and generalized types. Focal seizures originate within neuronal networks limited to one hemisphere, whereas generalized seizures rapidly engage

Table 1 Major seizure type and subtype classifications

Generalized seizures
Tonic–clonic
Absence
Myoclonic
Clonic
Tonic
Atonic
Focal seizures
Simple
Complex
Evolving to generalized
Mixed seizures (focal and generalized)
Unclassified

bilaterally distributed neuronal networks. Focal and generalized epileptic seizures present with variable signs and symptoms that depend on the spatial origin and extent of abnormal synchronous activity (Table 1). Within the UK, 60% of patients with epilepsy have tonic–clonic seizures, 20% have complex focal seizures, 12% have a mixed picture of several seizure types, 3% have simple focal seizures, and <5% have other seizure types.[3,8]

Management of epilepsy

The standard management of adults with a confirmed diagnosis of epilepsy is AED therapy. The mechanism of action of AEDs is via either suppression of excitatory impulses or facilitation of inhibitory impulses in the brain (Fig. 1).[9] Therapy choices are based on the seizure type and aetiology of epilepsy, with consideration taken of the patient's comorbidities and medications and the AED side-effect profile. The National Institute for Clinical Excellence (NICE) produced recommended treatment guidelines in 2012 (Table 2).[7] AED monotherapy is preferable, but if this fails, patients may be managed on more than one AED. The characteristics of the major AEDs are shown in Table 3.[10]

Patients with poor seizure control despite AED polytherapy should be referred to a specialist multidisciplinary epilepsy clinic. Epilepsy surgery is a treatment option in these cases and may be curative or palliative. Surgical options include implantation of a vagal nerve stimulator to reduce seizure frequency, curative resective surgery such as an anterior temporal lobectomy, or disconnective procedures that interrupt the propagation of seizures such as a corpus callosotomy or a multiple pial transection.

Women of childbearing age should be counselled regarding the risk of teratogenicity from AEDs and the potential interaction between AEDs and oral contraceptive drugs. Although some AEDs are linked to fetal malformations, data especially from newer drugs are limited and there are definite risks to the fetus and mother if a woman has a tonic–clonic seizure during pregnancy. In the period 2006–8, the UK Confidential Enquiries into Maternal Deaths recorded 14 deaths during pregnancy as a consequence of epilepsy.[11] Decisions regarding epilepsy treatment during pregnancy are therefore complex and should be made in consultation with a neurologist and obstetrician.

Individuals are no longer considered to have epilepsy if they have remained seizure-free for at least 10 yr off antiseizure medicines and there are no known risk factors associated with a high probability (≥75%) of future seizures or if they had an age-dependent epilepsy syndrome but are now past the applicable age. This reflects the finding that the risk of recurrent seizures is very low after 10 yr being seizure-free off antiepileptic medication.[12]

Prognosis for patients with epilepsy

In those patients with a defined epilepsy aetiology, their prognosis will depend on the underlying cause. Patients with idiopathic epilepsy have a normal lifespan if their seizures are well controlled, but this falls if seizure control is not achieved. This reflects the higher incidence of accidents and suicides in this group and also the risk of sudden unexpected death in epilepsy (SUDEP). SUDEP is the sudden death of a seemingly healthy individual with epilepsy, usually occurring during, or immediately after, a tonic–clonic seizure. The mechanisms are incompletely understood, but seizure-related respiratory depression, cardiac arrhythmias, cerebral depression, and autonomic dysfunction are all implicated.[13] Risk factors for SUDEP include male sex, long duration of epilepsy, frequent occurrence of tonic–clonic seizures, and AED polytherapy. Patients should be counselled and given advice regarding treatment and lifestyle choices to avoid poor seizure control and minimize the risk of SUDEP.

Management of patients with epilepsy for routine surgery

Preoperative evaluation

In addition to the standard preoperative history and examination, specific considerations in patients with epilepsy are described below.

Associated comorbidities

For patients with epilepsy of defined aetiology, there may be important effects on other organ systems. For example, congenital syndromes often have multisystem involvement, and epilepsy secondary to stroke is associated with other significant cardiovascular disease.

Seizure type and frequency

It is important to establish how well a patient's epilepsy is controlled to predict the risk of postoperative seizure occurrence. Awareness of the patient's normal seizure pattern helps to determine if postoperative events are likely to be part of their underlying disorder.

Antiepileptic medication

Current drug therapy, dosage regimes, time of most recent dose, and any recent changes in the medication regime should be established. Attempts should be made to minimize disruption to treatment regimes and anaesthetists should ensure that a patient has taken their scheduled medication on the morning of surgery.

Driving licence status

Patients with epilepsy will usually be allowed to hold a driving licence if they have been totally seizure-free, or have only had seizures in their sleep, or only had simple focal seizures with no functional impairment over a 1 yr period (sometimes 6 months in the case of a first seizure). A perioperative seizure in patients who hold driving licences can therefore have significant implications. The Driving and Vehicle Licensing Agency (www.gov.uk/government/organisations/driver-and-vehicle-licensing-agency) has detailed advice.

Preoperative tests

Patients should have preoperative tests in line with National Institute of Clinical Excellence guidelines (NICE, www.nice.org.uk)

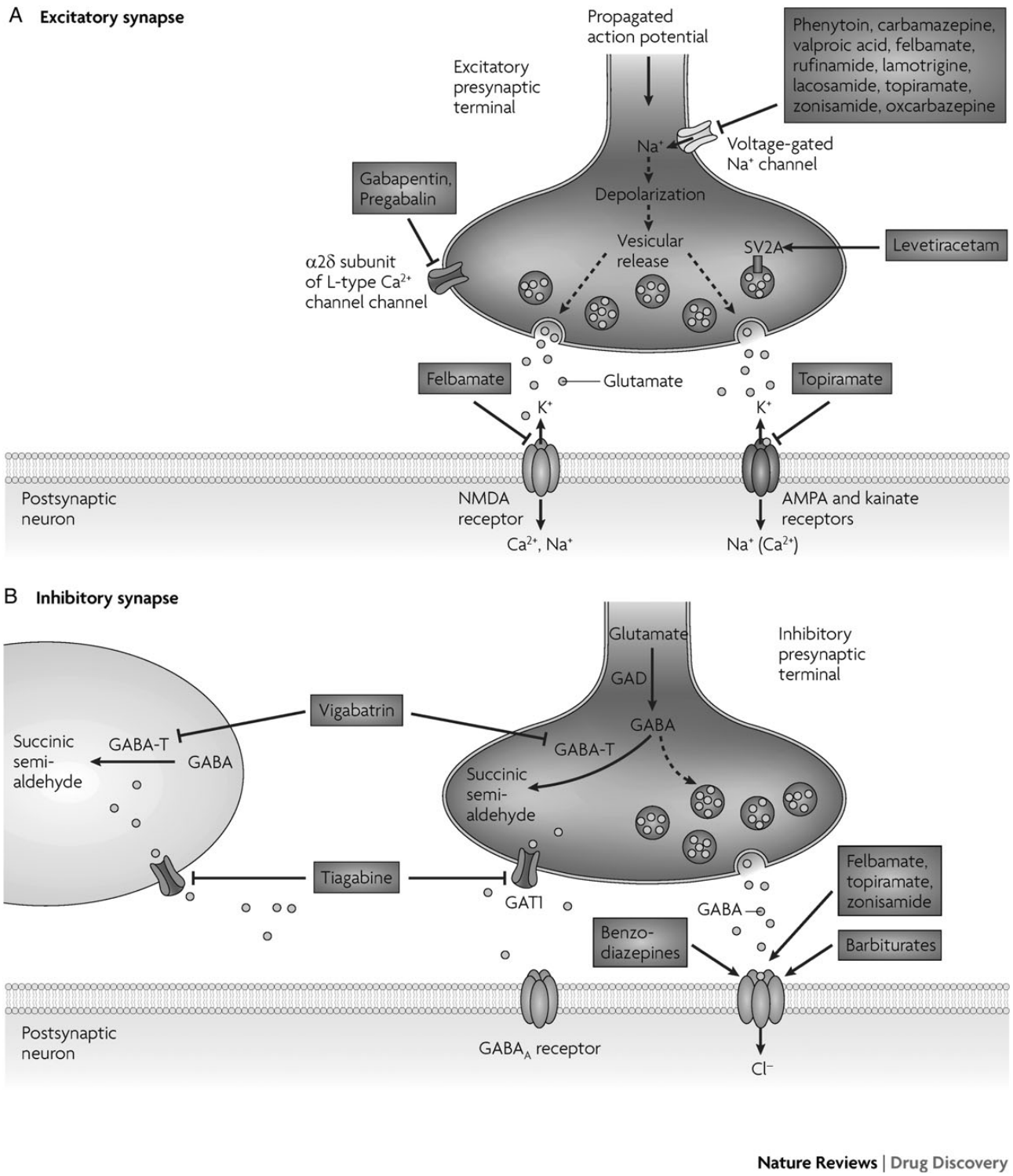

Fig 1 Proposed mechanisms of action of currently available AEDs at (A) excitatory and (B) inhibitory synapses (reproduced with permission from Bialer and White).[9] AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-amino-butyric acid; GABA-T, GABA transaminase; GAD, glutamic acid decarboxylase; GAT1, GABA transporter 1; NMDA, *N*-methyl-D-aspartate; SV2A, synaptic vesicle glycoprotein 2A.

depending on age, surgical severity, and ASA status. Within these guidelines, there are no specific recommendations regarding preoperative measurement of AED levels, and levels are not routinely measured. Exceptions to this are in patients who have poorly controlled epilepsy or a history of unstable AED levels and before major gastrointestinal surgery to establish baseline levels. Consultation with the patient's neurologist before surgery is probably appropriate in such circumstances.

Table 2 NICE guidelines for AED treatment[7]

Seizure type	First line	Adjunctive
Generalized tonic–clonic	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Clobazam Lamotrigine Levetiracetam Sodium valproate Topiramate
Tonic or atonic	Sodium valproate	Lamotrigine
Absence	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate
Myoclonic	Levetiracetam Sodium valproate Topiramate	Levetiracetam Sodium valproate Topiramate
Focal	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate

Conduct of anaesthesia

The multiple interactions between AEDs and anaesthetic agents are complex and beyond the scope of this article. However, a number of common and important interactions will be discussed with practical tips for management.

I.V. anaesthetics

The effects of i.v. anaesthetic agents on the EEG are complex, but they are generally proconvulsant at low levels and anticonvulsant at doses used for general anaesthesia. Thiopental is safe to use and is an established treatment for refractory status epilepticus because of its powerful anticonvulsant properties at anaesthetic doses. Propofol was previously avoided in patients with epilepsy because of the high rate of excitatory movements on induction and emergence. However, it is now widely used because of the recognition of its anticonvulsant properties at anaesthetic doses and because the abnormal movements are usually easy to distinguish from epileptic seizures. Etomidate has been reported to be more frequently associated with postoperative seizures and prolongs seizures when used for electroconvulsive therapy, and is therefore generally avoided. Ketamine is often avoided, particularly as a co-induction agent, because of its proconvulsant properties at low doses. However, it is anticonvulsant at anaesthetic doses. Benzodiazepines are all potent anticonvulsants and safe to use.

Inhalation anaesthetics

Nitrous oxide has been observed to provoke seizures in animal models, but this has not been replicated in humans and it is considered safe to use. Most inhalation agents cause burst suppression on the EEG and again are safe to use. The exception to this is enflurane, which can produce epileptiform discharges on the EEG and postoperative seizures, so should be avoided.

Opioids

Opioid analgesics all possess some degree of proconvulsant activity and are used to enhance EEG activity during seizure focus localization in epilepsy surgery. However, most opioids have a long history of safe use in patients with epilepsy. An exception to this is alfentanil, a particularly potent enhancer of EEG activity, which should be avoided or used with caution. Meperidine and tramadol should also be avoided as they increase the risk of seizures. Meperidine's metabolite normeperidine is a potent proconvulsant, and tramadol lowers the seizure threshold (probably because of its inhibition of monamine reuptake).

Neuromuscular blockers

Although succinylcholine has been observed to produce increased EEG activation, this has not been associated with seizure activity.[14] It is therefore considered safe to use except after prolonged status epilepticus where it may cause dangerous elevations in serum potassium. Non-depolarizing neuromuscular blockers (NMBs) are safe, but the enzyme-inducing effects of AEDs may cause resistance to the effects of aminosteroid NMBs such as rocuronium, pancuronium, and vecuronium. It is advisable to monitor the neuromuscular block with a nerve stimulator, as the dose and frequency of these drugs may need to be adjusted. Laudanosine, a metabolite of atracurium, has epileptogenic potential, but seizures have only been reported in animal studies.

Antiemetics

Dopamine antagonists are particularly associated with extrapyramidal effects and acute dystonic reactions, which might be confused with seizure activity. It is therefore advisable to avoid phenothiazines (e.g. prochlorperazine), benzamindes (e.g. metoclopramide), and butyrophenones (e.g. droperidol).

Local anaesthetics

Regional techniques are safe in patients with epilepsy and may help to minimize disruption of normal AED regimes. However, close attention should be paid to safe dosing as local anaesthetics can readily cross the blood–brain barrier and result in seizures if plasma levels are too high.

Seizures under anaesthesia

Seizures under general anaesthesia are relatively rare, but may occur in patients with poorly controlled epilepsy or in the context of high-risk surgery such as neurosurgery. They are difficult to diagnose, especially if NMBs have been used, but suggestive signs include increasing end-tidal carbon dioxide, tachycardia, hypertension, increased muscle tone, pupillary dilatation, and increased oxygen consumption. Immediate management includes deepening of anaesthesia, administration of 100% oxygen, correction of precipitating factors such as hypoglycaemia, hypoxia, and hypercarbia, and also consideration of differential diagnoses. If available, EEG may help with diagnosis.

Postoperative care

Of particular importance in the management of patients with epilepsy is minimization of disruption of their normal AED regime. I.V. forms of phenytoin, sodium valproate, and leviteracetam exist and carbamazepine can be given rectally. Early input from a neurologist should be sought if a patient is likely to be unable to resume their normal regime of oral AEDs after operation.

Postoperative prescriptions for patients with epilepsy should take into account the extensive pharmacokinetic and pharmacodynamic interactions of AEDs. Enzyme-inducing AEDs can reduce the serum concentration of multiple drugs, including some antimicrobials, paracetamol, and fentanyl. Conversely,

Table 3 Characteristics of AEDs (adapted with permission from Kofke).[10] CNS, central nervous system; CYP2B, cytochrome P450 2B; DIC, disseminated intravascular coagulation; $t_{½}$, elimination half-life; UGT, UDP-glucuronosyltransferase

Drug	Protein binding (%)	Effects on enzymes involved in drug metabolism	$t_{½}$ (h)	Elimination route (%)		Disadvantages and adverse effects
				Renal	Liver	
Carbamazepine	75	Broad-spectrum inducer	9–15	1	99	Diplopia, nystagmus, blurred vision, ataxia, dizziness, sedation, hyponatraemia, rash
Clonazepam	85	Induce CYP2B family	20–60	<5	>90	Sedation
Ethosuximide	0	None	30–60	<20	<80	Nausea, vomiting, gastrointestinal distress, drowsiness, ataxia
Felbamate	25	Mixed inducer and inhibitor	13–22	50	50	Risk of aplastic anaemia and liver toxicity, CNS and gastrointestinal side-effects, drug interactions, dizziness, blurred vision, ataxia, weight loss
Gabapentin	0	None	5–7	100	0	Efficacy limited to partial epilepsies, multiple daily dosing, high cost, mild drowsiness, encephalopathy, weight gain, peripheral oedema, weight change
Lamotrigine	55	Induces UGTs	12–62	10	90	Need for slow titration, hypersensitivity reactions, rash, Stevens–Johnson syndrome, toxic epidermal necrolysis (especially with concurrent valproate), hepatic and renal failure, DIC, arthritis, fever, red cell aplasia, tics, insomnia
Levetiracetam	<10	None	6–8	100	0	Irritability, behaviour change, somnolence
Oxcarbazepine	40	Mixed inducer and inhibitor	9	1	99	Interaction with oral contraceptives, hyponatraemia, rash
Phenobarbitol	45	Broad-spectrum inducer	75–110	25	75	Drowsiness, slurred speech, nystagmus, confusion, somnolence, ataxia, respiratory depression, coma, hypotension, sedation, behaviour disorders
Phenytoin	90	Broad-spectrum inducer	9–36	5	95	Vertigo, ataxia, slurred speech, nystagmus, diplopia, somnolence, stupor, coma, gingival hyperplasia, hirsutism. Hypotension and arrythmias (i.v.)
Primadone	0	Broad-spectrum inducer	6–8	100	0	Sedation and dizziness acutely, then similar to phenobarbital
Tigabine	96	None	7–9	2	98	CNS side-effects, interactions with oral contraceptives, nephrolithiasis, open-angle glaucoma, hypohidrosis, metabolic acidosis, weight loss
Topiramate	15	Mixed inducer and inhibitor	12–24	65	35	CNS side-effects, nephrolithiasis, open-angle glaucoma, hypohidrosis, metabolic acidosis, weight loss, language dysfunction
Valproate	90	Broad-spectrum inhibitor	6–18	2	98	Sedation, gastric disturbance, weight gain, diarrhoea, tremors, ataxia, somnolence, coma, thrombocytopenia, platelet dysfunction, hepatic failure, hair loss, drowsiness
Vigabatrin	0	None	5–7	100	0	Visual field defects, weight gain
Zonisamide	40	None	63	35	65	CNS side-effects, allergic reactions, rash, nephrolithiasis, hypohidrosis, irritability, photosensitivity, weight loss

drugs, including some antimicrobials, can increase the serum concentration of AEDs by inhibiting their metabolism, risking AED toxicity. In addition, highly protein-bound AEDs can compete with other protein-bound drugs for binding sites, altering free drug levels (Table 3). Proconvulsant drugs including tramadol, meperidine, and ketamine should be avoided, as should dopamine antagonists including haloperidol and antiemetics because of the risk of extrapyramidal side-effects. In view of the many and complex interactions, all postoperative medications should be checked for safety before prescribing.

Postoperative seizures

Abnormal movements in the postoperative setting may be seizures or a number of other diagnoses (Table 4). Management should focus on an ABC approach, determination of the likely cause and termination of seizures with benzodiazepines. If seizure resolution does not occur with benzodiazepine therapy, a loading dose of phenytoin (18 mg kg^{-1}) should be given and neurology advice sought. Patients with known epilepsy should be informed of the event as it may affect their lifestyle, for example, driving or working with heavy machinery. In patients without known epilepsy, precipitating factors such as metabolic disturbances or drug effects should be corrected and they should be referred for an urgent neurology opinion. The diagnosis of a first seizure in the postoperative setting should be made cautiously in view of the multiple other pathologies that may mimic a seizure.

Anaesthesia for epilepsy surgery

Patients with epilepsy refractory to AEDs may be suitable for surgery to remove the epileptogenic foci. These patients can present to the anaesthetist in two situations: for the implantation of intracranial electrodes and for the resection of the epileptic focus. Electrode implantation surgery is commonly performed

Table 4 Cause of postoperative seizure-type episodes

Epileptic seizure
Underlying epilepsy
Post-neurosurgery
Eclampsia
Metabolic disturbance
Alcohol withdrawal
Postoperative shivering
Acute dystonic drug reaction
Dopamine antagonists
Psychogenic non-epileptic seizure
Syncopal episode

under general anaesthesia with propofol or low levels of inhaled agent. It is generally recommended that benzodiazepines be avoided to prevent abolition of interictal epileptiform activity. Intraoperative pharmacoactivation (to encourage seizure activity under anaesthesia with the aim of identifying the seizure focus) may occasionally precipitate generalized seizures, which are effectively managed by the application of cold saline to the exposed part of the brain, small doses of propofol (10–30 mg) or anticonvulsant drugs, or both. The patients subsequently undergo telemetry monitoring in the postoperative period in order to localize the focus of epileptiform activity before a planned craniotomy and resection of the appropriate brain area. Patients presenting for the surgical resection of the foci often have had accurate presurgical localization using a multitude of investigations [including CT, MRI, single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetoencephalography (MEG)] and may also have intracortical/subdural electrodes *in situ*. Surgery in such situations is facilitated by either general anaesthesia or local anaesthesia ('awake craniotomy') if indicated. The latter technique may be preferable when the epileptogenic zone is anatomically close to eloquent areas of the brain, as it allows cognitive testing to identify critical functional regions of the brain.

The detailed perioperative management for these procedures is beyond the scope of this article and the reader is referred to recent comprehensive reviews on this topic.[15,16]

Status epilepticus

Convulsive status epilepticus

Convulsive status epilepticus (CSE) is a common medical emergency and is conventionally defined as >30 min of continuous seizure activity or sequential seizures without full recovery of consciousness between seizures. However, it is recognized that after 5 min of continuous seizure activity, spontaneous resolution is unlikely to occur, so treatment is advised to start at this time point. Emergency pharmacological management of CSE is summarized in Figure 2. Of note is the addition of ketamine to the management options for refractory CSE. Ketamine has recently been shown to be effective for refractory CSE in a case series of patients where other i.v. anaesthetics had not terminated CSE and should be considered as a second-line option.[17]

The management of CSE should include resuscitative measures such as airway management, supplemental oxygen, and establishing large-bore i.v. access in addition to cardiorespiratory assessment, arranging emergency investigations, identification of and treatment of underlying aetiology, and arranging intensive care admission in established/refractory cases. Emergency investigations include arterial blood gases and venous blood sampling for glucose, calcium, and magnesium levels; renal and liver functions; a full blood count, clotting screen, AED level assay, and toxicology screen. Other investigations including microbiology, lumbar puncture, and brain imaging will depend on the presentation and likely aetiology. The EEG is useful to monitor seizure activity in the anaesthetized and paralysed patient. A neurologist opinion should be sought if non-epileptic seizures are suspected.

Complications of refractory CSE include excitotoxic CNS injury, hyperthermia, pulmonary oedema, arrhythmias, cardiovascular collapse, metabolic derangement, acute kidney and liver injury, rhabdomyolysis, and fractures. Refractory CSE has a high-mortality rate and less than one-third of patients will return to their premorbid level of functioning.[14]

Non-convulsive status epilepticus

Non-convulsive status epilepticus (NCSE) refers to the finding of EEG evidence of uncontrolled seizures but without clinically

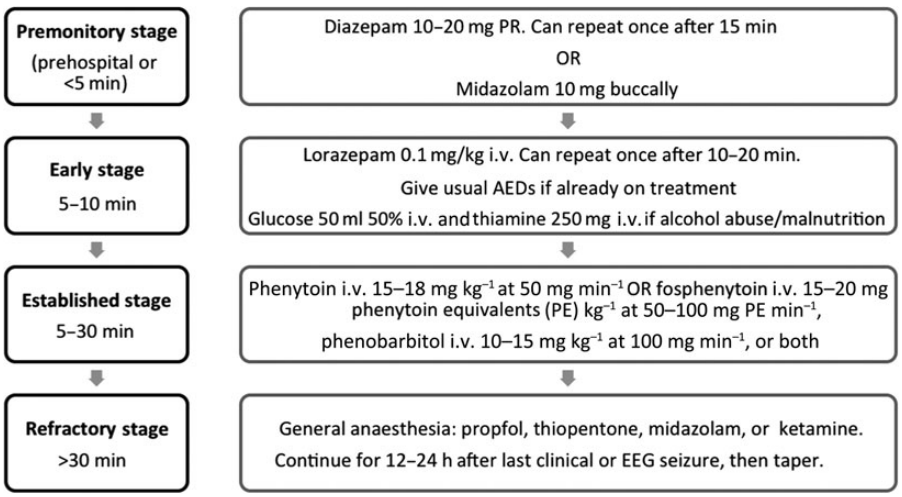

Fig 2 Pharmacological management of the stages of CSE. Administer phenytoin via a large-bore peripheral cannula or central line as the highly alkaline solution produces tissue necrosis if extravasated.

apparent tonic–clonic convulsions. This may occur with uncontrolled absence or complex partial seizures or in the intensive care setting in unconscious patients. The underlying aetiology in intensive care is either advanced CSE or an underlying neurological condition such as encephalitis, traumatic brain injury, or post-cardiac arrest. The EEG is often difficult to interpret in these patients and a neurology/neurophysiology opinion should be obtained to aid diagnosis. I.V. AEDs, anaesthetic agents, or both should be titrated to seizure suppression on the EEG. The NCSE indicates a poor prognosis for the underlying neurological condition.

Summary

Epilepsy is a common neurological condition that anaesthetists will frequently encounter in both the elective and emergency setting. Understanding the pathophysiology of epilepsy and its pharmacological therapies enables safe planning and delivery of care. Specific aims during routine anaesthetic care include minimizing disturbance of AED regimes and avoiding drugs that interact with AEDs or alter the seizure threshold. This reduces the chance of patients having seizures in the perioperative period. Prolonged non-resolving seizure activity is termed status epilepticus and is a medical emergency with significant associated morbidity and mortality. Prompt resuscitation, pharmacological management, and critical care support can maximize the chances of a good recovery for the patient.

Declaration of interest

None declared.

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