

## Treatment of tonic-clonic status epilepticus

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Tonic-clonic status epilepticus can be defined as a condition in which prolonged or recurrent tonic-clonic seizures persist for 30 minutes or more. Most tonic-clonic seizures last less than two minutes; nevertheless many seizures that continue for less than 30 minutes self-terminate. Treatment of the premonitory stages is likely to be more successful than treatment in the later stages and so treatment should commence as soon it is apparent that the seizure is persisting (a tonic-clonic seizure of more than five minutes' duration) or there is a significant worsening of a patient's normal seizure pattern.

From indirect studies, the annual incidence of tonic-clonic status epilepticus has been estimated to be approximately 18–28 cases per 100,000 persons (9000–14,000 new cases each year in the United Kingdom, or 45,000–70,000 cases in the United States), and these estimates have been largely confirmed in population-based studies. Tonic-clonic status epilepticus is most frequent in children, the mentally handicapped, and in those with structural cerebral pathology (especially in the frontal areas). In established epilepsy, status epilepticus can be precipitated by drug withdrawal, intercurrent illness or metabolic disturbance, or the progression of the underlying disease, and is commoner in symptomatic than in idiopathic epilepsy. About 5% of all adult clinic patients with epilepsy will have at least one episode of status epilepticus in the course of their epilepsy, and in children the proportion is higher (10–25%). Status epilepticus accounts for about 3.5% of admissions to neurological intensive care, and 0.13% of all visits to a university hospital casualty department. The mortality of status epilepticus is about 20%, most patients dying of the underlying condition rather than the status epilepticus itself or its treatment. Permanent neurological and mental deterioration may result from status epilepticus, particularly in young children; the risks of morbidity are greatly increased the longer the duration of the status epilepticus episode.

### General measures

For the new patient presenting as an emergency in status epilepticus, it is helpful to plan therapy in a series of progressive phases (Table I).

#### *1st stage (0–10 minutes)*

*Oxygen and cardiorespiratory resuscitation.* It is first essential to assess cardiorespiratory function, to secure the airway, and to resuscitate where necessary. Oxygen should always be administered, as hypoxia is often severe.

**Table I.** General measures for the patient presenting with tonic-clonic status epilepticus.

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*1st stage (0–10 minutes)*

- Assess cardiorespiratory function
- Secure airway and resuscitate
- Administer oxygen

*2nd stage (0–60 minutes)*

- Institute regular monitoring (see text)
- Emergency AED therapy (see text)
- Set up intravenous lines
- Emergency investigations (see text)
- Administer glucose (50 ml of 50% solution) and/or intravenous thiamine (250 mg) as high potency intravenous Pabrinex where appropriate
- Treat acidosis if severe

*3rd stage (0–60/90 minutes)*

- Establish aetiology
- Identify and treat medical complications
- Pressor therapy when appropriate

*4th stage (30–90 minutes)*

- Transfer to intensive care
- Establish intensive care and EEG monitoring (see text)
- Initiate intracranial pressure monitoring where appropriate
- Initiate long-term, maintenance, antiepileptic therapy

These four stages should be followed chronologically; the 1st and 2nd within 10 minutes, and stage 4 (transfer to intensive care unit) in most settings within 60–90 minutes of presentation.

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*2nd stage (0–60 minutes)*

*Monitoring.* Regular neurological observations and measurements of pulse, blood pressure, ECG, and temperature should be initiated. Metabolic abnormalities may cause status epilepticus, or develop during its course, and biochemical, blood gas, pH, clotting, and haematological measures should be monitored.

*Emergency anticonvulsant therapy* should be started.

*Intravenous lines* should be set up for fluid replacement and drug administration (preferably with 0.9% sodium chloride (normal or physiological saline) rather than 5% glucose solutions). Drugs should not be mixed and, if two antiepileptic drugs (AEDs) are needed (for example, phenytoin and diazepam), two intravenous lines should be sited. The lines should be in large veins, as many AEDs cause phlebitis and thrombosis at the site of infusion. Arterial lines must *never* be used for drug administration.

*Emergency investigations.* Blood should be drawn for the emergency measurement of blood gases, sugar, renal and liver function, calcium and magnesium levels, full haematological

screen (including platelets), blood clotting measures, and anticonvulsant levels; 50 ml of serum should also be saved for future analysis especially if the cause of the status epilepticus is uncertain. Other investigations depend on the clinical circumstances.

*Intravenous glucose and thiamine.* If hypoglycaemia is suspected, 50 ml of a 50% glucose solution should be given immediately by intravenous injection. If there is a history of alcoholism, or other compromised nutritional states, 250 mg of thiamine (for example, as the high potency intravenous formulation of Pabrinex, 10 ml of which contains 250 mg) should also be given intravenously. This is particularly important if glucose has been administered, as a glucose infusion increases the risk of Wernicke's encephalopathy in susceptible patients. Intravenous high-dose thiamine should be given slowly (for example, 10 ml of high potency Pabrinex over ten minutes), with facilities for treating anaphylaxis. Routine glucose administration in non-hypoglycaemic patients should be avoided as there is some evidence that this can aggravate neuronal damage.

*Acidosis.* If acidosis is severe, the administration of bicarbonate has been advocated in the hope of preventing shock, and mitigating the effects of hypotension and low cerebral bloodflow. In most cases, however, this is unnecessary and more effective is the rapid control of respiration and abolition of motor seizure activity.

#### *3rd stage (0–60/90 minutes)*

*Establish aetiology.* The range of causes of status epilepticus depends primarily on age and the presence or absence of established epilepsy. The investigations required depend on clinical circumstances; CT or MRI and CSF examination are often required. The latter should be carried out only with facilities for resuscitation available as intracranial pressure is often elevated in status epilepticus. If the status epilepticus has been precipitated by drug withdrawal, the immediate restitution of the withdrawn drug will usually rapidly terminate the status epilepticus.

*Physiological changes and medical complications.* The physiological changes of uncompensated status epilepticus may require specific therapy. Active treatment is most commonly required for: hypoxia, hypotension, raised intracranial pressure, pulmonary oedema and hypertension, cardiac arrhythmias, cardiac failure, lactic acidosis, hyperpyrexia, hypoglycaemia, electrolyte disturbance, acute hepatic or renal failure, rhabdomyolysis, or disseminated intravascular coagulation.

*Pressor therapy.* Failure to correct hypotension can lead to significant cerebral ischaemia and so blood pressure should be maintained by correcting hypovolaemia and if necessary through the use of pressor agents such as adrenaline, noradrenaline and dobutamine. These agents are almost invariably required in patients sedated with barbiturate anaesthesia.

#### *4th stage (30–90 minutes)*

*Intensive care.* If seizures are continuing in spite of the measures taken above, the patient must be transferred to an intensive care environment.

*Intensive care monitoring.* In severe established status epilepticus, intensive monitoring may be required, including: intra-arterial blood pressure, capnography, oximetry, central venous and pulmonary artery pressure monitoring.

*Magnesium.* Although effective in preventing eclampsia, there is no evidence to suggest that increasing magnesium serum concentrations to supranormal levels has any benefit in status epilepticus. Indeed, such a policy can result in motor paralysis, difficulty in detecting

clinical seizure activity and hypotension. However, serum magnesium can be low in alcoholics and patients on medication for HIV, and in these patients intravenous loading with 2–4 g of magnesium sulphate over 20 minutes may help with seizure control and prevention of arrhythmias.

*Seizure and EEG monitoring.* In prolonged status epilepticus, or in comatose ventilated patients, motor activity can be barely visible. In this situation, continuous EEG monitoring using a full EEG or a cerebral function monitor is necessary, and at the very least intermittent daily EEGs should be recorded. The latter must be calibrated individually to register both burst-suppression and seizure activity. Burst-suppression provides an arbitrary physiological target for the titration of barbiturate or anaesthetic therapy. Drug dosing is commonly set at a level that will produce burst-suppression with interburst intervals of between 2 and 30 seconds.

*Intracranial pressure monitoring and cerebral oedema.* Continuous intracranial pressure monitoring is sometimes needed, especially in children in the presence of persisting, severe, or progressive elevated intracranial pressure. The need for active therapy is usually determined by the underlying cause rather than the status epilepticus. Intermittent positive pressure ventilation, high-dose corticosteroid therapy (4 mg dexamethasone every six hours), or mannitol infusion may be used (the latter is usually reserved for temporary respite for patients in danger of tentorial coning). Neurosurgical decompression is occasionally required.

*Long-term anticonvulsant therapy.* Long-term, maintenance, anticonvulsant therapy must be given in tandem with emergency treatment. The choice of drug depends on previous therapy, the type of epilepsy, and the clinical setting. If phenytoin or phenobarbitone has been used in emergency treatment, maintenance doses can be continued orally (through a nasogastric tube) guided by serum level monitoring. Other maintenance AEDs can be started also, giving oral loading doses. Care needs to be taken with nasogastric feeds, which can interfere with the absorption of some AEDs (especially phenytoin).

### **Treatment of tonic-clonic status epilepticus**

Tonic-clonic status epilepticus is treated as an emergency in order to avoid both systemic complications and also cerebral damage. Cerebral damage is partly caused by physiological compromise and the consequent hypoxia/ischaemia, but it also results from excitotoxicity consequent upon continuous seizure activity. In the initial stages of a tonic-clonic seizure, there are compensatory mechanisms that result in increased cerebral perfusion. By 60–90 minutes these compensatory mechanisms fail; there is hypotension and, importantly, loss of cerebral autoregulation. This results in cerebral hypoperfusion and cerebral damage. In addition, at this stage, the continuous seizure activity results in intraneuronal calcium accumulation and neuronal death. Thus, treatment regimens should be staged. These stages are: the premonitory (pre-hospital) stage, the early status epilepticus stage from 0–30 minutes, the stage of established status epilepticus from 30–60/90 minutes and then the refractory (late) stage during which substantial neuronal damage can occur.

### **Stages in emergency drug treatment**

The suggested regimen for a typical new case presenting to a casualty department as an emergency is given in Table II. These are guidelines, and obviously in some circumstances intensive care management and general anaesthesia may be required earlier.

*Premonitory stage*

In patients with established epilepsy, tonic-clonic status epilepticus seldom develops without warning. Usually, a prodromal phase (the premonitory stage), during which seizures become increasingly frequent or severe, precedes status epilepticus. Urgent drug treatment will usually prevent the evolution into true status epilepticus. If regular AED treatment has been reduced or stopped by patient or doctor, this should be reinstated. Rectal diazepam has generally been the drug of choice. A dose of 0.5–1 mg/kg rectal diazepam solution results in therapeutic serum concentrations within one hour, and has been shown to be very effective in arresting acute seizures with minimal side effects.

A possible disadvantage of rectal diazepam is difficulty with and concern about the route of administration, especially in children so alternatives have been sought. Midazolam has the advantage over other benzodiazepines in that it can be administered by intranasal, buccal and intramuscular routes. Of these, buccal midazolam (10 mg in 2 ml) seems to be the most promising, showing superiority to rectal diazepam in a trial in children.

**Table II.** Suggested emergency antiepileptic drug regimen for status in newly presenting adult patients.

<i>Premonitory stage (pre-hospital)</i>	Diazepam 10–20 mg given rectally, repeated once 15 minutes later if status continues to threaten, or midazolam 10 mg given buccally  <i>If seizures continue, treat as below</i>
<i>Early status</i>	Lorazepam (i.v.) 0.07 mg/kg (usually a 4 mg bolus, repeated once after 10–20 minutes; rate not critical)  <i>If seizures continue 30 minutes after first injection, treat as below</i>
<i>Established status</i>	Phenytoin infusion at a dose of 15–18 mg/kg at a rate of 50 mg/minute <b>or</b> fosphenytoin infusion at a dose of 15–20 mg PE/kg at a rate of 150 mg PE/minute  <b>and/or</b>  Phenobarbitone bolus of 10 mg/kg at a rate of 100 mg/minute (usually 700 mg over seven minutes in an adult)
<i>Refractory status</i>	General anaesthesia, with either propofol, midazolam or thiopentone. Anaesthetic continued for 12–24 hours after the last clinical or electrographic seizure, then dose tapered

In the above scheme, the refractory stage (general anaesthesia) is reached 60/90 minutes after the initial therapy. This scheme is suitable for usual clinical hospital settings. In some situations, general anaesthesia should be initiated earlier and, occasionally, should be delayed.

The earlier treatment is given the better. It is easier to prevent the evolution of epilepsy to status epilepticus than to treat the established condition. If the patient is at home, AEDs should be administered before transfer to hospital, or in the casualty department before transfer to the ward. The acute administration of either diazepam or midazolam will cause drowsiness or sleep, and rarely cardiorespiratory collapse, and patients should be carefully supervised.

#### *Early status epilepticus (0–30 minutes)*

Once status epilepticus has developed, treatment should be carried out in hospital, under close supervision. For the first 30–60 minutes or so of continuous seizures, physiological mechanisms compensate for the greatly enhanced metabolic activity. This is the stage of *early status epilepticus*, and it is usual to administer a fast-acting benzodiazepine.

In most clinical settings, intravenous *lorazepam* (0.07 mg/kg to a maximum of 4 mg) is the drug of choice, and this dose can be repeated once if seizure activity does not stop. Other benzodiazepines such as diazepam, clonazepam and midazolam are alternatives but, due to its more prolonged action, lorazepam should be preferred. In most patients, therapy will be highly effective. Continuous 24-hour inpatient observation should follow. In previously non-epileptic patients, long-term AED therapy should be considered, and in those already on maintenance antiepileptic therapy, this should be reviewed.

#### *Established status epilepticus (30–60/90 minutes)*

This can be operationally defined as status epilepticus which has continued for 30 minutes in spite of early-stage treatment. The time period is chosen because physiological decompensation will usually have begun. Intensive care facilities are desirable. There are three alternative treatment options. These are subanaesthetic doses of phenobarbitone (10 mg/kg), phenytoin (15–20 mg/kg) or fosphenytoin (a phenytoin pro-drug); all are given by intravenous loading followed by repeated oral or intravenous supplementation.

Numerous alternative treatment options exist. Although once popular, continuous benzodiazepine and chlormethiazole infusions on the ward are hazardous and not now recommended. There have been promising studies of the use of intravenous sodium valproate at this stage at high doses (20–40 mg/kg); experience of sodium valproate in status epilepticus remains limited, but in future it may prove to be an alternative to phenytoin as it may have fewer adverse cardiac effects.

#### *Refractory status epilepticus (after 60/90 minutes)*

If seizures continue for 60–90 minutes after the initiation of therapy, the stage of refractory status epilepticus is reached and full anaesthesia required. In many emergency situations (for example, post-operative status epilepticus, severe or complicated convulsive status epilepticus, patients already in intensive care), anaesthesia can and should be introduced earlier. Prognosis will now be much poorer, and there is a very high mortality and morbidity.

Anaesthesia can be induced by barbiturate or non-barbiturate drugs. A number of anaesthetics have been administered, although few have been subjected to formal evaluation and all have drawbacks. The most commonly used anaesthetics are the intravenous barbiturate *thiopentone*, the intravenous non-barbiturate *propofol* or continuous *midazolam* infusion. A non-randomised comparison of propofol and thiopentone was unable to detect any clinically significant differences between the drugs. Other drugs in current use include the intravenous anaesthetic pentobarbitone (not available in the UK).

At this stage, the use of immunosuppression with steroids and even intravenous immunoglobulin/plasma exchange should be considered, as there is growing evidence for

the role of autoantibodies (especially against NMDA receptors) in the aetiology of refractory status epilepticus.

Patients require the full range of intensive care facilities, including EEG monitoring, and care should be shared between anaesthetist and neurologist. Experience with long-term administration (hours or days) of the newer anaesthetic drugs is very limited. The modern anaesthetics have, however, important pharmacokinetic advantages over the more traditional barbiturates.

Once the patient has been free of seizures for 12–24 hours and provided that there are adequate plasma levels of concomitant antiepileptic medication, then the anaesthetic should be slowly tapered.

### **Antiepileptic drugs**

#### *Diazepam*

Diazepam is highly effective in a range of seizure types. Its pharmacology and clinical effects have been extensively studied in adults, children, and the newborn, and it has been shown to be highly effective in a wide range of status epilepticus types. Diazepam can be given by intravenous bolus injections or by the rectal route in the premonitory stage, and has a rapid onset of action. Sufficient cerebral levels are reached within one minute of a standard intravenous injection, and rectal administration produces peak levels at about 20 minutes. Diazepam is rapidly redistributed after acute administration, and thus has a relatively short duration of action. After repeated dosing, diazepam accumulates, resulting in higher peak levels, which persist. This can result in sudden and unexpected CNS depression and cardiorespiratory collapse. Diazepam is metabolised by hepatic microsomal enzymes. Respiratory depression, hypotension, and sedation are the principal side effects. Sudden apnoea can occur, especially after repeated injections or if the injection is administered at too fast a rate.

Bolus intravenous doses of diazepam should be given in an undiluted form at a rate not exceeding 2–5 mg/minute, using the *Diazemuls* formulation. Diazepam may be given rectally, either in its intravenous preparation infused from a syringe via a plastic catheter, or as the ready-made, proprietary, rectal tube preparation *Stesolid*, which is a convenient and easy method. Diazepam suppositories should not be used, as absorption is too slow. The adult bolus intravenous or rectal dose in status epilepticus is 10–20 mg, and additional 10 mg doses can be given at 15 minute intervals, to a maximum of 40 mg. In children, the equivalent bolus dose is 0.2–0.3 mg/kg. A continuous infusion of benzodiazepine has also been used, but there is now little place for this mode of administration. The solution should be freshly prepared, and no drugs should be admixed.

The usual intravenous formulation is as an emulsion (*Diazemuls*) in a 1 ml ampoule containing 5 mg/ml or as a solution in 2 ml ampoules containing 5 mg/ml. *Stesolid* is the usual rectal formulation consisting of a 2.5 ml rectal tube containing 5 mg or 10 mg diazepam. The intravenous solution can also be instilled rectally.

#### *Midazolam*

Midazolam has the advantage over other benzodiazepines in that it is water soluble at a suitable pH; at physiological pH it becomes highly lipophilic permitting rapid transfer across the blood-brain barrier. This has resulted in the possibility of using midazolam by three other routes: intranasal, buccal and intramuscular. Recently midazolam (10 mg in 2 ml) squirted around the buccal mucosa was more effective than rectal diazepam (10 mg) in acute seizures in children, and was easier to administer. By this route, the maximum concentration is reached by 30 minutes (although the pharmacodynamic response may be

quicker), and the bioavailability is 75%. Intranasal midazolam has also been used successfully; a dose of 0.2 mg/kg intranasally results in a maximum serum concentration in 12 minutes with a bioavailability of 55%. Bioavailability after intramuscular injection is about 80–100%, and peak levels are reached after about 25 minutes although there is marked individual variation.

Midazolam has very short distribution and elimination half-lives. Its action is thus short-lived, and there is a strong tendency to relapse following a single bolus injection. Its kinetic characteristics and its smaller volume of distribution make it the benzodiazepine of choice for use as an infusion, as it has less propensity to accumulate. In the intensive care setting, midazolam can have a greater half-life and volume of distribution due to hepatic impairment. Midazolam exhibits the same toxic effects as other benzodiazepines, including sedation, hypotension, and cardiorespiratory depression. Respiratory arrest may occur occasionally, even after intramuscular injection, so careful monitoring is imperative.

Midazolam is given in premonitory status epilepticus intramuscularly, rectally, buccally or intranasally at a dose of 5–10 mg (in children 0.15–0.3 mg/kg), which can be repeated once after 15 minutes or so. As an intravenous infusion on the intensive care unit, it should be given as a loading dose of approximately 0.15 mg/kg followed by an infusion of 0.05–0.4 mg/kg/h. Midazolam is available in 5 ml ampoules containing 2 mg/ml or 2 ml ampoules containing 5 mg/ml.

#### *Lorazepam*

Lorazepam has a lesser volume of distribution and is less lipid soluble than diazepam. Its pharmacokinetic characteristics result in a slower onset of action, but a longer duration of action. Lorazepam is indicated in the early stage of status epilepticus only, where its lack of accumulation in lipid stores, strong cerebral binding, and long duration of action due to its distribution half-life are very significant advantages over diazepam. The pharmacology and clinical effects of lorazepam have been well characterised in adults, children, and the newborn, and the drug has been the subject of large-scale clinical trials. Lorazepam is remarkably effective in controlling seizures in the early stage of status epilepticus. Its main disadvantage is the rapid development of tolerance. Initial injections of lorazepam are effective for about 12 hours (longer than with diazepam), but repeated doses are much less effective, and the drug has no place as long-term therapy. Lorazepam has sedative effects shared by all the benzodiazepine drugs used in status epilepticus, but sudden hypotension or respiratory collapse is less likely because of its relative lipid insolubility and the lack of accumulation after single bolus injections.

Lorazepam is administered by intravenous bolus injection. As distribution is slow, the rate of injection is not critical. In adults, a bolus dose of 0.07 mg/kg (to a maximum of 4 mg) is given, and this can be repeated once after 20 minutes if no effect has been observed. In children under ten years, bolus doses of 0.1 mg/kg are recommended. Long-term infusion of lorazepam should not be used. It is usually available as a 1 ml ampoule containing 4 mg of lorazepam.

#### *Phenytoin*

Phenytoin is a drug of first choice in established status epilepticus. Its pharmacology and clinical effects are well documented, and there is extensive experience in status epilepticus in adults, children, and the new-born. It is a highly effective anticonvulsant, with the particular advantage of a long duration of action. It can also be continued as chronic therapy. Phenytoin causes relatively little respiratory or cerebral depression, although hypotension is more common. The initial infusion of phenytoin takes 20–30 minutes in an adult, and the onset of action is slow. It is therefore often administered in conjunction with a short-acting drug with a rapid onset of action, such as diazepam. The notorious saturable

pharmacokinetics of phenytoin cause fewer problems in the emergency setting than in chronic therapy, but careful monitoring of serum levels is essential. The usual phenytoin solutions have a pH of 12 and, if added to bags containing large volumes of fluid at lower than physiological pH (for example, 5% glucose), precipitation may occur in the bag or tubing; use in a solution of 0.9% sodium chloride (normal saline) (5–20 mg/ml) is safer. There is also a serious risk of precipitation if other drugs are added to the infusion solution. Administration via a side arm, or directly using an infusion pump, is preferable. Due to the high pH, phenytoin can cause thrombophlebitis (particularly with extravasation), and it is poorly and erratically absorbed after intramuscular injection. Also, its vehicle, propylene glycol, can cause hypotension.

The rate of infusion of phenytoin solution should not exceed 50 mg/minute, and it is prudent to reduce this to 20–30 mg/minute in the elderly. The adult dose is 15–20 mg/kg; this usually amounts to about 1000 mg and therefore takes at least 20 minutes to administer. Regrettably, a common and potentially serious mistake is to give a lower dose which results in suboptimal cerebral levels. Phenytoin therapy can be continued after intravenous loading by oral or further intravenous daily dosages of 5–6 mg/kg, guided by blood level measurements. For older children, the dose of phenytoin is the same as for adults. For the newborn a dose of 15–20 mg/kg, injected at a rate not exceeding 1 mg/kg per minute, should be given. Phenytoin is usually available as 5 ml ampoules containing phenytoin sodium 250 mg.

#### *Fosphenytoin*

In order to overcome the problems associated with physiochemical properties of phenytoin, fosphenytoin (3-phosphoryloxymethyl phenytoin disodium), a water-soluble phenytoin pro-drug, was developed. Fosphenytoin is inactive, but is metabolised to phenytoin with a half-life of 8–15 minutes. It is supplied in a ready-mixed solution. The equimolar equivalent of 1 mg of phenytoin is 1.5 mg of fosphenytoin, and the drug is supplied in a ready mixed solution of 50 mg phenytoin equivalents (PE) per ml (i.e. 75 mg/ml). This is to standardise the solution to that of parenteral phenytoin. Fosphenytoin should be given intravenously at 150 mg/minute to achieve a similar serum concentration time profile to that obtained with intravenous phenytoin in status epilepticus. Although fosphenytoin is more expensive than phenytoin, these costs may be balanced by less phlebitis, less hypotension, ease of administration and greater tolerability. Since it is water soluble, it can also be given as an intramuscular injection, although experience of this route in status epilepticus is very limited and therefore not advised. ECG monitoring is mandatory during intravenous administration of both phenytoin and fosphenytoin.

#### *Phenobarbitone*

Phenobarbitone is a drug of choice for the treatment of established status epilepticus. It is highly effective, has a rapid onset of action, and prolonged anticonvulsant effects. It has stable and non-reactive physical properties, as well as convenient pharmacokinetics. Wide experience has been gained of its use in adults and in children, and few drugs are as well tried in the newborn. It has stronger anticonvulsant properties than most other barbiturates, and may be preferentially concentrated in metabolically active epileptic foci. As well as excellent anticonvulsant properties, it may also have cerebral-protective action. Acute tolerance to the antiepileptic effect is unusual, in contrast to the benzodiazepines and, once controlled, seizures do not tend to recur. Indeed, there is evidence to suggest that given with barbiturate anaesthesia, it can reduce the relapse rate with anaesthetic withdrawal.

The main disadvantages of phenobarbitone are its potential to cause sedation, respiratory depression, and hypotension; although in practice these effects seem slight except at high levels or with rapidly rising levels, its safety at even high doses is well established. The well-known chronic side effects of phenobarbitone in long-term therapy are of little

relevance in the emergency situation of status epilepticus. The drug is eliminated slowly and, although this is of no importance on initial phenobarbitone loading, on prolonged therapy there is a danger of accumulation and blood level monitoring is essential. In the newborn period dosing is more difficult than in adults, as the pharmacokinetics change rapidly during the first weeks and months of life. The drug has a strong tendency to autoinduction. Phenobarbitone is a stable preparation, which does not easily decompose, and the drug is not absorbed by plastic. It should not be used in a solution containing other drugs (for example, phenytoin), as this may result in precipitation.

The usual recommended adult intravenous loading dose of phenobarbitone is 10 mg/kg (doses of up to 20 mg/kg have been used and recommended), given at a rate of 100 mg/minute (i.e. a total of about 700 mg in seven minutes). This should be followed by daily maintenance doses of 1–4 mg/kg. In neonates, initial phenobarbitone loading doses of between 12 and 20 mg/kg have been recommended to produce therapeutic levels, with subsequent supplementation of 3–4 mg/kg per day, to a maximum dose of 40 mg/kg. In older children, loading doses of between 5 and 20 mg/kg are recommended and maintenance doses of 1–4 mg/kg, although much higher doses have been safely given. After loading, maintenance doses can be given by the oral, intravenous, or intramuscular route. Phenobarbitone is usually presented in 1 ml ampoules containing 200 mg of phenobarbitone sodium.

#### *Valproate*

There is a long history of the anecdotal use of intravenous valproate in status epilepticus. Only recently have randomised trials demonstrated potential as a treatment in status epilepticus, although these trials are inconclusive and used inferior or inappropriate comparators. The possible advantages of valproate are a low incidence of respiratory and cardiac depression, but other potential side effects such as prolonged bleeding time, hepatic dysfunction, pancreatitis and hyperammonaemia have not been adequately assessed in large studies, and valproate should be avoided in patients with hepatic or mitochondrial disease. Valproate is available as an intravenous solution (100 mg/ml) and can be given by infusion at a dose of 20–30 mg/kg over about 15 minutes.

#### *Thiopentone*

Thiopentone is the compound traditionally used for barbiturate anaesthesia in status epilepticus, at least in Europe. It is an effective AED, and may have additional cerebral-protective effects. In the doses used in status epilepticus it has an anaesthetic action, and all patients require intubation and most artificial ventilation. The most troublesome side effect is persistent hypotension and many patients require pressor therapy. Thiopentone has saturable pharmacokinetics and a strong tendency to accumulate. Thus if large doses are given, blood levels may remain very high for protracted periods, and days may pass before consciousness is recovered after drug administration is discontinued. Blood level monitoring, both of the thiopentone and its active metabolite pentobarbitone, is therefore essential on prolonged therapy. Other toxic effects on prolonged therapy include pancreatitis and hepatic disturbance, and thiopentone may cause acute hypersensitivity. It should be administered cautiously in the elderly, and in those with cardiac, hepatic, or renal disease.

Although it has been in use since the 1960s in status epilepticus, formal clinical trials of its safety and effectiveness in either adults and children are few. A full range of intensive care facilities is required during thiopentone infusions. Central venous pressure should be monitored, and blood pressure monitored via an arterial line. Pulmonary artery pressure monitoring is sometimes advisable, and EEG or cerebral function monitoring is essential if thiopentone infusions are prolonged. A concomitant dopamine infusion is frequently needed to maintain blood pressure. Thiopentone can react with polyvinyl infusion bags or giving

sets. The continuous infusion should be made up in 0.9% sodium chloride (normal saline). The intravenous solution has a pH of 10.2–11.2, is incompatible with a large number of acidic or oxidising substances, and no drugs should be added. The aqueous solution is unstable if exposed to air.

The regimen commonly used is as follows: thiopentone is given as a 100–250 mg bolus over 20 seconds, with further 50 mg boluses every 2–3 minutes until seizures are controlled, with intubation and artificial ventilation. The intravenous infusion is then continued at the minimum dose required to control clinical and electrographic seizure activity, usually between 3 and 5 mg/kg per hour, and at thiopentone blood levels of about 40 mg/L. After 24 hours, the dose should be controlled by blood level monitoring. At this point, metabolism may be near saturation, and daily or twice daily blood level estimations should be made to ensure that levels do not rise excessively. The dose should be lowered if systolic blood pressure falls below 90 mmHg, or if vital functions are impaired. There is some evidence to suggest that barbiturate anaesthesia is more successful in those who have been loaded with phenobarbitone. Thiopentone should be continued for no less than 12 hours after seizure activity has ceased, and then slowly discontinued. The usual preparation is as a 2.5 g vial with 100 ml of diluent to produce a 2.5% solution.

### *Propofol*

In recent times, there has been a vogue for the use of non-barbiturate anaesthesia in status epilepticus; of the currently available compounds, propofol is probably the drug of choice. There is limited, but growing, published experience of its use in status epilepticus and as a long-term infusion. Propofol is a highly effective and non-toxic anaesthetic. In experimental models, it has anticonvulsant activity, probably via its action in potentiating GABA receptors. Propofol also has neuroexcitatory effects possibly through subcortical disinhibition resulting in muscle rigidity, opisthotonos, abnormal movements including myoclonus; these can be and have been mistaken for seizures. Seizures have, however, been reported with propofol withdrawal, and experimental evidence suggests that this is a rebound phenomenon similar to the GABA withdrawal syndrome.

Propofol has also been reported at low doses to activate the electrocorticogram, but this is a property that it shares with other anaesthetics including the barbiturates. Propofol is extremely soluble in lipid and has a high volume of distribution. It thus acts extremely rapidly in status epilepticus. Its effects are maintained while the infusion is continued, and recovery following discontinuation of the drug is also very quick. Propofol administration causes profound respiratory and cerebral depression, requiring the use of assisted respiration, the full panoply of intensive care and monitoring, but only mild hypotension, and has few cardiovascular side effects. Long-term administration (or high doses, > 5 mg/kg/h, over 48 hours) causes marked lipaemia and may result in acidosis, cardiac arrhythmias and rhabdomyolysis (propofol infusion syndrome) which can be fatal. This is especially so in young children in whom it should not generally be recommended.

In status epilepticus, the following regimen can be used: initially a 1–2 mg/kg bolus dose is given, which can be repeated if seizures continue, succeeded by an infusion of 1–15 mg/kg per hour guided by EEG. The dose should be gradually reduced, and the infusion tapered 12 hours after seizure activity is halted. Due to the risk of rebound seizures, the dose should be tapered at a rate of 5% of the maintenance infusion per hour (i.e. over approximately 24 hours). In the elderly, doses should be lower. It is available as 20 ml ampoules containing 10 mg/ml as an emulsion.

**Further reading**

LOWENSTEIN DH and ALLDREDGE BK (1998) Status epilepticus. *N Engl J Med* 338, 970-976.

SHORVON SD (1994) *Status Epilepticus: Its Clinical Features and Treatment in Children and Adults*. Cambridge University Press, Cambridge.

WALKER MC and SHORVON SD (2009) Emergency Treatment of Seizures and Status Epilepticus. In: *Treatment of Epilepsy*, 3<sup>rd</sup> Edition (Eds SD Shorvon et al). Wiley-Blackwell, Oxford.