Management of Status Epilepticus

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ABSTRACT

Objective: *To review the aetiology and treatment of status epilepticus and present a practical approach to its management.*

Data sources: *A review of studies reported from 1966 to 1998 and identified through a MEDLINE search of the English-language literature on metabolic and toxic seizures and status epilepticus.*

Summary of review: *Status epilepticus describes a condition of prolonged or repetitive seizures and is refractory if it lasts longer than 20-30 minutes despite therapy. It may cause primary cerebral injury due to prolonged uncontrolled neuronal discharge or secondary cerebral injury due to hypoxia and hypothermia. To minimise neural damage, resuscitation, correction of metabolic defects and termination of the seizures should be achieved rapidly (i.e. within 10 minutes). Initial treatment includes intravenous lorazepam (2-8 mg/70kg) or diazepam (5-20 mg/70kg) and phenytoin (1500 - 2000 mg/70 kg) which will control seizures in up to 70% of patients.*

If status epilepticus becomes resistant to the initial treatment, the patient should be managed in a monitored environment, as further therapy usually includes agents that may anaesthetise the patient. In an adult patient, 'second-line' drugs include intravenous phenobarbitone (100 -1000 mg), magnesium sulphate (10 - 15 mmol), midazolam (8-20 mg followed by an infusion at 4-30 mg/hour), propofol (50 - 150 mg followed by an infusion at 100 -500 mg/hour), thiopentone (200 - 500 mg followed by an infusion at 100 - 500 mg/hr), lignocaine (100 -150 mg followed by an infusion of 150-200 mg/h), ketamine (50 - 100 mg followed by 50 - 100 mg/h), or isoflurane (0.5 - 1.5%), added singly or in combination. If the patient requires paralysis to reduce the metabolic effects of a prolonged seizure then continuous electroencephalography is required.

Conclusions: *Status epilepticus is a medical emergency requiring urgent termination of seizures and management of the initiating factors. Lorazepam or diazepam and phenytoin are recommended as 'first-line' therapy* (**Critical Care and Resuscitation 1999; 1: 344-353**)

Key Words: Status epilepticus, seizures, pseudoseizures, toxic encephalopathy, antiepileptic therapy

The epilepsies are a group of disorders characterized by an intermittent and abnormal cerebral neural discharge, which usually have one or all of the clinical phases of, aura, tonic, clonic, unconscious, post ictal and sleep. Each episode of neurological dysfunction is known as a seizure, and is convulsive if it is accompanied by tonic and clonic motor movements.

Status epilepticus describes a state of prolonged (i.e. lasting more than 5 minutes) or repetitive, convulsive or nonconvulsive seizures that occur without a period of recovery between attacks. It differs from serial seizures where two or more attacks may occur within a brief period but the patient regains consciousness between the seizures. While status epilepticus has been defined as more than 20-30 minutes of continuous seizure activity,[1] this more correctly defines refractory status epilepticus as it usually reflects failure of treatment.[2]

AETIOLOGY

Seizures may be caused by any of the disorders listed in tables 1 and 2,[3] and while any of these disorders may lead to status epilepticus, in the critically ill adult it is commonly caused by metabolic and toxic causes (Table 2), opiate or alcohol withdrawal, reduction of anti-

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Table 1. Aetiology of seizures

Idiopathic or hereditary disorder
Alcohol or opiate withdrawal
Non-compliance, reduction or cessation of maintenance therapy or subtherapeutic maintenance therapy due to altered pharmacodynamics or kinetics of;
Antiepileptics, barbiturates, benzodiazepines,
Opiates or corticosteroids
Endocrine disorders
Thyrotoxicosis, Addison's disease,
Hyper- and hypoparathyroidism
Electrocution, electroconvulsive therapy
Eclampsia
Fat embolism
Amniotic fluid embolism
Cerebral disorder
Trauma, neoplasm, abscess, infarct
Meningitis
Encephalitis (particularly herpes simplex)
Hypertensive encephalopathy
Embolism
Arterial or venous thrombosis
Subarachnoid haemorrhage
AV malformation
Post procedure
Cerebral angiogram
Myelogram (using hyperosmolar ionic contrast)
Syncope induced
Systemic lupus erythematosis
Thrombotic thrombocytopaenic purpura
Multiple sclerosis
Dementia (Korsokov's psychosis)
Wernicke's encephalopathy,
Alzheimer's disease
Acute disseminated encephalomyelitis
Metabolic and toxic

epileptic medication or cerebral lesions (trauma, tumor, abscess, cerebrovascular accidents).[1,4,5]

The differential diagnosis of epilepsy include pseudoseizures, syncope and transient ischaemic attacks (TIAs).

A pseudoseizure is a simulated seizure and is one of the commonest hysterical conversion syndromes. It is often recurrent and commonly mistaken for resistant status epilepticus (i.e. 'pseudostatus epilepticus').[6,7]

A pseudoseizure is differentiated from a seizure by the features of; 1) atypical movements (e.g. asynchronous thrashing of all limbs, pelvic thrusting, rolling movements rather than a tonic and clonic phase) and, 2) retention of consciousness during a seizure (i.e. presence of a lash reflex during or immediately after a seizure, resistance to eye opening, retained awareness or vocalization, or resistance to dropping of the patient's

Table 2. Metabolic and toxic seizures

Metabolic abnormality
Hypo: -glycaemia, -natraemia, -calcaemia,
-magnesaemia, -phosphataemia
Hyper: -natraemia, -glycaemia, -calcaemia
TURP syndrome
Metabolic or respiratory alkalosis
Uraemia, dialysis disequilibrium
Hepatic failure
Porphyria
Pyridoxine deficiency
Pancreatitis
Febrile convulsion
Septic encephalopathy
Drug overdosage
Aminophylline, caffeine
Local anaesthetics (lignocaine, bupivacaine)
Anticholinergic drugs
Tricyclics, phenothiazines, antihistamines,
Olanzapine, clozapine, rispiridone
procainamide, disopyramide quinidine,
mexilitine, chloroquine, quinine
Pethidine, dextropropoxyphene, fentanyl
Insulin (due to hypoglycaemia)
Serotonin syndrome
Tranylcypromine, phenelzine, baclofen
Mefenamic acid
Carbamazepine, sodium valproate
Beta lactam antibiotics
Quinolone antibiotics (e.g. ciprofloxacin)
Cyclosporine A, tacrolimus, methotrexate, cisplatin
Isoniazid (due to pyridoxine deficiency)
Lithium, clozapine
Poisoning
Sympathomimetic 'designer' drugs
amphetamine, methamphetamine,
para-methoxyamphetamine,
3,4-methylenedioxyamphetamine,
3,4-methylenedioxymethamphetamine ('ecstasy')
cocaine, phencyclidine, lysergic acid diethylamide
Massive beta blocker overdosage
Organophosphates, carbamates
Methanol, ethylene glycol, ethanol
Iron, arsenic, barium, selenium, lead
Nicotine
Margosa oil, cicutoxin, gyromitrin esculenta
Strychnine, cyanide, lindane
Camphor, phenol, pentaborane, carbon monoxide
Methyl chloride, methyl bromide, methyl iodide

hand onto his or her face).[6,8] Pseudoseizures and particularly pseudostatus epilepticus (which can be treated effectively with antipsychotic therapy e.g. butyrophenones or phenothiazines) should be carefully differentiated from resistant status epilepticus because it often leads to inappropriate endotracheal intubation to control the abnormal movements.[9]

Syncope usually presents with a sudden loss of consciousness, occasionally exhibits convulsive movements (i.e. seizure) and does not cause status epilepticus. It is commonly caused by a sudden reduction in cerebral blood flow due to bradycardia and hypotension,[10] although it may have non-cardiac causes.[6,11,12] Intermittent complete heart block may present with syncopal episodes known as Stokes-Adams attacks (i.e. a sudden sense of fatigue with yawning, loss of consciousness and seizure). Reawakening is often associated with confusion, although the patient may have symptoms of palpitation, headache and facial flush.

Transient ischaemic attacks (TIAs) are associated with a transient alteration in neurological function and can be confused with a focal seizure (but not status epilepticus). However, TIAs are usually associated with a loss of function (e.g. paralysis, numbness, blindness) whereas a focal seizure is usually associated with an active neural function (e.g. twitching, parasthesia, visual hallucination).

INVESTIGATIONS

The investigations performed in a patient with status epilepticus include:

Serum biochemistry and drug screening: plasma glucose, sodium, calcium, magnesium, phosphate, pH, $PaCO_2$, and drug levels should be measured, particularly in overdose patients or those known to have epilepsy who are suddenly not controlled by their current medication.[13]

Computed Tomography (CT): cerebral CT or magnetic resonance (MR) imaging studies are used to identify structural brain disorders causing a seizure. Cerebral angiography or MR angiography may be used when vascular abnormalities are suspected.

ECG and echocardiography: echocardiography and ECG may be performed to determine whether a cardiac syncopal element or cardiac embolic focus exist.

Electroencephalography (EEG): the EEG remains the primary diagnostic tool for evaluating patients with known or suspected seizure disorders. It may also help to differentiate secondary generalization of focal seizures from primary generalized seizures.

Lumbar puncture: a lumbar puncture may be performed to detect xanthochromia if a subarachnoid haemorrhage is suspected, or polymerase chain reaction amplification of DNA extracted from CSF to allow the early detection of the herpes simplex viral genome in patients with herpes simplex encephalitis.[14]

TREATMENT

Treatment requires resuscitation and termination of the seizures, and management of precipitating causes with prevention of recurrence.[15] While the overall mortality in patients with grand mal status epilepticus is approximately 20%,[2] the mortality resulting from status epilepticus alone is approximately 2.5% and is directly related to the length of seizure.[16] Thus seizures should be controlled rapidly (e.g. within 10 minutes), as the patient is in danger of developing permanent brain damage from hypoxia and hyperthermia.

Continuous seizure activity for longer than 30-45 minutes may also cause neuronal damage in the absence of hypoxia and hyperthermia, some of which is due to glutamate-mediated excitotoxicity rather than excessive metabolic demand imposed by repetitive neuronal firing.[2] Multiple organ failure (e.g. renal failure, hepatic failure, respiratory failure) may also occur if hypoxia, hyperthermia, dehydration, rhabdomyolysis, acidiosis and disseminated intravascular coagulation (DIC) have developed from prolonged seizure activity.

Resuscitation

Immediate treatment requires both oxygen and airway maintenance (between seizures, an oral airway is inserted and the tongue is manoeuvred away from the teeth). Often the patient has already been given large doses of benzodiazepines and intubation with mechanical ventilation may be necessary. An intravenous cannula is inserted, blood is taken for biochemical analysis (e.g. glucose, sodium, calcium, magnesium, phosphate), blood gas analysis and anticonvulsant drug levels. Dextrose, calcium, hypertonic saline, magnesium or phosphate should be administered intravenously if hypoglycaemia, hypocalcaemia, hyponatraemia, hypomagnesaemia or hypophosphataemia, respectively, exist.

As hypoglycaemia is the commonest metabolic cause for seizures,[17] 50 mL of 50% glucose intravenously is often recommended empirically if there is a delay in assessing plasma glucose.[1] Intravenous thiamine is usually also administered (but should not delay glucose administration in the hypoglycaemic patient[18]) to the malnourished, cachectic or chronic alcoholic patient.[1] If the core temperature is 41°C or greater in adults, or 39°C or greater in children then measures to lower the temperature should be applied.

Antiepileptic therapy

Treatment is directed at preventing the generation

and conduction of an abnormal neural discharge, by using antiepileptic drugs, and eliminating the cause of the seizure, by correcting the metabolic disorder, drug toxicity or structural abnormality (e.g. surgical excision of an epileptic focus in patients who have resistant seizures).[19]

All central nervous system (CNS) neurones have receptors for the excitatory synaptic transmitters, glutamate or aspartate, and the inhibitory transmitter gamma-aminobutyric acid (GABA). Many epileptic disorders are caused by excessive excitation and/or deficient inhibition of CNS neurones, which may be reversed by antiepileptic agents.[20] Phenytoin, carbamazepine and sodium valproate, however, act largely by limiting the frequency of repetitive firing of neurones by acting on impulse formation and transmission, through voltage- and use-dependent blockade of sodium channels.[21] Barbiturates modify the GABA receptor to increase the duration of opening of the chloride ionophore by GABA, whereas benzodiazepines increase the frequency of the chloride channel opening by GABA.[20] Vigabatrin acts by irreversibly inhibiting the principal catabolic enzyme of GABA (i.e. GABA aminotransferase), thereby increasing cerebral GABA concentrations.[22-24] Tiagabine is a GABA uptake inhibitor.[25]

Antiepileptic therapy for status epilepticus

In one study, while the success rate of approximately 65% for the initial intravenous treatment of status epilepticus with lorazepam (0.1 mg/kg) was superior to phenytoin (18 mg/kg yielded a success rate of approximately 44%), it was not significantly different to diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg) or phenobarbital (15 mg/kg).[26] In Australian practice diazepam, and phenytoin are often used as the initial treatment rather than lorazepam. If the seizures continue despite diazepam and phenytoin (or lorazepam) before adding 'second-line' therapy (which may anaesthetise the patient) the patient should be managed in a monitored environment (e.g. critical care or intensive care unit).

Agents which have been used to manage status epilepticus include the following (Table 3).

Benzodiazepines

Lorazepam. An intravenous bolus of lorazepam (0.03 - 0.06 mg/kg or 2 - 4 mg/70 kg) is administered and may be repeated until a total of 8 mg/70 kg has been infused. Lorazepam is as effective as diazepam in initially controlling seizures,[27] however its longer duration of antiseizure effect (12 - 24 hours) compared with diazepam (15 - 30 minutes) has led to its recommendation in preference to diazepam for the initial treatment of status epilepticus.[1]

Diazepam. An intravenous bolus of diazepam (0.1 - 0.15 mg/kg or 5 -10 mg/70 kg) is administered and may be repeated every 5 minutes until a total of 0.3 mg/kg (or 20 mg/70 kg) has been infused. Rectal diazepam (0.5 mg/kg) may be used when intravenous access is not available.[28]

Table 3. Intravenous therapy in status epilepticus in a 70 kg adult

Lorazepam (2- 8 mg)
or
Diazepam (5 - 20 mg) and phenytoin (1500 - 2000 mg)
Then if required
Phenobarbitone (100 -1000 mg)
Magnesium sulphate (10 - 15 mmol)
Midazolam (8-20 mg, followed by 4-30 mg/h)
Propofol (50 - 150 mg, followed by 100 -500 mg/h)
Thiopentone (200 - 500 mg, followed by 100 - 500 mg/h)
Lignocaine (100 -150 mg, followed by150-200 mg/h)
Ketamine (50 - 100 mg followed by 50 - 100 mg/h)
Isoflurane (0.5 - 1.5%)

Phenytoin

After the first dose of diazepam, phenytoin 20 mg/kg at 50 mg/minute (1500 mg/70 kg over 30 minutes) is administered to patients who have not received phenytoin previously, and will achieve a full anticonvulsant effect within 10 minutes of the completion of the infusion.[29] The common practice of a loading dose of 1000 mg will be inadequate for many adults (in one series it occurred in more than 50%)[9] and may account for the continuation of seizure activity.[2]

If seizures remain uncontrolled and the loading dose is adequate (and there is not a persistent metabolic derangement e.g. hyponatraemia, hypoglycaemia, etc) then a further 5-10 mg/kg (i.e. up to a total of 2000 mg/70kg) of phenytoin may be infused.[30] For those who have been treated with phenytoin previously an intravenous dose of 300 - 500 mg/70kg may be used.

Slow administration of phenytoin is advised because it may cause AV block (up to 2% with infusion rates of 50 mg/minute) or hypotension (up to 50% with infusion rates of 50 mg/minute).[2] The water soluble phenytoin prodrug fosphenytoin (which is converted in vivo to phenytoin by non-specific phosphatases), is formulated without the phenytoin diluent propylene glycol, and can be infused at 150 mg/minute, which reduces the incidence of hypotension and bradycardia associated with intravenous phenytoin,[31] and achieves a free phenytoin level of about 2 μg/mL in 15 minutes (i.e. plasma phenytoin 20 mg/L), as opposed to 25 minutes

with phenytoin.[32] However, as fosphenytoin results in a lower cerebral tissue phenytoin level when compared with standard phenytoin, it is likely to have a similar onset to phenytoin in controlling status epilepticus.[2]

Phenytoin is less effective when compared with phenobarbitone, in controlling seizures associated with alcohol withdrawal and theophylline toxicity.[34]

Phenobarbitone

If the seizure is not controlled within 20 minutes, intravenous phenobarbitone (1.5mg/kg/minute or 100mg/70kg/minute up to 15mg/kg or 1000mg/70kg),[35] or magnesium sulphate (see below) may be used. Thereafter, if the seizure is not controlled, an infusion of midazolam, propofol or thiopentone (after endotracheal intubation and mechanical ventilation) may be used (see below) for 12 hours before withdrawing and observing for signs of a return in seizure activity.

Magnesium sulphate

Magnesium sulphate is used to control seizures associated with eclampsia (10 - 15 mmol intravenously over 5 minutes, followed by an infusion of 4 mmol/h, to achieve blood levels of 2.0 - 3.0 mmol/L). It has also been used in hypomagnesaemic patients with seizures as well as seizures in normomagnesaemic patients unrelated to eclampsia (e.g. seizures associated with cerebral ischaemia[36] and porphyria[37]).

It has been suggested that the antiepileptic activity of magnesium sulphate in eclampsia is not a specific anticonvulsant effect (e.g. N-methyl-D-aspartate receptor inhibitor[38]), but due to its ability to reverse the underlying pathophysiology of eclamptic seizures (i.e. reverses cerebral vasoconstriction[39]), as only a small amount of magnesium crosses the blood brain barrier in patients with preeclampsia undergoing magnesium therapy.[40] However, as the small rise in cerebrospinal fluid magnesium concentration is a significant one (e.g. up to 18% above physiological concentrations[41]), others believe that magnesium has a central anticonvulsant action which implicates the NMDA receptor in the therapeutic efficacy of magnesium sulphate.[42,43]

In the animal model, magnesium sulphate has been found to reduce the seizure activity associated with hyperbaric oxygen toxicity.[44]

Midazolam

Intravenous midazolam 0.1 - 0.3 mg/kg over 2 - 5 minutes (8 - 20 mg/70 kg), followed by 0.05 - 0.4 $mg.kg^{-1}.h^{-1}$ (4 - 30 mg/70 kg/h) may be administered until the proconvulsive processes (e.g. tricyclic or aminophylline toxicity) are remedied.[45] Buccal or nasal midazolam may be used if the intravenous route is unavailable.[28,46]

Propofol

Intravenous propofol (1-2 mg/kg, followed by 2-10 mg/kg /hour) has also been used as an anaesthetic agent to control refractory status epilepticus.[47] The importance of the proconvulsant effects of propofol in the management of these patients is unknown.

Thiopentone

Intravenous thiopentone 5 - 10 mg/kg over 10 minutes (in 200 mg/70 kg amounts) followed by an infusion at 100 - 400 mg/h, is administered to achieve a blood level of 160 - 480 μmol/L.[48] Generally, thiopentone anaesthesia will control all but the most resistant cases of status epilepticus.

Lignocaine

Lignocaine 1.5 - 2 mg/kg infused over 2-5 minutes followed by an infusion of 2-3 mg/kg/h for 12 hours has been used successfully in patients with refractory status epilepticus (not induced by class I antiarrhythmic agents).[49,50]

Ketamine

There have been experimental reports on the beneficial effects of the NMDA receptor inhibitor ketamine in status epilepticus,[51,52] and sporadic clinical reports of the successful use of ketamine (up to 100 mg/h intravenously) in the treatment of patients with refractory status epilepticus.[9,53]

Inhalational anaesthetic agents

Isoflurane has been used to control seizures in status epilepticus, refractory to phenytoin, benzodiazepines and thiopentone,[54] although it usually necessitates hemodynamic support with fluids and/or vasopressor agents during its use.[55]

Muscle relaxation

If seizures can not be controlled after 60 minutes by phenytoin, phenobarbitone, magnesium sulphate, thiopentone or midazolam, muscle relaxants may be required to avert the metabolic consequences of continued convulsions (i.e. rhabdomyolysis, acidosis, hyperkalaemia, DIC, and cerebral oedema). However, patients who require paralysis should undergo continuous electroencephalogram monitoring to detect seizure activity because if this is left uncontrolled neuronal damage may occur.[56]

MAINTENANCE THERAPY

A first-choice antiepileptic agent (e.g. sodium valproate, carbamazepine, phenytoin or phenobarbitone) will achieve control in up to 95% of patients.[57-59] Trough plasma drug levels (usually measured before the morning dose and after a steady state has been reached

i.e. after four to five times the half-life, if a loading dose has not been given) are used to monitor therapy (e.g. assess the probability of therapeutic or toxic effects of a drug) and assess compliance.[60]

If seizures reoccur when the drug has reached the 'therapeutic plasma level', the dose should be increased until seizures stop or toxic side-effects develop.[57,61-64] Thereafter, if seizures are uncontrolled, a second antiepileptic agent is added. When the therapeutic level of the second drug is achieved, if seizures are controlled, the first drug may be gradually reduced. If seizures are not controlled, a third drug may be added and the second drug is gradually withdrawn.[61] In patients in whom difficult control is a feature, alcohol, stress or poor compliance may be causative factors.

The basic pharmacological features of the common antiepileptic drugs are shown in table 4.[59,65] All of these agents are metabolized by the liver (apart from vigabatrin and gabapentin which are excreted largely unchanged by the kidney).

Sodium valproate. This is the drug of choice for primary generalized seizures. The dose ranges from 15 to 40 $mg.kg^{-1}.day^{-1}$ (i.e. 1000 - 3000 mg/70 kg/day) usually starting with 500 mg once or twice daily. As sodium valproate can take several weeks to become fully effective, the dose should only be increased after several weeks. It is the only major anticonvulsant that does not induce hepatic mono-oxygenase enzymes,[66] and may even inhibit the metabolism of other antiepileptic agents such as phenytoin, phenobarbitone, carbamazepine and ethosuximide.[66]

Side-effects include hepatotoxicity, thrombocytopenia (usually at doses greater than 2.5 g/day), pancreatitis, hypofibrinogenaemia, transient alopecia, tremors, nausea, vomiting, abdominal pain (which may be due to carnitine deficiency[67]) and weight gain. Platelet counts and liver function tests should be determined before therapy and every 2 weeks during the first 6 months of treatment.

Phenytoin. Because of its long half-life, phenytoin is administered as a once daily dose of 4 - 6 mg/kg (e.g. 300 - 400 mg/70 kg/day). Control is most often achieved when a steady state plasma concentration of 10 - 20 mg/L (40 - 80 μmol/L) is reached, although some patients remain free of seizures with concentrat-ions well below 10 mg/L (40 μmol/L), and others will tolerate more than 30 mg/L (120 μmol/L) with improved control, without developing neurotoxicity.[68]

Side-effects include, headache, confusion, nystagmus, ataxia and dysarthria which are often dose related and usually (although not always) develop at plasma concentrations in excess of 30 mg/L. Other side-effects include dysmorphic effects (e.g. gum hypertrophy, acne, coarsening of facial features and hirsutism), lymphadenopathy, cerebellar ataxia (cerebellar degeneration may occur with prolonged use), vitamin D antagonism (causing osteomalacia), vitamin K antagonism, folic acid antagonism (phenytoin competes with pteroyl glutamic acid for intestinal transport), peripheral neuropathy, rash, hyperkeratosis, erythema multiforme, fever and hepatitis. Unlike carbamazepine and phenobarbital, drowsiness is not a feature with phenytoin.

Carbamazepine. Carbamazepine between 10 - 20 $mg.kg^{-1}.day^{-1}$ (i.e. 600 - 1200 mg/70 kg/day) in divided doses is equally effective as phenytoin in controlling grand mal seizures and has fewer side-effects. It is usually initiated at doses of 3 - 6 $mg.kg^{-1}.day^{-1}$ (i.e. 200 - 400 mg/70 kg/day) and increased by 200 mg/day increments every 14 days until the maintenance dose is reached which controls the seizure activity completely.[21]

Table 4. Basic pharmacology of the common antiepileptic drugs

	Daily dose (mg/70 kg)	Daily dose (mg/kg)	half-life (h)	therapeutic serum level		% protein bound
Sodium Valproate	1000 - 3000	15 - 40	15	50 - 120 mg/L	(350-830 μmol/L)	90
Phenytoin	100 - 700	1 - 10	24	10 - 20 mg/L	(40-80 μmol/L)	90
Carbamazepine	400 - 1500	6 - 20	15	4 - 12 mg/L	(20-50 μmol/L)	75
Phenobarbitone	60 - 200	1 - 3	90	10 - 30 mg/L	(45-130 μmol/L)	50
Clonazepam	1 - 12	0.02 - 0.15	36	5 - 70 μg/L	(80-240 ηmol/L)	50
Vigabatrin	1000 - 4000	15 - 60	7	-	-	0
Lamotrigine	75 - 400	1 - 6	24	2 -14 mg/L	(8 - 55 μmol/L)	54
Tiagabine	32 - 56	0.2 - 0.8	2 - 9	40 - 80 ηg/L	(100-200 pmol/L)	96
Ethosuximide	750 - 1500	10 - 20	60	40 - 100 mg/L	(280-700 ηmol/L)	0

It is often used as the drug of choice in children, adolescents and women. Phenytoin, phenobarbital and carbamazepine (after the first few weeks of treatment) increase the metabolism of carbamazepine, reducing its half-life from 15 to 8 - 10 h. Carbamazepine also decreases the steady state levels of phenytoin, clonazepam, theophylline and warfarin, and reduces the metabolism of cimetidine, diltiazem, isoniazid and verapamil.[69]

Side-effects include dizziness, diplopia, headache, drowsiness, nausea, nystagmus, ataxia, rash, granulocytopenia, anaemia, oedema, SIADH, hepato-toxicity and complete heart block. Patients who continue to have seizures or have syncopal episodes following carbamazepine administration, may have a carbamazepine induced AV conduction defect causing Stokes-Adams attacks (particularly the elderly female) which occurs in the presence of therapeutic or only modestly elevated carbamazepine levels. Accordingly, all patients who are greater than 50 years old should have an ECG performed before and after carbamazepine administration, and a reduction in dose or an alternative therapy given if cardiac conduction abnormalities exist.[70,71] Massive carbamazepine overdose (particularly in the young) usually causes sinus tachycardia.[71]

Phenobarbitone. Phenobarbitone between 1 - 3 mg/kg (i.e. 60 - 200 mg/70 kg/day) in divided doses is an effective antiepileptic agent; however, it may produce drowsiness and a dulling of the intellect which often leads to poor patient compliance.

Clonazepam. Clonazepam between 0.1 and 0.2 mg/kg (i.e., 1 - 12 mg/70 kg/day) in divided doses is particularly useful for myoclonic seizures. Side-effects include drowsiness and ataxia.

Vigabatrin. Vigabatrin is used as adjunctive therapy for most refractory seizures, resulting in greater than 50% reduction in frequency of seizures in approximately half of adults given $\geq$ 2 g/day.[24] However, it may worsen myoclonic and absence seizures.[72] The usual adult dosage is 1 - 3 g/day (15 - 45 $mg.kg^{-1}.day^{-1}$) given orally in 1 or 2 divided doses and increased in increments of 0.5 g/day up to 4 g/day. There is no direct correlation between plasma concentration and efficacy of vigabatrin, and duration of effect is thought to be dependent more on the rate of GABA aminotransferase resynthesis rather than plasma concentration of the drug. As it is excreted largely by the kidneys, dosage reduction should occur in patients with renal failure.

Side-effects include weight gain, sedation, fatigue, headache, dizziness, confusion, delirium, aggression, ataxia, diplopia, memory impairment, psychosis and insomnia. Drug interactions are rare, as vigabatrin does not induce the hepatic cytochrome P_{450} enzymes and is not extensively metabolised or plasma protein bound. However, plasma concentrations of phenytoin are decreased by 20 to 30% by vigabatrin therapy,[24] and plasma alanine aminotransferase activity (ALT) is reduced, making ALT an unreliable marker of liver function in patients taking vigabatrin.[73]

Lamotrigine. Lamotrigine is believed to exert its anticonvulsant effects by blocking the voltage-dependent sodium channels, thus stabilizing the synaptic membrane and preventing the release of excitatory neurotransmitters (predominantly glutamic acid).[74] It is most effective as add-on therapy to patients with resistant partial seizures with or without secondary generalized seizures, although it may also be used as monotherapy for primary generalized (tonic-clonic) seizures. The dosage ranges from 75 - 400 mg/day, and varies depending on concomitant anticonvulsant therapy.[75] Lamotrigine has a plasma half-life of 25 hours and is 54% protein bound. Drug interactions are common, with sodium valproate prolonging the half-life from 25 h to 60 h and enzyme inducers (e.g. carbamazepine, phenytoin, barbiturates) reducing the half-life of lamotrigine to 15 h.[75]

Side-effects include headache, nausea, vomiting, dizziness, ataxia, tremor, diplopia, skin rash, fever, arthralgias and eosinophilia. In < 1% of patients, Stevens-Johnson syndrome develops.

Gabapentin. Gabapentin is a structural analogue of GABA with an uncertain mode of action, as it appears not to interact with GABA receptors and does not interfere with GABA metabolism (although it may enhance the release or action of GABA).[76] It is most active as add-on therapy to patients with refractory partial seizures with or without secondary generalized seizures.[77] The dosage ranges from 600 - 1800 mg/day, beginning at 300 mg/day and increasing every 1- 3 days.[78] Gabapentin is not protein bound, is not metabolised (it is excreted by the kidneys) and does not induce hepatic enzymes. It has a half-life of 6 h which is increased in patients with renal failure. Monitoring of gabapentin is unnecessary and the dose is adjusted according to the clinical response.[78]

Side-effects include somnolence, fatigue, dizziness, ataxia and gastrointestinal upset. There are no interactions with other antiepileptic drugs.

Tiagabine. The neuronal inhibitory action of GABA is limited largely by active reuptake of GABA into astrocytes and neurons. Tiagabine enhances GABAergic inhibition by specifically decreasing neuronal and astrocytic uptake of GABA, with the resultant increase in synaptic GABA accounting for the anticonvulsant activity of this compound. Tiagabine hydrochloride is completely absorbed orally and reaches its maximum plasma concentration within 90 minutes. Its elimination half-life is 7-9 hours in non-enzyme induced individuals

(2-3 hours in enzyme-induced patients), and it is metabolised largely by the hepatic cytochrome P_{450} system and excreted in the bile. The average daily dose varies between 32 - 56 mg, beginning with 4-5 mg twice-daily followed by weekly increments of 4 - 12 mg and changing to thrice daily dosage if more than 30 mg/day is administered.[25]

Side-effects include dizziness, asthenia, somnolence, nervousness, ataxia, confusion, tremor, diarrhoea, and depression. Overdosage may cause coma.

Other therapy. Ethosuximide, felbamate, methsuximide, and trimethadione have also been used in resistant cases. When seizure activity is secondary to structural lesions, surgical removal of the epileptogenic focus can eliminate the seizures.[19]

OUTCOME

Epilepsy is associated with an increased mortality (a three fold increase compared with non-epileptic patients[79]) and sudden unexpected death.[80] The mortality is reduced if the patient can be cured (e.g. with corrective surgery[81]).

Status epilepticus has a mortality rate of approximately 2%.[82] The prognosis of this disorder relates largely to the patients age, whether it is convulsive or non-convulsive (non-convulsive status epilepticus lasting for several days may still have a favorable outcome[83]), duration of seizures, presence of secondary injuries (hypoxia, aspiration pneumonia rhabdomyolysis, hyperpyrexia) and prevention or correction of reversible factors (hypoglycaemia, hyperglycaemia hyponatraemia, hypomagnesaemia).

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