

Essential Drugs

Drugs in Epilepsy

Epilepsy, in one form or another, has been estimated in many different communities to afflict about one in every 200 persons. Accurate identification and classification of the convulsive disorder is of paramount importance in its treatment. The cause of seizures should be sought in every case and any underlying disorder corrected whenever possible. In many instances, however, no obvious cause can be identified and antiepileptic drugs become the mainstay of treatment. This account of their use has been developed in collaboration with the World Federation of Neurology and the International League against Epilepsy.

Principles of anticonvulsant therapy

When to start

The decision to start treatment requires careful evaluation of the patient. The prognosis may not be evident after a single seizure in which case it is justifiable to await evidence of recurrence before prescribing anti-epileptic drugs.

Choice of drug

Treatment should always be started with a single drug, since many patients can be controlled with one of the available compounds. Whereas it is possible to provide general guidance on drug selection, there is no means of predicting which will be most effective. The initial choice should therefore be based on a general appreciation of the advantages and disadvantages that each compound offers to the individual patient. In practice, treatment is often influenced as much by the occurrence of adverse effects as by clearly demonstrable differences in efficacy. Patients thus need to remain under supervision throughout treatment.

It is widely believed that gradual augmentation of the dose to the effective level, or to the maximum tolerated level, will lessen the incidence of some adverse effects but in severe cases this is not practicable

since the need for immediate therapeutic control is the overriding factor.

If one drug fails to control the seizures after it has been used in full therapeutic dosage for an adequate period, or if it is not well tolerated, it should be gradually substituted with another. If monotherapy is ineffective two drugs should be tried in combination. Several regimens may need to be tried before the most appropriate one can be selected. Where the necessary laboratory facilities exist, it can be useful to measure plasma concentrations as an aid to dose adjustment or to determine whether the patient is actually taking the drugs.

When to stop

Treatment is usually continued for a minimum of two years after the last seizure and in some types of epilepsy for even longer. It should be reinstated for the same period if relapse subsequently occurs. There is no evidence that indefinite prolongation of treatment improves the eventual prognosis. Elective withdrawal should normally be extended over a period of several months since abrupt discontinuation can induce status epilepticus. None the less, many adult patients relapse once treatment is withdrawn. Thus, when the patient's livelihood could be endangered by a recurrence of seizures, indefinite continuation of treatment is justified. However, withdrawal of treatment is generally advisable in younger patients in whom the risk of recurrence is less, once remission has been sustained for two years.

Women of childbearing age

Oral contraceptives do not influence either the frequency or severity of seizures or the response to anti-epileptic therapy. However, there is an increased risk of oral contraceptive failure in women receiving carbamazepine, phenobarbital, phenytoin and primidone. Valproic acid has not been associated with this risk.

The incidence of birth defects in infants of epileptic mothers is greater than in the general population. Although this may be due to the underlying condition rather than to antiepileptic drugs, the associa-

tion of specific deformities with the use of particular drugs — perhaps with the exception of carbamazepine and ethosuximide — suggests that antiepileptics are partly responsible. This risk has to be weighed against the danger of seizures and there is some evidence to indicate that antiepileptic requirements can rise during pregnancy. However, it is important to avoid overdosage or unnecessary antiepileptic treatment in women of reproductive age. Abrupt discontinuation, because of the risk of status epilepticus, can endanger both the mother and the fetus.

Infants exposed *in utero* to phenobarbital, phenytoin or primidone may be vitamin K deficient. The risk of serious haemorrhage is reduced by routine administration of vitamin K supplements at birth.

Management of specific types of seizure

The classification adopted in this account is based on the following abstract of the Proposal from the Commission on Classification and Terminology of the International League against Epilepsy (1981).

Summary of seizure types

1. Partial seizures (focal, local seizures)

- A. Simple partial seizures.
- B. Complex partial seizures.
- C. Partial seizures secondarily generalized.

2. Generalized seizures

- A1. Absence seizures.
- A2. Atypical absence seizures.
- B. Myoclonic seizures.
- C. Clonic seizures.
- D. Tonic seizures.
- E. Tonic-clonic seizures.
- F. Atonic seizures.

Generalized tonic-clonic, simple partial and complex partial seizures

These are the most common types of epileptic disorder. They occur in all age groups. Phenobarbital, phenytoin, carbamazepine and valproic acid are widely used in their management. Each of these drugs is associated with dose-related and idio-

syncratic adverse effects. Consideration should always be given to the need to monitor haematological, hepatic and renal function. Until recently, most cases were treated initially with phenobarbital or phenytoin, which are relatively inexpensive. However, both drugs can affect learning and understanding, and phenobarbital can also cause troublesome sedation and behavioural disturbances especially in children. Moreover, long-term use of phenytoin can cause distressing skin eruptions, hirsutism, gingival hyperplasia and coarsening of the features especially in women. Drowsiness, ataxia, nystagmus and gastrointestinal disturbances are other dose-related effects that occasionally occur at therapeutic dosage. Carbamazepine is associated with fewer dose-related adverse effects. Fatal bone marrow depression has been reported but this is very rare. In resistant cases a combination of phenytoin and carbamazepine may be of particular value.

Valproic acid is also generally well accepted. However, it occasionally causes serious and even fatal liver damage. Most cases have occurred within the first six months of treatment in infants and young children. Recurrent vomiting and abdominal pain are warning signs of liver damage. Unless liver function tests show that this suspicion is unfounded the drug must be withdrawn immediately.

Primidone is now less used. It holds no major advantage over phenobarbital and it is associated with a higher incidence of adverse effects. However, it may be valuable in patients unresponsive to phenytoin or phenobarbital, and may be used in combination with phenytoin.

Absence seizures

These seizures are less common. They occur predominantly in children and usually remit spontaneously before adulthood. Ethosuximide or valproic acid are widely used in their management. Both are usually well accepted, but ethosuximide rarely causes lupus erythematosus and psychoses which call for immediate discontinuation. Absence seizures are commonly associated with tonic-clonic seizures. In these cases sodium valproate is preferred since it is effective in both disorders.

Tonic, atonic and atypical absence seizures

Phenobarbital or phenytoin are widely used for tonic seizures, valproic acid or clobazam for atonic seizures, and clobazam for atypical absence seizures.

Myoclonic seizures

Valproic acid is widely used for juvenile myoclonic seizures. Treatment is effective, but the relapse rate is high and, exceptionally, in these patients it is justifiable to continue therapy indefinitely. Other myoclonic seizures are often resistant to treatment and some do not have an epileptic basis. Valproic acid or clobazam can be of value and other anti-epileptic compounds may be useful in intractable cases. Both drugs are generally well accepted but tolerance has been reported to clobazam.

Infantile spasm (Infantile myoclonic epilepsy)

Infantile spasms, which are often associated with severe brain damage, can be resistant to antiepileptic drugs. However, they may be responsive to intramuscular adrenocorticotrophic hormone (ACTH) which holds advantage over corticosteroids. Clobazam is sometimes of value in resistant cases.

Neonatal seizures

Seizure disorders in neonates commonly result from acute brain damage or metabolic disturbances. If the seizures continue despite treatment of the underlying cause, long-term antiepileptic therapy is required.

Febrile convulsions

Febrile convulsions usually occur in children aged between 3 months and 5 years. Brief attacks respond to tepid sponging and antipyretics such as paracetamol. More severe attacks usually respond to rectal diazepam. Prolonged treatment is advisable when repeated seizures occur during the first 18 months of life and in children with evident neurological abnormalities. Phenobarbital is used for this purpose but careful clinical monitoring and dosage adjustment are necessary to minimize the risk of adverse effects. Valproic acid, although also effective, is not recommended because of the greater risk of hepatotoxicity in this age group. Alternatively, intermittent prophylaxis with rectal diazepam during febrile episodes can be of value.

Status epilepticus

Status epilepticus is a medical emergency which carries a high mortality. Maintenance of the airway and assisted ventilation are crucial even when the

seizures are controlled since the drugs used in its management may also depress respiration. Unresponsive patients require intensive care. An attempt must always be made to identify any remediable cause.

Intravenous diazepam is usually effective but, because its anti-epileptic activity is short-lasting, phenytoin should be administered, whenever feasible, by the same route immediately afterwards. When cannulation is impossible, diazepam may be administered rectally.

Rectal paraldehyde is also used when intravenous therapy is not feasible or where facilities for resuscitation are inadequate.

Intravenous phenobarbital is also effective and is preferred when status epilepticus occurs during withdrawal of oral phenobarbital.

If seizures continue despite treatment, general anaesthesia may be required.

Long-term antiepileptic treatment should be continued or, in patients not currently receiving treatment, started at the earliest opportunity. It may be necessary to administer the drugs initially through a nasogastric tube.

CARBAMAZEPINE

scored tablets 100 mg, 200 mg

The antiepileptic properties of carbamazepine are similar to those of phenytoin, but cases refractory to either drug alone sometimes respond to the two drugs in combination.

Peak plasma concentrations may not be attained until several hours after ingestion. The drug is extensively protein bound and is ultimately excreted in the urine as metabolites, including conjugates. The plasma half-life is initially very prolonged but decreases on repeated administration. It may be reduced to 5 to 10 hours when carbamazepine is taken in combination with some other antiepileptics.

Uses

Generalized tonic-clonic, simple partial and complex partial seizures. Carbamazepine should be used alone in the first instance. Phenobarbital, phenytoin or valproic acid should subsequently be tried in resistant cases and, if necessary, two drugs should be used in combination.

Acute attacks of trigeminal neuralgia.

Carbamazepine is **not** appropriate for the treatment of generalized absence seizures which may be exacerbated by the drug.

Dosage**Seizures**

Adults: Initially 100 mg twice daily, or 50 mg twice daily in frail or elderly patients. This is increased gradually, according to response, to a maximum of 2 g daily in divided dosage. Exceptionally, even higher doses have been used.

Children: Daily maintenance dosage usually lies between 10 and 20 mg/kg.

Twice daily dosage is often adequate but six or eight-hourly administration is advisable at higher dosages to avoid large fluctuations in plasma concentrations.

Therapeutic plasma concentrations are in the region of 4 to 12 µg/ml (17 to 50 µmol/l). Blood levels are reduced when carbamazepine is used with phenytoin, phenobarbital or primidone as a result of increased metabolic transformation in the liver.

Trigeminal neuralgia

100 mg increments every 12 hours until pain is relieved. The effective daily dose is usually 600 to 800 mg (or 10 to 15 mg/kg); it should not exceed 1200 mg. Once pain is relieved, treatment should be gradually withdrawn.

Carbamazepine has also been used at the same dosage to suppress attacks of trigeminal neuralgia. The need for such use must be balanced against the remote risk of serious adverse effects.

Contraindications

Hypersensitivity to carbamazepine or tricyclic antidepressants.

Atrioventricular conduction abnormalities.

Patients taking a monoamine oxidase inhibitor, or who have taken one within the previous 2 weeks.

Precautions

The incidence of dose-related adverse reactions can be reduced by increasing dosage gradually, and carefully adjusting the maintenance dose. Particular care is necessary in patients with severe cardiovascular disease, or with hepatic or renal disorders.

Dermatitis may be the first sign of a severe idiosyncratic reaction and is an indication for withdrawal of treatment.

Treatment should be withdrawn in the very rare event of severe bone marrow depression. Patients should be advised to stop taking the tablets and to report to their doctor immediately, should they develop sore throat or fever. This advice can be of greater value than routine monitoring of the white cell count during the first months of treatment.

Use in pregnancy

On the available evidence carbamazepine appears to be safer than some other antiepileptics taken during pregnancy. Abrupt discontinuation of treatment because of pregnancy is never warranted since this incurs a risk of status epilepticus.

Adverse effects

Dose-related reactions include gastrointestinal intolerance, dryness of the mouth, drowsiness, dizziness, blurred vision, diplopia and ataxia. Cutaneous eruptions are frequent and more serious skin conditions such as Stevens-Johnson syndrome have been reported.

Hypersensitivity reactions are usually mild and reversible but light-sensitive dermatitis has occurred.

Bone marrow depression and hepatic dysfunction are rare events.

Drug interactions

Repeated use of carbamazepine causes induction of hepatic enzymes. It thus promotes its own metabolism and that of other drugs metabolized in the liver, including phenobarbital, phenytoin and oral anticoagulants.

Carbamazepine can reduce the effectiveness of oral contraceptives, particularly if the estrogen content is

low. Breakthrough bleeding is an indication to use another method of contraception or a higher-dose estrogen product.

Concomitant administration of monoamine oxidase inhibitors has resulted in hypertensive crises, severe convulsions and death. Therefore, at least 2 weeks should elapse between the withdrawal of a monoamine oxidase inhibitor and the start of carbamazepine therapy.

Various drugs inhibit the metabolism of carbamazepine. These include macrolide antibiotics, isoniazid, some calcium antagonists, dextropropoxyphene, viloxazine and possibly cimetidine. This can result in raised plasma levels and consequent neurotoxicity.

Overdosage

The first symptoms of overdosage occur within 1 to 3 hours. Neuromuscular disturbances are prominent. Convulsions, tremor and excitation may develop. Tachycardia and variations in blood pressure are indicative of severe overdosage.

Emesis or gastric lavage are of value within a few hours of ingestion. Treatment is otherwise symptomatic and is directed to the maintenance of the airway, assisted respiration and treatment of shock. Administration of diazepam has been used successfully in the management of carbamazepine-induced convulsions.

Storage

Carbamazepine tablets should be kept in a tightly closed container.

DIAZEPAM

injection 5 mg/ml in 2 ml ampoule

A sedative and anxiolytic benzodiazepine with a central relaxant effect and transient antiepileptic action when administered intravenously or rectally. The drug is metabolized in the liver partly to other active moieties and is slowly excreted, mainly in the urine. However, the antiepileptic effect subsides after 20 to 30 minutes. A response may be expected within approximately 1 to 5 minutes of administration.

Uses

Treatment of status epilepticus. Both diazepam and phenytoin are required in the management of status

epilepticus. Diazepam because of the rapidity of its effect, and phenytoin because of its prolonged action.

Emergency management of recurrent seizures including febrile convulsions.

Treatment of seizures associated with poisoning and drug withdrawal.

Symptomatic treatment of alcohol withdrawal.

Dosage and administration

In order to ensure stability, diazepam should not be mixed with other drugs in syringes or infusion fluids, nor should it be diluted before use except in saline or glucose infusion. These solutions should be discarded within 6 hours.

It should be administered directly into the cubital vein at a rate of no more than 1 ml per minute to reduce the risk of thrombophlebitis. Under no circumstance should diazepam be injected intramuscularly.

Preparations of diazepam in an oil-in-water emulsion are available which reduce the risk of thrombophlebitis after injection.

Accidental intra-arterial injection can cause severe local necrosis.

Status epilepticus:

Adults: Initially 10 to 20 mg (0.15 to 0.3 mg/kg) by slow intravenous injection at a rate of 5 mg per minute. This can be repeated, if necessary, provided no more than 50 mg is administered within a 60 minute period. In resistant cases, a slow IV infusion of up to 3 mg/kg over a 24 hour period may be necessary provided that facilities for assisted ventilation are immediately available.

Children: 0.2 to 0.3 mg/kg by slow intravenous infusion.

Phenytoin 15 to 18 mg/kg should be administered at a rate not exceeding 50 mg/min immediately following the first injection of diazepam and using a separate syringe. It should be injected directly into a vein or into the IV tubing near the needle since it has a tendency to precipitate out when added to IV fluids.

If necessary, diazepam may alternatively be administered rectally at a dosage of 0.2 to 0.4 mg/kg using a cannula or catheter fitted to the syringe. This may be repeated if necessary after 30 minutes. In children, the same dose may be administered rectally up to a maximum of 5 mg in children less than 3 years and 10 mg in children over 3 years.

In refractory cases IV barbiturates, rectal paraldehyde or general anaesthesia should be considered.

Emergency treatment of rapidly recurrent (or closely spaced) seizures:

Adults and older children: 10 to 20 mg (0.15 to 0.3 mg/kg) by slow intravenous injection or rectally.

Children (1 - 3 years) and elderly patients: 0.2 to 0.3 mg/kg by slow intravenous injection or rectally.

Febrile convulsions:

0.5 mg/kg administered rectally. This may be repeated, if necessary, after 30 minutes up to a maximum of 10 mg.

Seizures associated with poisoning, drug and alcohol withdrawal:

10 mg IV repeated, if necessary, after 4 hours.

Contraindications and precautions

Diazepam should not be administered to patients with known hypersensitivity. It should be administered with particular caution to patients with myasthenia gravis.

Patients with chronic obstructive airways disease are at particular risk of respiratory depression.

Storage

Ampoules should be kept protected from light.

ETHOSUXIMIDE

capsule or tablet 250 mg
syrup 250 mg in 5 ml

An antiepileptic which suppresses the paroxysmal electroencephalographic spike and wave pattern characteristic of absence seizures. It is ineffective in the management of other types of seizures.

Peak plasma concentrations occur within 4 hours of ingestion. The plasma half-life is about 30 hours in children and 60 hours in adults. It is metabolized in the liver and excreted in the urine, partly unchanged, but largely as metabolites, including conjugates.

Uses

Generalized absence seizures. Ethosuximide should be used alone in the first instance. Valproic acid should subsequently be tried in resistant cases and, if necessary, the two drugs may be used in combination.

Dosage

The optimum plasma concentration lies between 50 and 100 µg/ml (350 and 700 µmol/l). Inadequate dosage is the major cause of therapeutic failure.

Adults and children over 6 years: Initially, 500 mg daily, subsequently adjusted according to response. Increments should be made in steps of 250 mg every 4 to 7 days to a maximum of 2 g daily, or until an adequate response is obtained or adverse effects occur.

The daily maintenance dose is usually within the range 20 to 30 mg/kg. Amounts of 1 g or more should be taken in two or more divided doses.

Children under six years: Infants and young children metabolize ethosuximide more rapidly than adults. They therefore require relatively higher and more frequent dosage. Initially, 10 mg/kg daily adjusted as above according to requirements to a maximum of 40 mg/kg daily.

Contraindications

Hypersensitivity to ethosuximide and its congeners methsuximide and phensuximide.

Precautions

Monitoring of plasma concentrations is advisable in patients with impaired hepatic or renal function.

Use in pregnancy

On the available evidence ethosuximide appears to be safer than some other antiepileptics taken during pregnancy. Abrupt discontinuation of treatment because of pregnancy is never warranted since this incurs a definite risk of status epilepticus.

Drug interactions

Concomitant use of monoamine oxidase inhibitors can suppress central nervous function and lower the seizure threshold.

Adverse effects

Gastrointestinal disturbances may occur, particularly during the initial phases of treatment. These include anorexia, hiccup, nausea and vomiting, epigastric pain. Weight loss, drowsiness, dizziness, ataxia, headache, depression and mild euphoria may also be troublesome.

Rarely, psychotic states, rashes including erythema multiforme and the more serious Stevens-Johnson syndrome, lupus erythematosus, disturbances of liver function and haematological disorders, including leucopenia, agranulocytosis and bone marrow depression have been reported.

Overdosage

Emesis or gastric lavage is of value within a few hours of ingestion. Treatment is otherwise symptomatic and is directed particularly to respiratory depression and shock.

Storage

Ethosuximide tablets and capsules should be kept in a tightly closed container, protected from light. Ethosuximide syrup should be kept protected from light.

PHENOBARBITAL

tablet 15 - 100mg

elixir 15 mg/5 ml

injection 200 mg (sodium salt)/ml

A barbiturate with marked antiepileptic activity at sub-hypnotic dosage that inhibits the spread of seizure activity and raises the seizure threshold.

Phenobarbital is almost completely absorbed following oral administration but peak serum concentrations may not occur for several hours. It is partly protein bound and has a half-life of several days. It is

excreted in the urine partly unchanged, but mainly as meta-bolites, including conjugates.

Uses

Treatment of generalized tonic-clonic seizures, simple partial and complex partial seizures. Phenobarbital should be used alone, in the first instance. Carbamazepine, phenytoin or valproic acid should subsequently be tried in resistant cases and, if necessary, two drugs should be used in combination.

Treatment of neonatal seizures and febrile seizures. Treatment of status epilepticus occurring during withdrawal of phenobarbital or in patients unresponsive to diazepam and phenytoin.

Phenobarbital is **not** effective in generalized absence seizures.

Dosage

Oral dosage forms (All indications other than status epilepticus)

The optimum plasma concentration usually lies between 10 and 30 µg/ml (45 and 130 µmol/l).

Adults: Initially 2 mg/kg daily (to a maximum of 100 mg) as a single dose at night. If necessary, this may be increased incrementally, according to the response, to a maximum of 6 mg/kg daily in two or more divided doses.

Children: Initially 3 to 4 mg/kg daily but, in infants, up to 8 mg/kg may be required in order to achieve therapeutic plasma concentrations.

Injectable dosage forms (Status epilepticus)

Adults and children: 10 to 20 mg/kg is infused intravenously at a rate not exceeding 50 mg per minute (see precautions) until either an adequate response is obtained or hypotension and respiratory depression occur. In general, children and neonates tend to require proportionally higher dosages.

Intravenous therapy should be discontinued as soon as seizures are controlled.

In unresponsive cases rectal paraldehyde or general anaesthesia should be considered.

Contraindications

Hypersensitivity to barbiturates.

Acute intermittent porphyria.

Precautions

Sedation occurs, in some degree, in all patients at the outset of therapy. This, together with the risk of further convulsions, renders driving and the operation of machinery dangerous. Some patients subsequently develop tolerance to the sedative effect but not to the antiepileptic action.

The use of phenobarbital in children needs to be weighed against the possibility of behavioural changes and hyperactivity. The maintenance dosage should be set at the minimum compatible with good control. Plasma concentrations should be maintained below 40 µg/ml (170 µmol/l) whenever possible.

Abrupt discontinuation of treatment may induce status epilepticus refractory to drugs other than phenobarbital itself.

Careful monitoring of dosage is particularly important in the elderly, and in patients with reduced respiratory reserve, or hepatic or renal insufficiency.

The injectable sodium salt is highly alkaline. It must be administered by slow intravenous injection. Rapid injection may cause respiratory depression or hypotension. Local extravasation can cause extensive necrosis and intra-arterial injection may cause spasm, severe pain and possibly gangrene.

Use in pregnancy

Safe use in pregnancy has not been established. However, abrupt discontinuation of treatment is never warranted because of pregnancy since this incurs a definite risk of status epilepticus. Phenobarbital is excreted in breast milk. Nursing should be discontinued if the infant becomes unusually sleepy or drowsy.

Adverse effects

Dose-related reactions include sedation, nystagmus and ataxia. Learning ability and understanding can be impaired. In children, irritability, behavioural

problems and hyperactivity are liable to occur. In the elderly confusion is common.

Rashes and other signs of allergy occur in a few patients, but serious hypersensitivity reactions, which include exfoliative dermatitis, are rare. Prolonged therapy occasionally results in megaloblastic anaemia responsive to folic acid, and in osteomalacia responsive to high doses of vitamin D.

Like all barbiturates, phenobarbital produces dependence but it is less likely to cause serious withdrawal effects than shorter-acting congeners.

Drug Interactions

Repeated use of phenobarbital induces hepatic enzymes. This results in tolerance and a reduced response to other drugs metabolized in the liver, including carbamazepine, phenytoin, oral anti-coagulants and steroids.

Phenobarbital can reduce the effectiveness of combined oral contraceptives, particularly if the estrogen content is low. Breakthrough bleeding is an indication to use another method of contraception or a higher dose estrogen product.

Plasma concentrations of phenobarbital may rise by up to 50 per cent when valproic acid is given concurrently, presumably as a result of hepatic inhibition. All patients receiving concomitant valproic acid therapy should be closely monitored for signs of neurological toxicity since profound sedation can sometimes occur.

Concomitant use of monoamine oxidase inhibitors can suppress central nervous function and lower the seizure threshold. The effect of alcohol may be potentiated.

Overdosage

Overdosage produces severe, long-lasting respiratory depression. Emesis or gastric lavage is of value within a few hours of ingestion. Subsequently, excretion can be promoted by forced alkaline diuresis, haemodialysis or extracorporeal haemoperfusion.

Treatment is otherwise supportive and is directed to maintaining respiration, cardiovascular and renal function, and electrolyte balance. Antibiotics may be required to prevent the development of pneumonia.

Storage

Phenobarbital tablets should be kept in a well-closed container. Phenobarbital injection and elixir should be kept protected from light.

PHENYTOIN

**capsule or tablet 25 mg,
50 mg, 100 mg(sodium salt)
injection 50 mg (sodium salt)/ml
in 5 ml vial**

An antiepileptic that is thought to act by stabilizing neuronal membranes and reducing post-tetanic potentiation of synaptic transmission.

Absorption can vary widely from one preparation to another. Peak plasma concentrations may not be attained for 6 hours or even longer and plasma half-life is of the order of 24 hours. Metabolites, including conjugates, are ultimately excreted in the urine. Steady state conditions are attained after 1 to 3 weeks of uninterrupted treatment. However, small changes in dose can lead to disproportionately large changes in plasma levels.

Uses

Generalized tonic-clonic, simple partial and complex partial seizures. Phenytoin should be used alone in the first instance. Carbamazepine, phenobarbital or valproic acid should subsequently be tried in resistant cases, and, if necessary, two drugs should be used in combination.

Treatment of status epilepticus. Both diazepam and phenytoin are required in the management of status epilepticus. Diazepam because of the rapidity of its effect, and phenytoin because of its prolonged action.

Phenytoin is **not** appropriate for the treatment of generalized absence seizures which may be exacerbated by the drug.

Dosage

Oral dosage forms (All indications other than status epilepticus)

Adults: Initially 4 to 5 mg/kg daily. This is frequently given as 100 mg two or three times daily. However, many adult patients can be adequately controlled on one daily dose. This should be increased by 25 mg daily at two-weekly intervals, according to the response, to a maximum of about 8 mg/kg daily.

Children: Initially 5 mg/kg daily always administered in two divided doses increasing, as above, to a maximum of 8 mg/kg daily.

The optimum plasma concentration usually lies between 10 and 20 µg/ml (40 to 80 µmol/l). Because protein binding is reduced in neonates and patients with impaired renal or hepatic function, dosage should be adjusted in these patients to produce somewhat lower plasma concentrations.

Injectable dosage forms (status epilepticus)

Injectable phenytoin should not be used if the solution is not clear or if a precipitate is present. It should be administered directly into a vein or into the IV tubing near the needle since the drug has a tendency to precipitate out when added to IV fluids. Administration of phenytoin is preceded by an initial IV injection of diazepam.

Adults: 15 to 18 mg/kg as a loading dose by IV injection at a rate not exceeding 50 mg per minute. An additional 5 mg/kg may be given after 12 hours if necessary.

Children: 10 to 15 mg/kg by IV injection at a rate of 0.5 to 1.5 mg/kg per minute.

In refractory cases use of IV barbiturates, rectal paraldehyde or general anaesthesia should be considered.

Contraindications

Hypersensitivity to hydantoins.

Parenteral phenytoin is contraindicated in patients with sinus bradycardia, sinoatrial block, or second or third degree atrioventricular block.

Precautions

Plasma concentrations should be monitored, where this is feasible, in patients who either respond inadequately or react adversely. Phenytoin has a narrow therapeutic index, and unpredictable

variations in plasma levels can occur from time to time without alteration of dosage.

Diplopia and ataxia are indications for lowering dosage. Withdrawal or reduction of dosage should not be undertaken at a rate greater than 25 mg in any 7-day period. Preferably, a plan should be adopted to phase out dosage over a 6-month period.

Use in pregnancy

Use of phenytoin during early pregnancy has been reported to increase the risk of fetal malformations. Its subsequent use may result in hypoprothrombinemia of the newborn which is responsive to vitamin K. However, abrupt discontinuation of treatment is never warranted, because of pregnancy, since this incurs a definite risk of status epilepticus.

Adverse effects

Gastric intolerance, sleeplessness and agitation are sometimes troublesome during the initial phases of treatment.

Functional neurological disturbances are usually reversible on dosage reduction. These include sedation, confusion, blurred vision, ataxia, nystagmus, diplopia, vertigo, cerebellar-vestibular symptoms, behavioural disturbances and hallucinations.

Other sequelae of treatment not directly related to dosage or to plasma concentrations include:

- mucocutaneous changes: gingival hyperplasia, skin eruptions, coarse facies, hirsutism;
- neurological changes: peripheral neuropathy, choreiform movements, impaired learning and understanding;
- metabolic changes: osteomalacia and occasionally rickets associated with reduced plasma calcium levels; hyperglycaemia due to inhibition of insulin secretion; megaloblastic anaemia due to folate deficiency.

A variety of immunologically-determined effects have also occasionally been reported:

- hypersensitivity reactions including erythema, generalized lymph node enlargement and, very rarely, Stevens-Johnson syndrome, systemic lupus erythematosus, hepatic necrosis, nephrosis and poly-arthritis;

- haematological reactions including leucopenia and, more rarely, thrombocytopenia, agranulocytosis and bone marrow depression.

Administered parenterally, phenytoin may cause hypotension and ventricular dysrhythmias.

Drug interactions

Many drugs can increase effective plasma concentrations of phenytoin either by:

- inhibiting its metabolism in the liver: acetylsalicylic acid, sulfaphenazole, phenylbutazone, disulfiram, products of dicoumarol, isoniazid, cycloserine, diazepam, chloramphenicol, sultiame, ethosuximide, mephenytoin and methylphenidate.
- interfering with protein binding: acetylsalicylic acid, phenylbutazone, tolbutamide and some sulfonamides.

Conversely, plasma concentrations are reduced by other drugs that induce hepatic enzymes including: carbamazepine, clobazam and, possibly, phenobarbital.

A more complex interaction occurs with valproic acid resulting in a transient increase followed by a subsequent reduction in serum concentrations of phenytoin occasionally resulting in seizures.

Concomitant use of monoamine oxidase inhibitors can suppress central nervous function and lower the seizure threshold.

Phenytoin, by inducing hepatic enzymes, can reduce the effectiveness of combined oral contraceptives, particularly if the estrogen content is low. Breakthrough bleeding is an indication to use another method of contraception or a higher-dose estrogen product.

Overdosage

Single doses of as little as 2 g have been fatal. Ataxia, nystagmus, dysarthria and mental disorders are distinctive initial signs that become evident at plasma concentrations of between 30 and 40 µg/ml (120 and 160 µmol/l). If life-threatening doses have been taken these signs are rapidly succeeded by coma, hypotension and respiratory depression.

Emesis or gastric lavage is of value within a few hours of ingestion. Treatment is otherwise symptomatic and is directed to maintenance of respiration and treatment of shock. Plasma levels can be reduced by haemodialysis and total exchange transfusion has been successfully accomplished in infants.

Storage

Phenytoin tablets and capsules should be kept in a tightly closed container.

Phenytoin injection should be kept protected from light.

VALPROIC ACID

enteric coated tablet 200 mg, 500 mg
(sodium salt)

A simple, branched-chain carboxylic acid with broad antiepileptic properties which may act by modifying the metabolism of gamma aminobutyric acid. Absorption is almost complete following oral administration. Peak plasma concentrations occur after 2 to 8 hours and decay with a half life of about 8 to 15 hours. The half life in infants and children is considerably longer. It is excreted as metabolites, including conjugates, largely in the urine.

Uses

Treatment of generalized absence seizures. Valproic acid should be used alone in the first instance. Ethosuximide should subsequently be tried in resistant cases and, if necessary, the two drugs may be used in combination.

Treatment of generalized tonic-clonic, simple partial and complex partial seizures, myoclonic and atonic seizures. Valproic acid should be used alone in the first instance. Carbamazepine, phenobarbital or phenytoin should subsequently be tried in resistant cases and, if necessary, two drugs should be used in combination.

Dosage

Adults: Initially 15 mg/kg daily in one or two divided doses increased, according to the response, by 200 mg daily at twice weekly intervals. Daily doses in excess of 30 mg/kg are rarely needed.

Infants and children: Initially 15 mg/kg daily in divided doses, increasing according to response. Rarely, daily doses of more than 30 mg/kg are needed in children, and infants may require up to 40 mg/kg.

Enteric-coated tablets are necessary if symptoms of gastrointestinal irritation are to be avoided.

The effective plasma concentration is in the region of 40 to 100 µg/ml (280 to 690 µmol/l). However, the correlation between therapeutic efficacy and plasma levels is poor and the latter have limited value in management except as an indication of non-compliance or to monitor the effects of a change in dosage or the addition of another drug to the regimen.

Contraindications

Hypersensitivity to valproic acid.

Pre-existing impaired hepatic or pancreatic function.

Bleeding disorders.

Precautions

Cases of fatal hepatic failure have occurred in patients receiving sodium valproate. Infants and young children are at greatest risk during the first six months of therapy. In particular, valproic acid should be used in children with generalized tonic-clonic, simple partial or complex partial seizures only when these are resistant to other therapy. Other risk factors include severe epilepsy, mental retardation and congenital metabolic disorders.

Non-specific clinical symptoms such as loss of seizure control, malaise, weakness, lethargy, facial oedema and vomiting may precede any change in laboratory tests and provide a warning to withdraw treatment. Significantly high transaminase levels also provide an indication for immediate withdrawal of treatment. However, although biochemical testing is widely practised during the first six months of treatment, its value is compromised because subclinical disturbances of hepatic function are common.

Valproic acid should also be withdrawn immediately if spontaneous bruising or bleeding indicates the development of thrombocytopenia. The bleeding time and platelet count should always be checked before

a treated patient undergoes surgery or receives oral anticoagulants.

Use in pregnancy

Use of valproic acid in the first trimester has been associated with spina bifida in the offspring. Its use in early pregnancy is thus best avoided. For women who become pregnant while taking valproic acid an ultrasound examination and tests for determination of alpha-fetoprotein are advised where facilities for elective termination are available.

Adverse effects

The rare and potentially fatal complications of hepatic failure and thrombocytopenia are described under "precautions". Rarely, severe or fatal pancreatitis has also been reported.

Other adverse effects include weight gain resulting from increased appetite, partial or complete hair loss, tremor, paraesthesia, drowsiness and ataxia.

Sedation is particularly common when the drug is used in combination with phenobarbital.

Drug interactions

Plasma concentrations of phenobarbital may rise by up to 500 per cent when valproic acid is given concurrently, presumably as a result of hepatic enzyme inhibition. All patients receiving concomitant barbiturate therapy should be closely monitored for signs of neurological toxicity.

A more complex interaction occurs with phenytoin resulting in a transient increase followed by a subsequent reduction in serum concentrations of phenytoin occasionally resulting in seizure breakthrough.

Concomitant use of monoamine oxidase inhibitors can suppress central nervous function and lower the seizure threshold.

Because of a possible prolongation of bleeding time caution is also indicated in patients taking large doses of oral anticoagulants or acetylsalicylic acid.

Ketonic metabolites may interfere with urine testing of inpatients with diabetes.

Overdosage

Overdosage may result in deep coma. However, recovery after ingestion of 30 g has been reported. Emesis and lavage are of value within a few hours of ingestion. Treatment is otherwise supportive. Assisted ventilation and forced diuresis, or dialysis may be necessary.

Storage

Valproic acid enteric-coated tablets should be kept in a tightly closed container, protected from light.