

cyanide is commonly used and effective but is time consuming and requires very strict safety precautions; authorised contractors must provide a certificate of clearance before re-entry to the aircraft is allowed. Disinfection and deratting procedures will be required on arrival if a person suffering from plague has been on board.

Next week's article covers further aspects of airline operations—aircrew schedules and emergency considerations.

References

- ¹ Anonymous. *Occupational health and safety in civil aviation*. Geneva: International Labour Office, 1977:5.
- ² Anonymous. World scheduled traffic increases. *Flight International* 1983 Jan 15;123:113.
- ³ Preston FS. An outbreak of gastroenteritis in aircrew. *Aviat Space Environ Med* 1968;39:519-21.
- ⁴ Peffers ASR. Food sanitation and air safety. *Aviat Space Environ Med* 1976;46:1107-8.
- ⁵ Bailey J. *Guide to hygiene and sanitation in aviation*. Geneva: World Health Organisation, 1977.
- ⁶ *The food hygiene (general) regulations 1970. Statutory instruments 1970, part II, section 2, Nos 1013 to 1281*. London: HMSO, 1970; 3940-55.
- ⁷ WHO. *International standards for drinking water*. 3rd ed. Geneva: World Health Organisation, 1971.
- ⁸ Rondle CJM, Ramesh B, Krahn JB, Sherriff R. Cholera: possible infection from aircraft effluent. *J Hyg (Camb)* 1978;81:361-71.
- ⁹ Turner AC. Fever in the international traveller. *Medicine (Oxford)* 1981; 1:83-6.
- ¹⁰ WHO. *International health regulations (1969)*. 2nd annotated edition. Geneva: World Health Organisation, 1974.
- ¹¹ Perin M. Transportation in commercial aircraft of passengers having contagious diseases. *Aviat Space Environ Med* 1976;47:1109-13.

New Drugs

Anticonvulsant drugs

D L W DAVIDSON

A physician now may be understandably uncertain about which anticonvulsant drug to choose from the many available. The older drugs, phenytoin, phenobarbitone, and primidone, may be used wisely with some understanding of their pharmacokinetics, measurement of serum drug concentration, and, when possible, the use of one anticonvulsant only. The choice was extended with the introduction of ethosuximide in the 1950s, diazepam and carbamazepine in the '60s, and clonazepam, valproate, and chlormethiazole in the '70s. In this review the main points in the pharmacology and use of the newer drugs are discussed. The doses and costs are summarised in table I, which includes information regarding the older drugs for comparison. The management of seizures in the neonatal period and early childhood is not considered.

Carbamazepine

Carbamazepine has a tricyclic structure, and like all anticonvulsants the mechanism of action is poorly understood. It now has well established effects in preventing tonic-clonic (grand mal) and partial seizures—for instance, temporal lobe epilepsy—but no effect on absence attacks (petit mal). It is readily absorbed from the gut and is not available for parenteral use. The peak serum concentration occurs four to six hours after a single dose. This is important as peak concentrations may be associated with transient adverse effects. The half life is about 35 hours at the start of treatment, and therefore it takes about seven days—that is, four to five half lives—to reach a steady state on maintenance treatment. As carbamazepine is

metabolised in the liver impaired excretion in renal failure is not a problem. Carbamazepine stimulates its own metabolism. In the first four weeks after starting treatment the half life shortens, and the dose needs to be increased to maintain anticonvulsant effects. Thus 100 or 200 mg twice daily may be given at the start and increased at intervals of one to two weeks to a maintenance dose (table I). Some important drug interactions may occur through hepatic metabolism. Serum concentrations of carbamazepine may fall with the introduction of phenytoin or barbiturates, which induce the hepatic enzymes. The induction of liver metabolism by carbamazepine may reduce the efficacy of oral contraceptives and may increase the metabolism of warfarin or dicoumarol.

The plasma protein binding of carbamazepine is 70-80%, less than that for phenytoin and valproate, and it is less prone to displacement by other drugs so that drug interactions on this basis are seldom important. The "therapeutic" or "optimal range" of serum concentrations is quoted as between 25 and 50 $\mu\text{mol/l}$ (6-12 $\mu\text{g/ml}$) but, as with other anticonvulsant assays, the range should be used only as a guide to treatment. The lower end of this optimal range is poorly defined for seizures may be controlled with serum concentrations below the quoted range, and the dose should not be increased further. The upper level is also poorly defined as some patients may tolerate higher concentrations without adverse effects. Nevertheless, the assays are useful as a guide to treatment if seizures are uncontrolled for lower concentrations may occur from poor compliance or rapid metabolism or the concentration may be adequate indicating a drug failure. Serum concentrations are also useful if multiple drugs are used because drug interactions may produce complex changes. There is a linear increase in serum concentrations with dosage of carbamazepine, in contrast to phenytoin where toxicity may rapidly develop with small increments above the therapeutic range because the metabolism of phenytoin becomes saturated. Some paediatric centres use salivary estimations as these correlate well with the concentration of unbound carbamazepine in the serum.

Section of Neurology, Department of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY

D L W DAVIDSON, MB, FRCPD, consultant neurologist

In pregnancy increasing doses may be needed towards term. Some patients have had uneventful pregnancies while taking carbamazepine, but its possible teratogenic effects still have to be studied adequately. Carbamazepine does not enter the breast milk in sufficient quantities to have important effects on the neonate.

The main adverse effects are on the central nervous system. Drowsiness may occur, although less commonly than with barbiturates and phenytoin. Indeed, some patients improve in mood and alertness. It is still not clear whether this beneficial effect is inherent in the drug's action or whether it is seen only when the more sedative anticonvulsants are withdrawn. Dizziness, ataxia, and nystagmus are also early effects, as with phenytoin. Various transient visual disturbances, including diplopia, may occur around the time of the peak serum concentration. Some patients are unduly sensitive to these adverse central effects of carbamazepine at the start of treatment, and it is wise to introduce carbamazepine gradually. As with phenytoin, overdosage with carbamazepine may cause an increase in the number of seizures.

Alimentary disturbances are uncommon. Various rashes may occur. Carbamazepine does not produce the coarsening of the facial features and hirsutism that may occur with phenytoin. Serious marrow depression was reported soon after carbamazepine was introduced, but recent experience has not substantiated these observations. Reversible leucopenia and thrombocytopenia occur more commonly, however. Carbamazepine may have an antidiuretic hormone stimulating effect in high dose, but clinical problems of water intoxication are rare.

Valproate

Valproic acid and its sodium salt, sodium valproate, have a broad range of anticonvulsant effects. Valproate, like ethosuximide, is effective for absence attacks but it may also prevent tonic-clonic seizures. It is less useful against partial (focal) seizures than generalised seizures, like all anticonvulsants. The clinical impression that carbamazepine is more effective than valproate for partial seizures has not been fully studied, and some recent evidence shows that valproate may be as effective as phenytoin for such seizures.

Valproate is rapidly absorbed, with a peak concentration occurring one to four hours after ingestion. It is conjugated in the liver and has a short half life (table I). As it is 80-90% bound to plasma proteins, drug interactions may occur. For example, if a patient who is already taking phenytoin and has serum concentrations in the optimal range starts taking valproate phenytoin toxicity may result from displacement effects. As with phenytoin, plasma binding is reduced in chronic renal failure. Drug interactions occur in the liver also—for instance, valproate may increase serum phenobarbitone concentrations substantially, probably by inhibiting phenobarbitone metabolism. It may also interact with phenobarbitone and clonazepam at receptor sites.

Many biochemical laboratories now estimate the serum concentrations and quote optimal ranges (table I). The relation of these serum concentrations to the therapeutic action of valproate, however, is less clear than for the other anticonvulsants, for there is clinical and experimental evidence that valproate has a much longer action than its half life suggests. A practical implication of this long action is that valproate may be effective in a regimen of a twice daily or even a once daily dose despite the rapid clearance from the blood.

An attractive feature of valproate is that sedative effects are fewer than with barbiturates and phenytoin, and probably fewer than with carbamazepine. Most adverse effects are mild and reversible. Oesophageal discomfort and nausea still occur, although they have been reduced by the manufacturers' change to enteric coated formulations. Taking the tablets at mealtimes may help. Diarrhoea may occur. Weight gain may be a problem. Mild tremor sometimes occurs at high dosages. Transient alopecia may occur and, curiously, the hair may regrow curly. Platelet numbers and adhesiveness may be reduced, producing a tendency to bleed, but serious haemorrhagic complications are rare. Preliminary evidence suggests that the use of valproate in early pregnancy may be associated with deformities of the spinal cord.

The most serious adverse effects are the rare idiosyncratic responses producing severe or fatal hepatic toxicity and the even less common pancreatitis. Fatal hepatic toxicity is more likely to occur in children than adults, in patients with pre-existing neurological or metabolic disorders, and within six months of the start of treatment. It is not clear whether routine

TABLE I—Comparison of oral anticonvulsant drugs

Anticonvulsant	Maintenance dose range	Optimal serum concentrations $\mu\text{mol/l}$ ($\mu\text{g/ml}$)	Half life (hours)	Annual cost* (common daily dose used in calculation)	Important adverse effects
Carbamazepine (Tegretol)	A 300–1600 mg (start at 100 mg twice daily, increase over 4 weeks) C 9–20 mg/kg	25–50 (6–12)	25–50 Initially chronic treatment 10–30 C 5–30	£59 (600 mg)	Drowsiness, dizziness, visual disturbances, rashes, leucopenia
Clonazepam (Rivotril)	A 1.5–8 mg (start at 0.5 mg twice daily dose, increase over 2–4 weeks) C 0.5–6 mg	Not generally available	20–60	£38 (6 mg)	Drowsiness, unsteadiness, behaviour disorders, bronchial hypersecretion
Ethosuximide (Zarontin)	A 500–2000 mg (start at 250 mg twice daily) C 250–1000 mg	300–750 (40–100)	A 30–70 C 30	£83 (1000 mg)	Nausea, vomiting, tiredness, dizziness, mood disturbances, leucopenia, rashes
Phenytoin (Epanutin)	A 150–600 mg (start at 100 mg twice daily) C 5–8 mg/kg	40–80 (10–20)	A 10–60 (longer with higher dose) C 5–12	£26 (300 mg)	Drowsiness, ataxia, gum hypertrophy, hirsutism, acne, facial coarsening
Phenobarbitone	A 60–240 mg (start at 30 mg daily) C 30–180 mg	80–180 (15–40)	A 70–120 C 40–70	£13 (180 mg)	Drowsiness, behaviour disorders
Primidone (Mysoline)	A 250–1500 mg (start at 125 mg daily) C 125–1000 mg (low dose initially)		4–11 (phenobarbitone metabolite as above)	£19 (£1000 mg)	Drowsiness, behaviour disorders
Valproate (Epilim)	A 400–2600 mg (start at 200 mg twice daily) C 20–30 mg/kg	350–700 (50–100)	A 6–15 C 4–14	£103 (800 mg)	Nausea, weight gain, tremor, alopecia, bleeding tendency, hepatotoxicity (rare)

* Approximate cost based on proprietary preparation. A = Adults; C = Children.

TABLE II—Choice of anticonvulsant drugs

Type of seizure	First choices	Alternatives
Partial (focal) including temporal lobe and Jacksonian	Carbamazepine, phenytoin	Clonazepam, valproate, primidone, phenobarbitone
Tonic-clonic (grand mal)	Valproate, phenytoin, carbamazepine	Clonazepam, primidone, phenobarbitone
Absence only (petit mal)	Ethosuximide	Valproate, clonazepam
Absence and other seizures	Valproate	Clonazepam, ethosuximide plus phenytoin or carbamazepine, nitrazepam
Myoclonus	Valproate, clonazepam	Nitrazepam
Status epilepticus	Intravenous diazepam or clonazepam	Chlormethiazole, phenytoin, or thiopentone intravenously, paraldehyde intramuscularly

assessment of liver function tests helps to predict this problem, but patients who develop nausea, anorexia, abdominal pain, or jaundice within a few months of starting valproate should stop taking the drug immediately.

Benzodiazepines

Diazepam, clonazepam, and nitrazepam have important anticonvulsant effects. Diazepam is important for the control of status epilepticus, but its anticonvulsant effects are not sustained on oral medication. Clonazepam may be used parenterally for status epilepticus and taken by mouth for absence attacks, tonic-clonic seizures, and myoclonus. It is less effective in preventing partial seizures than generalised seizures.

Clonazepam is completely absorbed after ingestion and is metabolised in the liver. The half life is long and declines during chronic treatment. Drug interactions seldom present problems. Drowsiness, fatigue, and slight dizziness are the commonest adverse effects and may be reduced by the gradual introduction of clonazepam. Irritability and behavioural disturbances may occur in children similar to those that sometimes occur with barbiturates. Bronchial and salivary hypersecretion may occur with parenteral use.

Nitrazepam may also be used in children with refractory atypical absence attacks, or in myoclonus.

Chlormethiazole

Chlormethiazole (Heminevrin) is derived from the thiazole moiety of the thiamine molecule and is used intravenously in treating status epilepticus. As it has a short half life of about 50 minutes, side effects are rapidly reversible. It is relatively free from hypotensive and respiratory depressant effects but it may potentiate the respiratory depressant effect of barbiturates. It is best used when intensive care facilities are available. It is infused as a solution of 8 mg/ml (40–100 ml) in 5–10 minutes and thereafter according to the clinical response.

Choice of anticonvulsant drug

The aim of treatment should be to try to control the seizures with a single drug. But which drug? As the main choices seem similarly (in)effective the physician has to consider the adverse effects and costs (table II). Many studies suggest that the drugs used for partial and for tonic-clonic seizures are all of roughly similar effectiveness, although extensive carefully controlled trials are lacking for comparing some anticonvulsants. About 70–80% of patients with tonic-clonic seizures and only 30–40% of patients with partial seizures may be controlled with anticonvulsants. If low costs are essential then phenytoin is clearly the treatment of choice, with phenobarbitone or primidone as an alternative. But the quality of the mental function and learning ability, particularly in children and adolescents, is

important and thus carbamazepine or valproate may be preferred in many patients. Furthermore, hirsutism, acne, and facial coarsening make phenytoin less satisfactory in young women. Fear of hepatotoxicity, rare but disastrous, may restrict the use of valproate.

I prefer to use the following. For *partial seizures*, most commonly complex partial seizures (temporal lobe epilepsy) and for *secondary tonic-clonic seizures* in children and adolescents, carbamazepine is preferred to avoid the subtle dulling of mental function that may occur with the older drugs. In older patients phenytoin is usually satisfactory. When *primary tonic-clonic seizures* (grand mal) occur only in young people, valproate is preferred; phenytoin is used in older patients. If absence attacks or myoclonus also occur in addition to tonic-clonic seizures valproate is clearly the treatment of choice, but clonazepam is an important alternative. Phenobarbitone and primidone are second line drugs because of sedation and behaviour disorders.

When *absence attacks* (petit mal) only occur, ethosuximide may be preferable to valproate only because of hepatotoxicity with valproate, but if there are other types of seizures valproate becomes preferable despite the hepatic risks.

Myoclonus may be treated either with valproate or, if ineffective, with clonazepam. Other anticonvulsants are much less effective.

For *status epilepticus* intravenous diazepam (0.15–0.25 mg/kg at a rate of 2.5 mg per minute) or clonazepam (adults 1 mg, children 0.5 mg over 30 seconds) are the treatments of choice. If control is not rapidly achieved it is better to change to another regimen than to continue to load with benzodiazepines. The choices are intravenous chlormethiazole or intravenous phenytoin, for paraldehyde has declined in use. Phenytoin, given as a loading intravenous infusion of 10–15 mg/kg at a rate of under 50 mg/minute (not intramuscularly), has the advantage that the transition to oral anticonvulsants is easier, whereas other anticonvulsants have to be introduced for maintenance treatment after intravenous chlormethiazole. Intravenous thiopentone administered in an intensive care unit, with facilities for ventilation and preferably for electroencephalographic monitoring also, is a last resort, and is usually effective.

Bibliography

- Bruni J, Wilder BJ. Valproic acid. Review of a new anti-epileptic drug. *Arch Neurol* 1979;36:393–8.
- A good review dealing with the possible mode of action, pharmacology, and clinical use of this drug.
- Edie MJ, Tyrer JH. *Anticonvulsant therapy*. 2nd ed. Edinburgh: Churchill Livingstone, 1980.
- A thorough recent review of anticonvulsants.
- Tyrer JH, ed. The treatment of epilepsy. In: *Current status of modern therapy*. Vol 5. Lancaster: MTP Press, 1980.
- An excellent multiauthor book dealing with general aspects of management of epilepsy as well as drug treatment.
- Laidlaw J, Riches A. *A textbook of epilepsy*. Edinburgh: Churchill Livingstone, 1982.
- An up to date authoritative book on epilepsy, recommended for the discussion of other aspects of epilepsy as well as drug treatment.