

abnormal movements, and for the treatment of panic disorder (see Psychiatric Disorders, below).

For **epilepsy** and **myoclonus** treatment is started with small doses that are progressively increased to an optimum dose according to response. Total daily doses may initially be taken in 3 or 4 divided doses; however, once the maintenance dose has been reached, the daily amount may be given as a single dose at night. In the UK the initial oral dose is 1 mg (500 micrograms in the elderly) at night for 4 nights gradually increased over 2 to 4 weeks to a usual maintenance dose of 4 to 8 mg daily; it is recommended that the total dose should not exceed 20 mg daily. Dosage recommendations in the USA are generally similar although initial doses of up to 1.5 mg daily are permitted and dosage increments of 0.5 to 1 mg every 3 days are recommended. There is little value in routinely monitoring plasma-clonazepam concentrations.

Clonazepam may be an alternative to other benzodiazepines in the emergency management of **status epilepticus**. The usual dose is 1 mg given by slow intravenous injection over at least 2 minutes or by intravenous infusion, repeated if necessary to a maximum total dose of 20 mg.

For doses in children, see below.

As with other antiepileptics, withdrawal of clonazepam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465 and above.

In the treatment of **panic disorder**, clonazepam is given in an initial oral dose of 250 micrograms twice daily. This may be increased after 3 days to a total of 1 mg daily; a few patients may benefit from further increases, up to a maximum of 4 mg daily. In order to minimise drowsiness, clonazepam may be taken as a single dose at bedtime. Withdrawal should again be gradual.

Administration. Serum concentrations of clonazepam after buccal, intranasal, or intravenous dosage were measured in a crossover study¹ in 7 healthy males. The results showed that intranasal clonazepam may offer an alternative to buccal use in patients with serial seizures but the initial concentrations were too low to recommend its use as an alternative to intravenous clonazepam in the management of status epilepticus. The nasal formulation used in this study contained dimethyl-β-cyclodextrin as a solubiliser and absorption enhancer.

1. Schols-Hendriks MWG, *et al.* Absorption of clonazepam after intranasal and buccal administration. *Br J Clin Pharmacol* 1995; **39**: 449–51.

Administration in children. For **epilepsy** and **myoclonus** treatment with clonazepam is started with small doses that are progressively increased to an optimum dose according to response. Total daily doses are taken in 3 divided doses; however, once the maintenance dose has been reached, the daily amount may be given as a single dose at night. Alternatively, the *BNFC* suggests giving the initial dose at night for 4 nights and gradually increasing it over 2 to 4 weeks. In the UK, the recommended initial oral daily dose is up to 250 micrograms for infants and children aged up to 5 years, or up to 500 micrograms for older children. The following usual maintenance doses are given according to age:

- neonate to 1 year (although the *BNFC* recommends a minimum age of 1 month): 0.5 to 1 mg daily
- 1 to 5 years: 1 to 3 mg daily
- 5 to 12 years: 3 to 6 mg daily

Older children may be given the usual adult dose (see above).

If control of childhood epilepsy ceases to be adequate with clonazepam, the dose may be increased, or treatment interrupted for 2 or 3 weeks. The *BNFC* states that the UK injection formulation (*Rivotril*; Roche, UK) can be given orally if necessary; this may not apply to other injection formulations available elsewhere.

In the USA, doses may be given according to body weight. Infants and children aged up to 10 years or weighing up to 30 kg may be given an initial daily dose of 10 to 30 micrograms/kg (maximum 50 micrograms/kg) in 2 or 3 divided doses. This may be increased by a total of 250 to 500 micrograms every 3 days to a maintenance dose of 100 to 200 micrograms/kg daily given in 3 divided doses.

In the emergency management of **status epilepticus**, clonazepam is used as an alternative to other benzodiazepines. The usual dose in children is 500 micrograms given by slow intravenous injection or by intravenous infusion. Alternatively, the

BNFC suggests giving the following doses by slow intravenous injection over at least 2 minutes according to age:

- neonates: 100 micrograms/kg, repeated if necessary after 24 hours
- 1 month to 12 years: 50 micrograms/kg (maximum 1 mg), repeated if necessary

Older children may be given the usual adult dose.

In children aged over 1 month, these doses by injection may be followed by an intravenous infusion of 10 micrograms/kg per hour, adjusted according to response to a maximum of 60 micrograms/kg per hour.

Extrapyramidal disorders. Clonazepam may be of benefit in some extrapyramidal disorders. It has been tried in the management of patients with *tic disorders* such as *Tourette's syndrome* (p.954) but evidence of efficacy from controlled studies is limited.¹ Some use clonazepam in preference to haloperidol² since it does not carry the risk of tardive dyskinesia associated with such antipsychotics and a case report³ described the successful use of clonazepam for haloperidol-induced tardive Tourette's syndrome in an adult patient. There is also limited evidence of benefit with clonazepam in antipsychotic-induced *akathisia*^{4,5} and *tardive dyskinesia*^{6,7} (see under Extrapyramidal Disorders, p.971), and of improvement in *dysarthria* in a study in patients with parkinsonism.⁸

- Goetz CG. Clonidine and clonazepam in Tourette syndrome. *Adv Neurol* 1992; **58**: 245–51.
- Truong DD, *et al.* Clonazepam, haloperidol, and clonidine in tic disorders. *South Med J* 1988; **81**: 1103–5.
- Reid SD. Neuroleptic-induced tardive Tourette treated with clonazepam: a case report and literature review. *Clin Neuropharmacol* 2004; **27**: 101–4.
- Kutcher S, *et al.* Successful clonazepam treatment of neuroleptic-induced akathisia in older adolescents and young adults: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 1989; **9**: 403–6.
- Pujalte D, *et al.* A double-blind comparison of clonazepam and placebo in the treatment of neuroleptic-induced akathisia. *Clin Neuropharmacol* 1994; **17**: 236–42.
- Thaker GK, *et al.* Clonazepam treatment of tardive dyskinesia: a practical GABA-mimetic strategy. *Am J Psychiatry* 1990; **147**: 445–51.
- Shapleske J, *et al.* Successful treatment of tardive dystonia with clonazepam and clonazepam. *Br J Psychiatry* 1996; **168**: 516–18.
- Biary N, *et al.* A double-blind trial of clonazepam in the treatment of parkinsonian dysarthria. *Neurology* 1988; **38**: 255–8.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976. Clonazepam may also be of value, especially in neurogenic hiccups.

Neuropathic pain. The management of *phantom limb pain* (p.9) can be difficult, and tricyclic antidepressants and antiepileptics are used for the neuropathic components of the pain. Rapid and marked pain relief was achieved in 2 patients with lancinating phantom limb pain after treatment with clonazepam with or without amitriptyline.¹

Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p.9), clonazepam may be used in carbamazepine-intolerant patients.

- Bartusch SL, *et al.* Clonazepam for the treatment of lancinating phantom limb pain. *Clin J Pain* 1996; **12**: 59–62.

Psychiatric disorders. Although the risk of dependence with benzodiazepines may outweigh their benefits in panic disorder (p.952), clonazepam has been used for the treatment of panic disorder with or without agoraphobia, and reported benefit in such patients¹ suggests a similar action to alprazolam. A literature review² evaluated the use of clonazepam in a range of psychiatric disorders and found that it may also be effective in the treatment of social anxiety disorder (see Phobic Disorders, p.953) although further studies are warranted. There was evidence to suggest that clonazepam may be useful in acute mania (p.372) and for the augmentation of antidepressant therapy with SSRIs in depression (p.373). A study³ found that augmentation was significantly more effective with a daily dose of 3 mg of clonazepam than with lower doses.

- Davidson JRT, Moroz G. Pivotal studies of clonazepam in panic disorder. *Psychopharmacol Bull* 1998; **34**: 169–74.
- Nardi AE, Perna G. Clonazepam in the treatment of psychiatric disorders: an update. *Int Clin Psychopharmacol* 2006; **21**: 131–42.
- Morishita S, Aoki S. Clonazepam in the treatment of prolonged depression. *J Affect Disord* 1999; **53**: 275–8.

Sleep-associated movement disorders. Treatment of sleep-associated movement disorders (p.958) including sleep behaviour disorder, restless legs syndrome, and periodic limb movements in sleep is largely empirical, but benzodiazepines such as clonazepam are often used.¹ Small studies have provided some evidence for benefit with clonazepam therapy in these disorders,^{2,4} including bruxism.⁵

- Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med* 1996; **100**: 333–7.
- Montagna P, *et al.* Clonazepam and vibration in restless legs syndrome. *Acta Neurol Scand* 1984; **69**: 428–30.

- Peled R, Lavie P. Double-blind evaluation of clonazepam on periodic leg movements in sleep. *J Neurol Neurosurg Psychiatry* 1987; **50**: 1679–81.
- Saletu M, *et al.* Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *Eur Neuropsychopharmacol* 2001; **11**: 153–61.
- Saletu A, *et al.* On the pharmacotherapy of sleep bruxism: placebo-controlled polysomnographic and psychometric studies with clonazepam. *Neuropsychobiology* 2005; **51**: 214–25.

Stiff-man syndrome. Clonazepam has been used as an alternative to diazepam in the management of stiff-man syndrome (see under Muscle Spasm, p.993) and is reported¹ to be effective for familial startle disease, a rare congenital form of stiff-man syndrome.

- Ryan SG, *et al.* Startle disease, or hyperekplexia: response to clonazepam and assignment of the gene (STHE) to chromosome 5q by linkage analysis. *Ann Neurol* 1992; **31**: 663–8.

Tinnitus. Clonazepam is one of many drugs that have been tried in tinnitus (p.1866), but although it has been reported to be effective in some patients it is rarely used because of problems with adverse effects.

References.

- Gananca MM, *et al.* Clonazepam in the pharmacological treatment of vertigo and tinnitus. *Int Tinnitus J* 2002; **8**: 50–3.
- Albertino S, *et al.* Pulsatile tinnitus: treatment with clonazepam and propranolol. *Rev Bras Otorrinolaringol (Engl Ed)* 2005; **71**: 111–13.

Preparations

BP 2008: Clonazepam Injection;

USP 31: Clonazepam Oral Suspension; Clonazepam Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Alerion; Ciclox; Clonabay; Clonagin; Clonax; Clonazen 2; Cloner; Diocam; Edictum; Felanor; Flozepam; Induzepam; Leptic; Miozepam; Neuryl; Oliner; Placidax; Riudonax; Rivotril; Sedovanon; Sensaron; Solifidin; **Aust.:** Paxam; **Austria:** Austria; Rivotril; **Belg.:** Rivotril; **Braz.:** Clonotril; Clonapax; Epileptil; Navotrax; Rivotril; Uni Clonazepam; **Canad.:** Clonapam; Rivotril; **Chile:** Acepran; Clonapam; Clonex; Clozanil; Crismol; Neuryl; Ravotril; Ropsil; Valpac; **Cz.:** Anteplepsin; Rivotril; **Denm.:** Rivotril; **Fin.:** Rivatril; **Fr.:** Rivotril; **Ger.:** Anteplepsin; Rivotril; **Gr.:** Rivotril; **Hong Kong:** Rivotril; **Hung.:** Clonapam; Clonogal; Rivotril; **India:** Epitril; Epizam; Ozepam; **Indon.:** Rivotril; **Irl.:** Rivotril; **Israel:** Clonex; Rivotril; **Ital.:** Rivotril; **Malaysia:** Rivotril; **Mex.:** Kenoket; Kiadex; Rivotril; Zymanta; **Neth.:** Rivotril; **Norw.:** Rivotril; **NZ:** Paxam; Rivotril; **Philipp.:** Rivotril; **Pol.:** Rivotril; **Port.:** Rivotril; **S.Afr.:** Rivotril; **Spain:** Rivotril; **Swed.:** Iktoril; **Switz.:** Rivotril; **Thai.:** Povanil; Rivotril; **Turk.:** Rivotril; **UK:** Rivotril; **USA:** Klonopin; **Venez.:** Rivotril.

Ethadione

Etadiona. 3-Ethyl-5,5-dimethyl-2,4-oxazolidinedione.

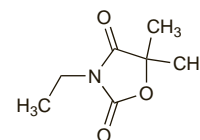
Этадион

$C_7H_{11}NO_3$ = 157.2.

CAS — 520-77-4.

ATC — N03AC03.

ATC Vet — QN03AC03.



Profile

Ethadione is an oxazolidinedione antiepileptic that has been given orally to treat epilepsy in patients with absence seizures resistant to other therapy.

Preparations

Ethosuximide (BAN, USAN, rINN)

CI-366; CN-10395; Ethosuximid; Éthosuximide; Ethosuximidum; Etoşüksimid; Etoşüksimidas; Etoşüksimidi; Etoşüksimidi; Etoşüksimid; Etoşüksimide; Etoşüksimide; NSC-64013; PM-671. 2-Ethyl-2-methylsuccinimide.

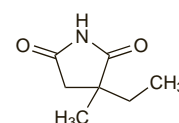
Этосуксимида

$C_7H_{11}NO_2$ = 141.2.

CAS — 77-67-8.

ATC — N03AD01.

ATC Vet — QN03AD01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.* and *US*. **Ph. Eur. 6.2** (Ethosuximide). A white or almost white powder or waxy solid. It exhibits polymorphism. Freely soluble in water;