very soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Ethosuximide). A white to off-white crystalline powder or waxy solid, having a characteristic odour. Freely soluble in water and in chloroform; very soluble in alcohol and in ether; very slightly soluble in petroleum spirit. Store in airtight containers.

Adverse Effects and Treatment

Gastrointestinal adverse effects including nausea, vomiting, diarrhoea, anorexia, gastric upset, and abdominal pain occur quite often with ethosuximide. Other effects that may occur include headache, fatigue, lethargy, drowsiness, dizziness, ataxia, hiccup, and mild euphoria.

More rarely dyskinesias, personality changes, depression, psychosis, sleep disturbances including night terrors, skin rashes, erythema multiforme or Stevens-Johnson syndrome, SLE, photophobia, gum hypertrophy, tongue swelling, myopia, increased libido, and vaginal bleeding have been reported. There are a few reports of blood disorders including eosinophilia, leucopenia, agranulocytosis, thrombocytopenia, pancytopenia, and aplastic anaemia; fatalities have occurred.

Abnormal renal and liver function values have been recorded.

Effects on mental function. For the effects of antiepileptic therapy on cognition and mood, including the risk of suicidal ideation, see p.468.

Precautions

Ethosuximide should be used with caution in patients with impaired hepatic or renal function. Licensed product information recommends regular hepatic and renal-function tests (and some suggest blood counts) during treatment with ethosuximide, although the practical value of such monitoring has been questioned. Patients or their carers should be told how to recognise signs of blood toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop.

Care is required when withdrawing ethosuximide therapy—see also Uses and Administration, below.

Breast feeding. Ethosuximide is distributed in significant amounts into breast milk; hyperexcitability and poor suckling have been reported in the infant. Although licensed product information recommends that breast feeding should be avoided, the American Academy of Pediatrics[1] considers that ethosuximide is usually compatible with breast feeding.

For further comment on antiepileptic therapy and breast feeding, see p.467.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Porphyria. Ethosuximide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Antibacterials. *Isoniazid* raises the plasma concentration of ethosuximide and increases the risk of toxicity. Psychotic behaviour has been reported[1] in a patient stabilised on ethosuximide and sodium valproate, after the introduction of isoniazid. Serum-ethosuximide concentrations rose substantially until both ethosuximide and isoniazid were stopped.

1. van Wieringen A, Vrijlandt CM. Ethosuximide intoxication caused by interaction with isoniazid. *Neurology* 1983; **33:** 1227–8.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of ethosuximide by lowering the convulsive threshold.

Antiepileptics. Since ethosuximide has a limited spectrum of antiepileptic action, patients with mixed seizure syndromes may require addition of other antiepileptics. *Carbamazepine*, *phenobarbital*, and *phenytoin* have all been shown[1] to increase the clearance of ethosuximide and thus reduce plasma concentrations. This interaction is likely to be clinically relevant and higher ethosuximide dosages may be necessary to achieve therapeutic drug levels. The effect of *valproic acid* on ethosuximide concentrations is unclear. One study[2] showed a marked increase in serum ethosuximide concentrations once valproate was added to combination therapies; increases in ethosuximide concentrations have also been noted in healthy subjects when taken with valproic acid.[3] Conversely, other studies have reported reductions[4] or no significant changes in serum ethosuximide concentrations[5,6] with valproic acid. For the effect of ethosuximide on valproic acid, see p.511.

1. Giaccone M, *et al.* Effect of enzyme inducing anticonvulsants on ethosuximide pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* 1996; **41:** 575–9.
2. Mattson RH, Cramer JA. Valproic acid and ethosuximide interaction. *Ann Neurol* 1980; **7:** 583–4.
3. Pisani F, *et al.* Valproic acid-ethosuximide interaction: a pharmacokinetic study. *Epilepsia* 1984; **25:** 229–33.
4. Battino D, *et al.* Ethosuximide plasma concentrations: influence of age and associated concomitant therapy. *Clin Pharmacokinet* 1982; **7:** 176–80.
5. Fowler GW. Effect of dipropylacetate on serum levels of anticonvulsants in children. *Proc West Pharmacol Soc* 1978; **21:** 37–40.
6. Bauer LA, *et al.* Ethosuximide kinetics: possible interaction with valproic acid. *Clin Pharmacol Ther* 1982; **31:** 741–5.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of ethosuximide by lowering the convulsive threshold.

Pharmacokinetics

Ethosuximide is readily absorbed from the gastrointestinal tract and extensively hydroxylated in the liver to its principal metabolite which is reported to be inactive. Ethosuximide is excreted in the urine mainly in the form of its metabolites, either free or conjugated, but about 12 to 20% is also excreted unchanged.

Ethosuximide is widely distributed throughout the body, but is not significantly bound to plasma proteins. A half-life of about 40 to 60 hours has been reported for adults with a shorter half-life of about 30 hours in children.

Monitoring of plasma concentrations has been suggested as an aid in assessing control and the therapeutic range of ethosuximide is usually quoted as being 40 to 100 micrograms/mL (about 300 to 700 micromoles/litre); concentrations in saliva and tears have also been measured.

Ethosuximide crosses the placental barrier, and is distributed into breast milk.

The pharmacokinetics of ethosuximide are affected by use with other antiepileptics (see under Interactions, above).

Uses and Administration

Ethosuximide is a succinimide antiepileptic used in the treatment of absence seizures (below). It may also be used for myoclonic seizures. Ethosuximide is ineffective against tonic-clonic seizures and may unmask them if given alone in mixed seizure types.

A plasma-ethosuximide concentration of 40 to 100 micrograms/mL (about 300 to 700 micromoles/litre) appears to be generally necessary. The initial dose is 500 mg daily by mouth. The dosage is then adjusted in steps of 250 mg every 4 to 7 days, according to response. Control of seizures is usually produced with a daily dose of 1 to 1.5 g, although some patients may require doses of up to 2 g; strict supervision is necessary when the dose exceeds 1.5 g. Daily doses at the higher end of the range should be given in 2 divided doses.

For doses in children, see below.

As with other antiepileptics, withdrawal of ethosuximide 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.

Administration in children. Ethosuximide may be used in the treatment of absence (petit mal) seizures and for myoclonic seizures in infants and children. In the UK, the following recommended oral doses are given according to age:

- up to 6 years of age: an initial dose of 250 mg daily, increased gradually in small steps every few days to a usual dose of 20 mg/kg daily; licensed information for one product (*Emeside; Chemidex, UK*) recommends that the dose should not exceed 1 g. (Similar dosages are recommended in the USA for children aged between 3 to 6 years). The *BNFC* suggests giving the daily dose as 2, or if necessary 3, divided doses
- aged 6 years and above: usual adult doses (see above)

Epilepsy. Ethosuximide is a drug of choice in the treatment of absence seizures; it may also be used for myoclonic, atonic, and tonic seizures but is ineffective in other forms of epilepsy (p.465). Ethosuximide may be given with other antiepileptics in the treatment of mixed-seizure syndromes that include absences. It has been suggested that ethosuximide may provoke tonic-clonic seizures, but there is not a great deal of evidence for this. One early report indicated that 22 of 85 patients receiving a regimen of ethosuximide, mesuximide, and trimethadione for absence seizures developed tonic-clonic seizures[1] and another of similar vintage reported exacerbation of mixed-seizure types in 7 patients receiving ethosuximide.[2] However, it is recognised that patients with absence seizures have a high incidence of generalised tonic-clonic seizures[3] and it would presumably be difficult to distinguish such attacks from any putative effect of ethosuximide. Furthermore, ethosuximide is not effective against tonic-clonic seizures, and in patients with mixed-seizure types it might be expected to unmask the non-absence components of the disease.

Ethosuximide has also been tried in the management of absence status epilepticus (p.469).

1. Friedel B, Lempp R. Grand-mal-Provokation bei der Behandlung kindlicher petit-mal mit Oxazolidinen oder Succinimiden und ihre therapeutischen Konsequenzen. *Z Kinderheilk* 1962; **87:** 42–51.
2. de Haas AML, Kuilman M. Ethosuximide (α-ethyl-α-methylsuccinimide) and grand mal. *Epilepsia* 1964; **5:** 90–6.
3. Glauser TA. Succinimides: Adverse Effects. In: Levy RG, *et al.*, eds. *Antiepileptic drugs* 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002; 658–64.

Preparations

BP 2008: Ethosuximide Capsules; Ethosuximide Oral Solution;
USP 31: Ethosuximide Capsules; Ethosuximide Oral Solution.

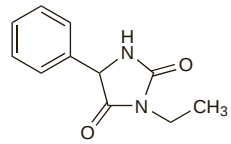
Proprietary Preparations (details are given in Part 3)
Arg.: Zarontin; ***Austral.:*** Zarontin; ***Austria:*** Petinimid; Suxinutin; ***Belg.:*** Zarontin; ***Canad.:*** Zarontin; ***Chile:*** Suxinutin; ***Cz.:*** Petinimid; Suxilep†; ***Denm.:*** Zarondan; ***Fin.:*** Suxinutin; ***Fr.:*** Zarontin; ***Ger.:*** Petnidan; Suxilep; Suxinutin†; ***Gr.:*** Zarontin; ***Hung.:*** Petnidan; Suxinutin†; ***Irl.:*** Zarontin; ***Israel:*** Zarontin†; ***Ital.:*** Zarontin; ***Mex.:*** Fluozoid; ***Neth.:*** Ethymal; Zarontin†; ***NZ:*** Zarontin; ***Pol.:*** Petinimid; ***Rus.:*** Suxilep (Суксилеп); ***S.Afr.:*** Zarontin; ***Spain:*** Zarontin†; ***Swed.:*** Suxinutin; ***Switz.:*** Petinimid; Suxinutin†; ***UK:*** Emeside; Zarontin; ***USA:*** Zarontin.

Ethotoin *(BAN, rINN)*

Éthotoïne; Ethotoinum; Etotoiini; Etotoin; Etotoína. 3-Ethyl-5-phenylhydantoin.

Этотоин

$C_{11}H_{12}N_2O_2$ = 204.2.
CAS — 86-35-1.
ATC — N03AB01.
ATC Vet — QN03AB01.



Pharmacopoeias. In *US.*

USP 31 (Ethotoin). A white crystalline powder. Insoluble in water; freely soluble in dehydrated alcohol and in chloroform; soluble in ether. Store in airtight containers.

Profile

Ethotoin is a hydantoin antiepileptic with actions similar to those of phenytoin (p.495), but it is reported to be both less toxic and less effective and is not commonly used in epilepsy (p.465).

Ethotoin is given orally for tonic-clonic and complex partial seizures in initial doses of up to 1 g daily, increased gradually at intervals of several days to 2 to 3 g daily, given in 4 to 6 divided doses after meals.

Administration. A study[1] of the pharmacokinetics of ethotoin given at more convenient intervals of every 8 hours.

1. Browne TR, Szabo GK. A pharmacokinetic rationale for three times daily administration of ethotoin (Peganone). *J Clin Pharmacol* 1989; **29:** 270–1.

Porphyria. Ethotoin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

USP 31: Ethotoin Tablets.

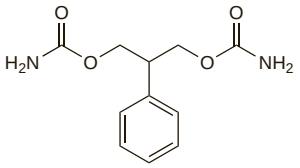
Proprietary Preparations (details are given in Part 3)
USA: Peganone.

Felbamate *(USAN, rINN)*

AD-03055; Felbamato; Felbamatum; W-554. 2-Phenyl-1,3-propanediol dicarbamate.

Фелбамат

$C_{11}H_{14}N_2O_4$ = 238.2.
CAS — 25451-15-4.
ATC — N03AX10.
ATC Vet — QN03AX10.



Adverse Effects

The most frequently reported adverse effects with felbamate are anorexia, weight loss, nausea and vomiting, rash, insomnia, headache, dizziness, somnolence, and diplopia. Aplastic anaemia or acute liver failure, sometimes fatal, have occurred rarely, and there have been reports of Stevens-Johnson syndrome.

Effects on the kidneys. A 15-year-old boy receiving up to 3 g of felbamate daily developed urethral obstruction due to formation of urethral stones composed of felbamate.[1] Records revealed that unidentified urinary crystals had been found in the patient's urine 2 years before presentation with acute urolithiasis.

For reports of crystalluria associated with felbamate overdosage, see below.

1. Sparagana SP, *et al.* Felbamate urolithiasis. *Epilepsia* 2001; **42:** 682–5.

Effects on mental function. For the effects of antiepileptic therapy on cognition and mood, including the risk of suicidal ideation, see p.468

Effects on the skin. Toxic epidermal necrolysis has been reported[1] in a patient 16 days after she started monotherapy with felbamate for partial complex seizures.

1. Travaglini MT, *et al.* Toxic epidermal necrolysis after initiation of felbamate therapy. *Pharmacotherapy* 1995; **15:** 260–4.

Overdosage. A 20-year-old woman presented with slurred speech and nausea 4 hours after ingesting 18 g of felbamate and 12 to 25 g of sodium valproate.[1] Over the next 4 to 5 hours she became combative, uncooperative, and progressively obtunded and eventually required endotracheal intubation and assisted ventilation. Peak plasma concentrations of 200 micrograms/mL for felbamate and 470 micrograms/mL for sodium valproate occurred 12 and 14 hours respectively after ingestion. Large quantities of macroscopic crystals, identified as containing felbamate, were noted in the urine 18 hours after ingestion and the patient developed renal failure. The crystalluria and renal failure responded to parenteral hydration. In another case report,[2] a 3-year-old child ingested 232 mg/kg of felbamate resulting in ataxia, vomiting, crystalluria, haematuria, and mild tachycardia. The plasma concentration of felbamate 15 hours after ingestion was 138 micrograms/mL. She was successfully treated with an infusion of sodium chloride 0.9% and intravenous metoclopramide; no renal impairment was seen.

1. Rengstorff DS, *et al.* Felbamate overdose complicated by massive crystalluria and acute renal failure. *J Toxicol Clin Toxicol* 2000; **38:** 667–9.
2. Meier KH, *et al.* Acute felbamate overdose with crystalluria. *Clin Toxicol* 2005; **43:** 189–92.

Precautions

Felbamate is contra-indicated in patients with a history of blood disorders or hepatic impairment. It should be used only in the treatment of severe epilepsy refractory to other antiepileptics because of the risk of fatal aplastic anaemia or acute liver failure. Patients or their carers should be advised of the symptoms of aplastic anaemia and be told to report immediately should any such symptoms develop. Complete blood counts should be carried out before the patient starts treatment and regularly during treatment (but see Epilepsy, under Uses and Administration, below). Aplastic anaemia may occur after felbamate has been stopped so patients should continue to be monitored for some time. Liver function tests are also recommended before starting and regularly (at 1- to 2-week intervals) during treatment. Felbamate should be stopped if there is any evidence of bone marrow depression or liver abnormalities.

Felbamate should be used with caution in patients with renal impairment. Felbamate may cause photosensitivity reactions and patients should be advised to take protective measures against exposure to UV radiation.

Care is required when withdrawing felbamate therapy—see also Uses and Administration, below.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

The elderly. Felbamate may need to be given with care in elderly patients (see Administration in the Elderly, below).

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The metabolism of felbamate is enhanced by enzyme inducers such as phenytoin, phenobarbital, or carbamazepine. In contrast, the half-life of felbamate may be prolonged by gabapentin. Felbamate inhibits or enhances the metabolism of several other antiepileptics and care is required when it is added to therapy.

Anticoagulants. For the effect of felbamate on *warfarin*, see p.1429.

Antiepileptics. For some references to the effect of felbamate on other antiepileptics, see under *Carbamazepine*, p.474, *Phenobarbital*, p.493, *Phenytoin*, p.498, and *Valproate* p.511.

Sex hormones. For the effect of felbamate on *oral contraceptives* see p.2068 and also under Gestodene, p.2105.

Pharmacokinetics

Felbamate is well absorbed from the gastrointestinal tract and peak plasma concentrations have been reported 1 to 6 hours after oral doses. Protein binding is reported to be about 22 to 25%. It is partly metabolised in the liver by hydroxylation and conjugation to inactive metabolites. Felbamate is excreted mainly in the urine as metabolites and unchanged drug (40 to 50%); less than 5% appears in the faeces. The terminal half-life is reported to be between 16 and 23 hours. Felbamate is distributed into breast milk.

The pharmacokinetics of felbamate are reported to be linear at the doses used clinically. Therapeutic plasma concentrations have been reported to be between 30 and 80 micrograms/mL.

The pharmacokinetics of felbamate are affected by use with other antiepileptics (see Interactions, above).

◊ See under Uses and Administration (below) for mention of pharmacokinetic studies of felbamate in the elderly and in patients with renal impairment.

Uses and Administration

Felbamate is a carbamate structurally related to meprobamate (p.1006). It is used in the treatment of epilepsy (see below); however, because of its toxicity, it should only be used in severe cases unresponsive to other drugs.

Felbamate is given orally as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation. It is used in children as adjunctive therapy in controlling the seizures associated with the Lennox-Gastaut syndrome (see below).

The initial dose of felbamate when given as *monotherapy* is 1.2 g daily in 3 or 4 divided doses. The daily dose should be increased gradually under close supervision; increments of 600 mg every 2 weeks are given according to response, up to 2.4 g daily. Thereafter doses may be further increased to a maximum of 3.6 g daily if necessary.

Similar initial doses are given as *adjunctive* therapy, but the doses of the other antiepileptics should be decreased as necessary. This adjunctive dose may be increased by 1.2 g at weekly intervals, up to a maximum of 3.6 g.

As with other antiepileptics, withdrawal of felbamate 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.

◊ References.

1. Pellock JM, *et al.* Felbamate: consensus of current clinical experience. *Epilepsy Res* 2006; **71:** 89–101.

Administration in children. As an adjunct in Lennox-Gastaut syndrome, the initial oral dose of felbamate in children aged 2 to 14 years is 15 mg/kg daily in 3 to 4 divided doses. This may be increased gradually in increments of 15 mg/kg at weekly intervals to a maximum of 45 mg/kg daily; the doses of other antiepileptics should be decreased as necessary.

Those aged 14 years and over may be given the usual adult dose (see above) as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation.

Administration in the elderly. The elderly may require lower initial doses of felbamate and slower dose titration. After single doses of felbamate, plasma concentrations and half-lives were greater and mean clearance lower in elderly than in young subjects, whereas pharmacokinetic parameters after multiple dosing schedules were similar.[1]

1. Richens A, *et al.* Single and multiple dose pharmacokinetics of felbamate in the elderly. *Br J Clin Pharmacol* 1997; **44:** 129–34.

Administration in renal impairment. A single-dose pharmacokinetic study[1] indicated that in patients with renal impairment the initial dose of felbamate may need to be lower and increases made more cautiously than in patients with normal renal function (licensed product information suggests halving initial and maintenance doses).

1. Glue P, *et al.* Single-dose pharmacokinetics of felbamate in patients with renal dysfunction. *Br J Clin Pharmacol* 1997; **44:** 91–3.

Epilepsy. Although felbamate was well tolerated in clinical studies, rare but serious adverse effects were noted during early postmarketing use.[1,2] Aplastic anaemia and serious hepatotoxic reactions, sometimes with fatal outcomes, developed in some patients. Patients taking felbamate should have frequent blood counts and monitoring of liver enzymes. However there is no evidence that such monitoring will prevent adverse outcomes; in addition, the risk of aplastic anaemia is thought to decrease after the first year of therapy, and the need for ongoing blood counts is still less clear.[3] Even if detected early, aplastic anaemia and hepatic impairment may not be reversible.[1] Usage in the USA is restricted to patients with refractory partial seizures with or without secondary generalisation or for adjunctive therapy for children with Lennox-Gastaut syndrome. Guidelines on appropriate use have been issued.[3]

The overall management of epilepsy is discussed on p.465.

1. Dichter MA, Brodie MJ. New antiepileptic drugs. *N Engl J Med* 1996; **334:** 1583–90.
2. Appleton RE. The new antiepileptic drugs. *Arch Dis Child* 1996; **75:** 256–62.
3. French J, *et al.* The use of felbamate in the treatment of patients with intractable epilepsy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 1999; **40:** 803–8. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/119061174/PDFSTART (accessed 01/09/08)

Preparations

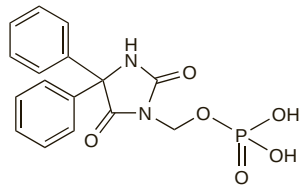
Proprietary Preparations (details are given in Part 3)
Arg.: Felbamyl; ***Austria:*** Taloxa; ***Belg.:*** Taloxa; ***Cz.:*** Taloxa†; ***Fr.:*** Taloxa; ***Ger.:*** Taloxa; ***Hung.:*** Taloxa; ***Ital.:*** Taloxa; ***Neth.:*** Taloxa; ***Norw.:*** Taloxa; ***Port.:*** Taloxa; ***Swed.:*** Taloxa; ***Switz.:*** Taloxa; ***USA:*** Felbatol.

Fosphenytoin Sodium *(BANM, USAN, rINNM)*

ACC-9653; ACC-9653-010; CI-982 (fosphenytoin or fosphenytoin sodium); Fosfenitoin Sodyum; Fosfenitoína sódica; Fosphénytoïne Sodique; Natrii Fosphenytoinum; PD-135711-15B. 5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium; 3-(Hydroxymethyl)-5,5-diphenylhydantoin disodium phosphate; 2,5-Dioxo-4,4-diphenylimidazolidin-1-ylmethyl phosphate disodium.

Натрий Фосфенитоин

$C_{16}H_{13}N_2Na_2O_6P$ = 406.2.
CAS — 93390-81-9 (fosphenytoin); 92134-98-0 (fosphenytoin sodium).
ATC — N03AB05.
ATC Vet — QN03AB05.



(fosphenytoin)

Pharmacopoeias. In *US.*
USP 31 (Fosphenytoin Sodium). A white to pale yellow solid. Freely soluble in water. pH of a 7.5% solution in water is between 8.5 and 9.5. Store in airtight containers.

Stability. References.

1. Fischer JH, *et al.* Stability of fosphenytoin sodium with intravenous solutions in glass bottles, polyvinyl chloride bags, and polypropylene syringes. *Ann Pharmacother* 1997; **31**: 553–9.

Adverse Effects and Precautions

As for Phenytoin, p.495.

Severe cardiovascular reactions, sometimes fatal, have been reported after intravenous doses of fosphenytoin. Therefore, continuous monitoring of ECG, blood pressure, and respiratory function is recommended during the infusion, and the patient should be kept under observation for at least 30 minutes after the end of the infusion. Hypotension may occur with recommended doses and rates of infusion; a reduction in the infusion rate or stopping therapy may be necessary. Fosphenytoin is contra-indicated in patients with sinus bradycar-