Psychiatric disorders. Case reports[1,2] in children and adolescents and a randomised, placebo-controlled study[3] in adults have indicated some benefit from oxcarbazepine in the treatment of *aggression* and *disturbed behaviour*(p.954). A retrospective review[4] of 14 children and adolescents with various psychiatric and behavioural disorders found moderate symptomatic improvement in 50% after the addition of oxcarbazepine. Oxcarbazepine has also been tried in the treatment of *schizophrenia*[5] (p.955) and *post-traumatic stress disorder*[6] (p.953). For use in *bipolar disorder* see above.

1. Kapetanovic S. Oxcarbazepine in youths with autistic disorder and significant disruptive behaviors. *Am J Psychiatry* 2007; **164:** 832–3.
2. Gaudino MP, *et al.* Use of oxcarbazepine for treatment-resistant aggression. *Psychiatr Serv* 2003; **54:** 1166–7.
3. Mattes JA. Oxcarbazepine in patients with impulsive aggression: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2005; **25:** 575–9.
4. Staller JA, *et al.* Oxcarbazepine in the treatment of child psychiatric disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol* 2005; **15:** 964–9.
5. Leweke FM, *et al.* Oxcarbazepine as an adjunct for schizophrenia. *Am J Psychiatry* 2004; **161:** 1130–1.
6. Malek-Ahmadi P, Hanretta AT. Possible reduction in posttraumatic stress disorder symptoms with oxcarbazepine in a patient with bipolar disorder. *Ann Pharmacother* 2004; **38:** 1852–4.

Withdrawal syndromes and abstinence. Oxcarbazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Although it was not found[1] to be superior to placebo in the treatment of symptoms of the *alcohol withdrawal syndrome* (p.1626), oxcarbazepine has been reported[2-4] to be of benefit in relapse prevention; further studies are considered warranted. It has also been tried[5] during *benzodiazepine withdrawal* but such adjunct therapy is not usually indicated (see p.987).

1. Koethe D, *et al.* Oxcarbazepine—efficacy and tolerability during treatment of alcohol withdrawal: a double-blind, randomized, placebo-controlled multicenter pilot study. *Alcohol Clin Exp Res* 2007; **31:** 1188–94.
2. Croissant B, *et al.* Oxcarbazepine in alcohol relapse prevention: a case series. *Pharmacopsychiatry* 2004; **37:** 306–7.
3. Croissant B, *et al.* A pilot study of oxcarbazepine versus acamprosate in alcohol-dependent patients. *Alcohol Clin Exp Res* 2006; **30:** 630–5.
4. Martinotti G, *et al.* High and low dosage oxcarbazepine versus naltrexone for the prevention of relapse in alcohol-dependent patients. *Hum Psychopharmacol* 2007; **22:** 149–56.
5. Croissant B, *et al.* Scheme-based benzodiazepine detoxification with oxcarbazepine: a case report. *Pharmacopsychiatry* 2005; **38:** 222–3.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Atoxecar†; Aurene; Oxca; Oxcazen†; Rupox; Trileptal; ***Austral.:*** Trileptal; ***Austria:*** Trileptal; ***Belg.:*** Trileptal; ***Braz.:*** Auram; Oleptal; Oxcarb; Trileptal; ***Canad.:*** Trileptal; ***Chile:*** Alox†; Oxicodal; Trileptal; ***Cz.:*** Trileptal; ***Denm.:*** Apydan; Trileptal; ***Fin.:*** Apydan; Trileptal; ***Fr.:*** Trileptal; ***Ger.:*** Timox; Trileptal; ***Gr.:*** Trileptal; ***Hong Kong:*** Trileptal; ***Hung.:*** Apydan; Trileptal; ***India:*** Oxcarb; Oxrate; ***Indon.:*** Barzepin; Prolepsi; Trileptal; ***Irl.:*** Trileptal; ***Israel:*** Trileptin; ***Ital.:*** Tolep; ***Malaysia:*** Trileptal; ***Mex.:*** Actinium; Deprectal; Oxetol; Trileptal; ***Neth.:*** Trileptal; ***Norw.:*** Trileptal; ***NZ:*** Trileptal; ***Philipp.:*** Trileptal; ***Pol.:*** Apydan; Trileptal; ***Port.:*** Epilfarmo; Proaxen; Zigabal; ***Rus.:*** Trileptal (Трилептал); ***S.Afr.:*** Trileptal; ***Spain:*** Trileptal; ***Swed.:*** Trileptal; ***Switz.:*** Trileptal; ***Thai.:*** Trileptal; ***Turk.:*** Trileptal; ***UK:*** Trileptal; ***USA:*** Trileptal; ***Venez.:*** Trileptal.

Pheneturide *(BAN, rINN)*

Ethylphenacemide; Feneturida; Phénéturide; Pheneturidum; S-46. (2-Phenylbutyryl)urea.

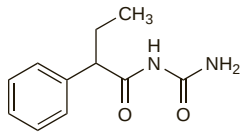
Фенетурид

$C_{11}H_{14}N_2O_2$ = 206.2.

CAS — 90-49-3.

ATC — N03AX13.

ATC Vet — QN03AX13.



Profile

Pheneturide is an acetylurea antiepileptic used in the treatment of complex partial seizures with or without secondary generalisation (p.465). It is given in usual oral daily doses of 300 to 600 mg in 2 or 3 divided doses, up to a maximum of 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Laburide.

Phenobarbital *(BAN, rINN)*

Ácido feniletilbarbitúrico; Fenobarbitaali; Fenobarbitál; Fenobarbital; Fenobarbitalis; Fenobarbitona; Phenemalum; Phénobarbital; Phenobarbitalum; Phenobarbitone; Phenylethylbarbituric Acid; Phenylethylmalonylurea. 5-Ethyl-5-phenylbarbituric acid.

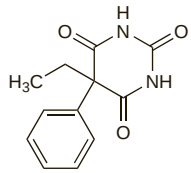
Фенобарбитал

$C_{12}H_{12}N_2O_3$ = 232.2.

CAS — 50-06-6.

ATC — N03AA02.

ATC Vet — QN03AA02.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of phenobarbital: Feenies; Phennies; Phenos.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet*.

Ph. Eur. 6.2 (Phenobarbital). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; freely soluble in alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 31 (Phenobarbital). White, odourless, glistening, small crystals or a white crystalline powder. It may exhibit polymorphism. Soluble 1 in 1000 of water and 1 in 10 of alcohol; sparingly soluble in chloroform; soluble in ether and in solutions of fixed alkali hydroxides and carbonates. A saturated solution in water has a pH of about 5.

Phenobarbital Sodium *(BANM, rINN)*

Fenobarbitaalinatrium; Fenobarbital sódico; Fenobarbital sodná sůl; Fenobarbital sodowy; Fenobarbitalio natrio druska; Fenobarbitalnatrium; Fenobarbitál-nátrium; Natrii Phenobarbitalum; Phenemalnatrium; Phénobarbital sodique; Phenobarbitalum natricum; Phenobarbitone Sodium; Sodium Phenylethylbarbiturate; Soluble Phenobarbitone. Sodium 5-ethyl-5-phenylbarbiturate.

Натрий Фенобарбитал

$C_{12}H_{11}N_2NaO_3$ = 254.2.

CAS — 57-30-7.

ATC — N03AA02.

ATC Vet — QN03AA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US*.

Ph. Eur. 6.2 (Phenobarbital Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in carbon dioxide-free water (a small amount may be insoluble); soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH not greater than 10.2. Store in airtight containers.

USP 31 (Phenobarbital Sodium). Flaky crystals, or white crystalline granules, or a white powder. It is odourless and hygroscopic. Very soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 10% solution in water is between 9.2 and 10.2. Solutions decompose on standing. Store in airtight containers.

Incompatibility. Phenobarbital sodium is incompatible with many other drugs and phenobarbital may be precipitated from mixtures containing phenobarbital sodium. This precipitation is dependent upon the concentration and the pH, and also on the presence of other solvents.

Stability. Extemporaneous oral preparations of phenobarbital 10 mg/mL in a 1:1 mixture of *Ora-Plus* and either *Ora-Sweet* or *Ora-Sweet SF* (*Paddock, USA*) were found[1] to be stable for at least 115 days in amber plastic bottles stored at room temperature.

1. Cober MP, Johnson CE. Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. *Am J Health-Syst Pharm* 2007; **64:** 644–6.

Dependence and Withdrawal

As for the barbiturates (see Amobarbital, p.962).

Adverse Effects

The most frequent adverse effect associated with phenobarbital is sedation, but this often becomes less marked with continued use. Like some of the other antiepileptics, phenobarbital may produce subtle mood changes and impairment of cognition and memory that may not be apparent without testing. Depression may occur.

Prolonged use can occasionally result in folate deficiency; rarely, megaloblastic anaemia has been reported. There is some evidence that phenobarbital interferes with vitamin D metabolism.

At high doses nystagmus and ataxia may occur and the typical barbiturate-induced respiratory depression may become severe. Overdosage can prove fatal; toxic effects include coma, severe respiratory and cardiovascular depression, with hypotension and shock leading to renal failure. Hypothermia may occur, with associated pyrexia during recovery. Skin blisters (bullae) reportedly occur in about 6% of patients with barbiturate overdose.

Sodium salts of barbiturates have a very high pH in solution, and necrosis has followed subcutaneous injection or extravasation. Intravenous injections can be hazardous and cause hypotension, shock, laryngospasm, and apnoea, especially if given too rapidly.

Hypersensitivity reactions occur in a small proportion of patients; skin reactions are reported in 1 to 3% of patients taking phenobarbital, and are most commonly maculopapular, morbilliform, or scarlatiniform rashes. More severe reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are extremely rare. Hepatitis and disturbances of liver function have been reported.

Paradoxical excitement, restlessness, and confusion may sometimes occur in the elderly, and irritability and hyperactivity may occur in children.

Neonatal drug dependence and symptoms resembling vitamin K deficiency have been reported in infants born to mothers who received phenobarbital during pregnancy. Congenital malformations have been reported in children of women who received phenobarbital during pregnancy but the causal role of the drug is a matter of some debate.

Effects on the blood. For the effects of antiepileptics including phenobarbital on serum folate, see under Phenytoin, p.495.

Effects on bone. For the effects of antiepileptics including phenobarbital on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on connective tissue. The use of phenobarbital and primidone has been associated with the development of Dupuytren's contracture, frozen shoulder, Ledderhose's syndrome, Peyronie's disease, fibromas, and general joint pain.[1]

1. Mattson RH, *et al.* Barbiturate-related connective tissue disorders. *Arch Intern Med* 1989; **149:** 911–14.

Effects on the endocrine system. For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p.496.

Barbiturates may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p.2172.

Effects on the liver. For mention of the effects of phenobarbital on the liver, see under Phenytoin, p.496.

Effects on mental function. For a review of the effects of antiepileptics, including phenobarbital, on *cognition* and *mood* (including the risk of suicidal ideation), see p.468.

DEPRESSION. Follow-up of 28 patients aged 6 to 16 who had received phenobarbital or carbamazepine for epilepsy indicated that the rate of major depression was significantly higher in those receiving phenobarbital.[1] It was recommended that treatment with phenobarbital should be avoided particularly in patients with a personal or family history of an affective disorder; patients who do receive it should be monitored for symptoms of depression.

1. Brent DA, *et al.* Phenobarbital treatment and major depressive disorder in children with epilepsy: a naturalistic follow-up. *Pediatrics* 1990; **85:** 1086–91.

DISTURBED BEHAVIOUR. Disturbed behaviour is a recognised adverse effect of phenobarbital, especially in children and the elderly; however, no excess in behavioural adverse effects was seen[1] on follow-up for up to 12 months in 40 children who took phenobarbital when compared with 45 who took carbamazepine.

1. Banu SH, *et al.* Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial. Abridged version: *BMJ* 2007; **334:** 1207–10. Full version: http://www.bmj.com/cgi/reprint/334/7605/1207 (accessed 09/06/08)

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some antiepileptics including phenobarbital.[1,2] Some have estimated the incidence at 1 in 1000 to 1 in 10 000

new exposures to aromatic anticonvulsants,[1,2] but the true incidence is unknown due to variations in presentation and reporting. The syndrome occurs most frequently on first exposure to the drug, with initial symptoms starting anywhere between 1 and 8 weeks after exposure. In previously sensitised individuals the reaction may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is about 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[1]

1. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21:** 489–501.
2. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35:** 533–8.

Treatment of Adverse Effects

In the treatment of phenobarbital overdosage repeated oral doses of activated charcoal may be helpful after recent ingestion of doses above 10 mg/kg; the aim is not only to prevent absorption but also aid elimination. Care should be taken to protect the airway. The prime objectives of management are then intensive symptomatic and supportive therapy with particular attention being paid to the maintenance of cardiovascular, respiratory, and renal functions and to the maintenance of electrolyte balance.

Charcoal haemoperfusion may be considered for patients with severe refractory poisoning; other methods aimed at the active removal of phenobarbital include haemodialysis and urine alkalinisation, although the latter appears to be less effective than multiple doses of activated charcoal.

Precautions

Phenobarbital and other barbiturates should be used with care in children and in elderly or debilitated patients, in those in acute pain, and in those with depressive disorders. Phenobarbital should be used with caution in patients with impaired hepatic, renal, or respiratory function; its use is contra-indicated in those with severe respiratory depression.

Breast feeding. The American Academy of Pediatrics[1] considers that phenobarbital should be given with caution to breast-feeding mothers, since there have been significant adverse effects including sedation and methaemoglobinaemia in nursing infants. The *BNF* recommends that phenobarbital should be avoided where possible during breast feeding. Both authorities make similar recommendations for primidone.

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.

Neonates. Care should be taken when giving phenobarbital orally as the elixir to neonates because regular dosing could result in alcohol toxicity [the BP 2008 formulation contains 38% v/v alcohol].[1] Aqueous preparations are more readily made using the sodium salt than the acid.[2]

1. Colquhoun-Flannery W, Wheeler R. Treating neonatal jaundice with phenobarbitone: the inadvertent administration of significant doses of ethyl alcohol. *Arch Dis Child* 1992; **67:** 152.
2. Leach F. Treating neonatal jaundice with phenobarbitone: the inadvertent administration of significant doses of ethyl alcohol. *Arch Dis Child* 1992; **67:** 152.

Porphyria. Phenobarbital 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.

Congenital craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described with antiepileptics including phenobarbital. *In utero* exposure to phenobarbital might result in neonatal sedation and drug dependence and also in neonatal bleeding due to vitamin K deficiency.

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. Valproate and phenytoin have been reported to cause rises in phenobarbital (and primidone) concentrations in plasma.

The effects of phenobarbital and other barbiturates are enhanced by other CNS depressants including alcohol.

Phenobarbital and other barbiturates may reduce the activity of many drugs by increasing the rate of metabolism through induction of drug-metabolising enzymes in liver microsomes.

Analgesics. *Dextropropoxyphene* 65 mg given three times daily to 4 epileptic patients stabilised on phenobarbital therapy increased serum-phenobarbital concentration by 8 to 29% but this was not considered of major importance in the light of the normally accepted therapeutic range for phenobarbital.[1]

For the effect of phenobarbital on *fenoprofen*, *methadone*, and *pethidine*, see p.55, p.84, and p.114, respectively. Enzyme-inducing antiepileptics such as phenobarbital also affect the threshold for the use of antidote in the treatment of *paracetamol* poisoning, see p.110.

1. Hansen BS, *et al.* Influence of dextropropoxyphene on steady state serum levels and protein binding of three anti-epileptic drugs in man. *Acta Neurol Scand* 1980; **61:** 357–67.

Antiarrhythmics. For the effect of phenobarbital on *disopyramide*, *lidocaine*, and *quinidine*, see p.1270, p.1863, and p.1384, respectively.

Antibacterials. Serum concentrations of phenytoin and phenobarbital in a previously stabilised patient were increased when he took *chloramphenicol*.[1] Subsequent monitoring revealed a similar effect when chloramphenicol was taken with phenobarbital alone. In turn, phenobarbital may affect serum concentrations of chloramphenicol (see p.240).

Barbiturates such as phenobarbital and primidone may enhance the metabolism of *doxycycline*.[2]

1. Koup JR, *et al.* Interaction of chloramphenicol with phenytoin and phenobarbital. *Clin Pharmacol Ther* 1978; **24:** 571–5.
2. Neuvonen PJ, *et al.* Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* 1975; **9:** 147–54.

Anticoagulants. For the effect of barbiturates such as phenobarbital and primidone on *warfarin* and other coumarins, see p.1429.

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

St John's wort has been shown to induce several drug metabolising enzymes (see p.423) and so might reduce the blood concentrations of phenobarbital, and increase the seizure risk.[1]

For the effect of phenobarbital on antidepressants, see under the monographs for *amitriptyline* (under Barbiturates, p.380), *bupropion* (p.384), *fluoxetine* (p.396), *lithium* (p.404), and *mianserin* (p.409).

Inhibition of drug-metabolising enzymes by *MAOIs* may enhance the effects of barbiturates.

1. Committee on Safety of Medicines/Medicines Control Agency. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Antiepileptics. Interactions may occur if phenobarbital is given with other antiepileptics, of which probably the most significant is the interaction with *valproate*. Valproate increases plasma-phenobarbital concentration by a reported 17 to 48%,[1] and it may be necessary to reduce the dose of phenobarbital in some patients.[1,2] The mechanism for the increase appears to be inhibition of the metabolism of phenobarbital, resulting in reduced clearance;[2,3] valproate appears to inhibit both the direct *N*-glucosidation of phenobarbital and the *O*-glucuronidation of *p*-hydroxyphenobarbital.[4] However, phenobarbital reciprocally increases the clearance of valproate, and the valproate dose may also need to be adjusted.[5]

A similarly complex interaction exists between phenobarbital and *phenytoin*. Phenytoin can increase plasma concentrations of phenobarbital in some patients[6] since the two drugs compete for metabolism by the same enzyme system, but other evidence suggests that where this occurs it is rarely of significant magnitude.[7] Similarly, although phenobarbital induces the metabolism of phenytoin it is also, as stated, a competitive inhibitor and in practice the two effects appear to balance out, with rarely any need for dose adjustment.[7-9] However, dosage adjustment of phenobarbital may be crucial for some patients.[10] Measurement of serum concentrations of phenytoin and phenobarbital in one patient[10] showed that, in her case, large increases in serum-phenobarbital concentrations resulted from use with phenytoin; the increases were concentration-dependent.

The GABA-agonist, *progabide* has also been reported to cause a significant increase in phenobarbital concentrations when the two were given together to healthy subjects.[11]

Neurotoxicity, attributed to an increase in plasma concentrations of phenobarbital, has been seen[12] in one patient taking phenobarbital and sodium valproate when *felbamate* was added to treatment. The dosage of phenobarbital had already been reduced before treatment with felbamate was started. Data from a pharmacokinetic study[13] indicated that the interaction may result from the inhibition of phenobarbital hydroxylation by felbamate.

Vigabatrin has been reported to lower plasma concentrations of phenobarbital in some patients,[14] although dosage changes were not necessary in these patients.

High dose of *oxcarbazepine* may increase the plasma concentrations of phenobarbital but this was thought unlikely to be clinically significant;[15] conversely phenobarbital may reduce the plasma concentrations of the active metabolite of oxcarbazepine (p.491).

For the effect of phenobarbital on the metabolism of other antiepileptics, see under *Carbamazepine*, p.474, *Diazepam*, p.990, *Ethosuximide*, p.480, *Lamotrigine*, p.486, *Tiagabine*, p.505, and *Zonisamide*, p.515.

1. Richens A, Ahmad S. Controlled trial of sodium valproate in severe epilepsy. *BMJ* 1975; **4:** 255–6.
2. Patel IH, *et al.* Phenobarbital-valproic acid interaction. *Clin Pharmacol Ther* 1980; **27:** 515–21.
3. Kapetanović IM, *et al.* Mechanism of valproate-phenobarbital interaction in epileptic patients. *Clin Pharmacol Ther* 1981; **29:** 480–6.
4. Bernus I, *et al.* Inhibition of phenobarbitone N-glucosidation by valproate. *Br J Clin Pharmacol* 1994; **38:** 411–16.
5. Perucca E, *et al.* Disposition of sodium valproate in epileptic patients. *Br J Clin Pharmacol* 1978; **5:** 495–9.
6. Morselli PL, *et al.* Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. *Ann N Y Acad Sci* 1971; **179:** 88–107.
7. Eadie MJ, *et al.* Factors influencing plasma phenobarbitone levels in epileptic patients. *Br J Clin Pharmacol* 1977; **4:** 541–7.
8. Cucinell SA, *et al.* Drug interactions in man: lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin). *Clin Pharmacol Ther* 1965; **6:** 420–9.
9. Booker HE, *et al.* Concurrent administration of phenobarbital and diphenylhydantoin: lack of an interference effect. *Neurology* 1971; **21:** 383–5.
10. Kuranari M, *et al.* Effect of phenytoin on phenobarbital pharmacokinetics in a patient with epilepsy. *Ann Pharmacother* 1995; **29:** 83–4.
11. Bianchetti G, *et al.* Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia* 1987; **28:** 68–73.
12. Gidal BE, Zupanc ML. Potential pharmacokinetic interaction between felbamate and phenobarbital. *Ann Pharmacother* 1994; **28:** 455–8.
13. Reidenberg P, *et al.* Effects of felbamate on the pharmacokinetics of phenobarbital. *Clin Pharmacol Ther* 1995; **58:** 279–87.
14. Browne TR, *et al.* A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* 1989; **27** (suppl): 95S–100S.
15. Hossain M, *et al.* Drug-drug interaction profile of oxcarbazepine in children and adults. *Neurology* 1999; **52** (suppl 2): A525.

Antifungals. For the effect of phenobarbital on *griseofulvin*, see p.536, and on *itraconazole*, see p.537.

Antineoplastics. For the effect of phenobarbital on *teniposide*, see p.778.

Antiprotozoals. For the effect of phenobarbital on *metronidazole*, see p.838.

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

For the effect of phenobarbital on antipsychotics, see under Chlorpromazine, p.974.

Antivirals. A patient stabilised on phenobarbital 100 mg daily had an episode of seizures 4 weeks after starting HAART therapy with abacavir, didanosine, ritonavir-boosted tipranavir, and enfuvirtide.[1] The patient's phenobarbital plasma concentrations had fallen from 16 to 8 micrograms/mL and an increase in the phenobarbital dosage to 150 mg daily was required to restore concentrations. The tipranavir/ritonavir component of HAART therapy was considered to be responsible.

For the possible effect of phenobarbital on *HIV-protease inhibitors*, see p.883.

1. Bonora S, *et al.* Clinically significant drug interaction between tipranavir-ritonavir and phenobarbital in an HIV-infected subject. *Clin Infect Dis* 2007; **45:** 1654–5.

Beta blockers. For the effect of barbiturates on beta blockers, see Anxiolytics and Antipsychotics under Interactions of Beta Blockers, p.1228.

Calcium-channel blockers. For the effect of phenobarbital on *dihydropyridine calcium-channel blockers*, see under Nifedipine, p.1353, and on *verapamil*, see p.1422.

Cardiac glycosides. Phenobarbital may greatly accelerate the metabolism of *digitoxin* (p.1259).

Ciclosporin. For the effect of phenobarbital on ciclosporin, see p.1826.

Corticosteroids. For the effect of phenobarbital on corticosteroids, see p.1494.

Diuretics. Serum-phenobarbital concentrations were raised in 8 of 10 epileptic patients taking phenobarbital and additional antiepileptics when given *furosemide* 40 mg three times daily for 4 weeks.[1] This might have been the cause of drowsiness in 5 of 14 patients, 3 of whom had to stop furosemide.

1. Ahmad S, *et al.* Controlled trial of frusemide as an antiepileptic drug in focal epilepsy. *Br J Clin Pharmacol* 1976; **3:** 621–5.

Levothyroxine. For the effects of barbiturates on levothyroxine, see p.2172.

Montelukast. For the effect of phenobarbital on montelukast, see p.1126.

Sex hormones. For the effect of phenobarbital on sex hormones in *oral contraceptives*, see p.2068.

Theophylline. For the effect of phenobarbital on theophylline, see p.1143.

Vaccines. *Influenza vaccination* can cause prolonged rises in serum-phenobarbital concentrations in some patients.[1]

1. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* 1986; **5:** 817–20.

Vitamins. *Pyridoxine* reduced serum-phenobarbital concentrations in 5 patients.[1] Plasma concentrations of phenobarbital and primidone are possibly reduced by *folic acid* and *folinic acid*. For the effect of antiepileptics, including phenobarbital, on *vitamin D* concentrations, see Effects on Bone under Adverse Effects of Phenytoin, p.496.

1. Hansson O, Sillanpaa M. Pyridoxine and serum concentration of phenytoin and phenobarbitone. *Lancet* 1976; **i:** 256.

Pharmacokinetics

Like other barbiturates phenobarbital is readily absorbed from the gastrointestinal tract, although it is relatively lipid-insoluble; peak concentrations are reached in about 2 hours after oral doses and within 4 hours of intramuscular doses.

Phenobarbital is about 45 to 60% bound to plasma proteins and is only partly metabolised in the liver. About 25% of a dose is excreted in the urine unchanged at normal urinary pH. The plasma half-life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. There is considerable interindividual variation in phenobarbital kinetics.

Monitoring of plasma concentrations has been performed as an aid in assessing control and the therapeutic range of plasma-phenobarbital has been quoted as 15 to 40 micrograms/mL or around 60 to 180 micromoles/litre.

Phenobarbital crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of phenobarbital are affected if given with other antiepileptics (see under Interactions, above).

Uses and Administration

Phenobarbital is a barbiturate that may be used as an antiepileptic to control partial and generalised tonic-clonic seizures. It is also used as part of the emergency management of acute seizures including status epilepticus.

The dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires plasma concentrations of 15 to 40 micrograms/mL or around 60 to 180 micromoles/litre. In the UK, the usual oral dose is 60 to 180 mg daily, taken at night. In the USA, total daily doses of up to 300 mg have been given.

Phenobarbital sodium may be given parenterally as part of the emergency management of acute seizures including status epilepticus. Doses of 200 mg have been given by intramuscular injection, repeated after 6 hours if necessary. Doubts have been expressed about the efficacy of the intramuscular route owing to the delay in achieving adequate blood concentrations, and the subcutaneous route may cause tissue necrosis. In the UK, for the control of status epilepticus, doses of 10 mg/kg to a maximum of 1 g may be given intravenously. The *BNF* recommends that an intravenous injection solution containing 200 mg/mL should be diluted 1 in 10 and given at a rate not exceeding 100 mg/minute.

For doses in children, see below.

As with other antiepileptics, withdrawal of phenobarbital 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.

Phenobarbital has also been used as a hypnotic and sedative but drugs such as the benzodiazepines are preferred.

Phenobarbital stimulates the enzymes in hepatic microsomes responsible for the metabolism of some drugs and normal body constituents including bilirubin, and for this reason it has been used to reduce hyperbilirubinaemia in neonatal jaundice.

Phenobarbital magnesium and phenobarbital diethylamine have also been used.

Tetrabamate is a complex of phenobarbital, difebarbamate, and febarbamate but its use has been associated with the development of hepatitis.

Administration in children. Phenobarbital may be used in children as an antiepileptic to control partial and generalised tonic-clonic seizures. It is also used as part of the emergency management of status epilepticus. The doses given below for all indications are those recommended by the *BNFC* in the UK.

For treatment of epilepsy, the following doses are given orally, unless stated otherwise, according to age:

- neonates: an initial dose of 20 mg/kg by slow intravenous injection, then 2.5 to 5 mg/kg once daily by slow intravenous injection or orally, adjusted according to response
- 1 month to 12 years: an initial dose of 1 to 1.5 mg/kg twice daily, increased by 2 mg/kg daily if necessary to a usual maintenance dose of 2.5 to 4 mg/kg once or twice daily
- 12 to 18 years: 60 to 180 mg daily

For status epilepticus, an intravenous injection solution containing 200 mg/mL should be diluted 1 in 10 and given by intravenous injection over 20 minutes, at a rate not exceeding 1 mg/kg per minute, in the following doses according to age:

- neonate to 12 years: an initial dose of 20 mg/kg, followed by 2.5 to 5 mg/kg once or twice daily
- 12 to 18 years: an initial dose of 20 mg/kg (to a maximum of 1 g), followed by 300 mg twice daily

Alcohol withdrawal syndrome. Phenobarbital is used in some centres for the management of alcohol withdrawal syndrome (p.1626), but has a lower safety profile than benzodiazepines (the treatment of choice) and creates the potential for multiple drug interactions. Additionally, a lack of well-defined studies make its role difficult to assess.[1]

1. Rodgers JE, Crouch MA. Phenobarbital for alcohol withdrawal syndrome. *Am J Health-Syst Pharm* 1999; **56:** 175–8.

Cerebral malaria. Phenobarbital has been used to prevent convulsions in patients with cerebral malaria (p.594) but a systematic review[1] concluded that, although it was an effective anticonvulsant, it should not be given routinely to patients with cerebral malaria as it might increase mortality. The optimal dose, particularly in children, has yet to be confirmed. In an early study[2] a single intramuscular injection of phenobarbital sodium 3.5 mg/kg, or 200 mg in patients over 60 kg was effective. A dose of 10 to 15 mg/kg was later suggested.[3] Although a single intramuscular dose of phenobarbital 20 mg/kg markedly reduced seizure frequency in young children with cerebral malaria, it was also associated with a doubling of mortality.[4] The frequency of respiratory arrest was higher in the phenobarbital group than in controls given placebo, and mortality was greatly increased in those given phenobarbital who required 3 or more doses of diazepam. Intravenous use has also been tried, and a study[5] suggested giving a loading dose of phenobarbital 15 mg/kg by intravenous infusion followed by 2.5 mg/kg 24 and 48 hours later. WHO recommends[6] that a dose of 20 mg/kg should not be given without respiratory support but states that it is unknown whether ventilation would prevent the increase in mortality; it is also unknown whether lower doses are effective and safer.

1. Meremikwu M, Marson AG. Routine anticonvulsants for treating cerebral malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 09/06/08).
2. White NJ, *et al.* Single dose phenobarbitone prevents convulsions in cerebral malaria. *Lancet* 1988; **ii:** 64–6.
3. Gilles HM. *Management of severe and complicated malaria.* Geneva: WHO, 1991.
4. Crawley J, *et al.* Effect of phenobarbitone on seizure frequency and mortality in childhood cerebral malaria: a randomized, controlled intervention study. *Lancet* 2000; **355:** 701–6.
5. Kokwaro GO, *et al.* Pharmacokinetics and clinical effect of phenobarbital in children with severe falciparum malaria and convulsions. *Br J Clin Pharmacol* 2003; **56:** 453–7.
6. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 09/06/08)

Epilepsy. Phenobarbital is used in the treatment of epilepsy (p.465) for partial seizures with or without secondary generalisation and for primary generalised tonic-clonic seizures. It may also be tried for atypical absence, atonic, and tonic seizures but is not effective in absence seizures. However, the usefulness of phenobarbital is limited by problems of sedation in adults and paradoxical excitement in children. There is also concern about its effects on behaviour and cognition in children. Phenobarbital is therefore usually reserved for use in cases unresponsive to other antiepileptics, although some have suggested that its low cost and broad efficacy make it a suitable first-line drug in developing countries.

References.

1. Pal DK, *et al.* Randomised controlled trial to assess acceptability of phenobarbital for childhood epilepsy in rural India. *Lancet* 1998; **351:** 19–23.
2. Kwan P, Brodie MJ. Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. *Epilepsia* 2004; **45:** 1141–9.
3. Wilmshurst JM, van Toorn R. Use of phenobarbitone for treating childhood epilepsy in resource-poor countries. *S Afr Med J* 2005; **95:** 392, 394, 396.
4. Wang WZ, *et al.* Efficacy assessment of phenobarbital in epilepsy: a large community-based intervention trial in rural China. *Lancet Neurol* 2006; **5:** 46–52.

Febrile convulsions. Phenobarbital has been used prophylactically in children thought to be at risk of recurrence of febrile convulsions (p.470), but routine use of antiepileptics is no longer recommended.

References.

1. Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988; **63:** 1189–91.
2. Farwell JR, *et al.* Phenobarbital for febrile seizures: effects on intelligence and on seizure recurrence. *N Engl J Med* 1990; **322:** 364–9. Correction. *ibid.* 1992; **326:** 144.

Neonatal abstinence syndrome. For reference to the use of phenobarbital for the treatment of neonates with opioid abstinence syndrome, see p.102.

Neonatal intraventricular haemorrhage. Phenobarbital is one of several drugs that has been tried to prevent the development of neonatal intraventricular haemorrhage (p.1050). Initial studies[1-3] of antenatal use in the mother were promising, but a larger randomised study[4] in 610 women failed to show any effect of antenatal phenobarbital on incidence or severity of intraventricular haemorrhage. An assessment of surviving infants that could be traced at about 20 months of age also found that antenatal phenobarbital had no apparent effect on neurodevelopmental outcome.[5] A systematic review[6] of these and other studies concluded that giving phenobarbital before preterm birth cannot be recommended for routine clinical practice; strategies for future studies were suggested to improve methodology. Studies of use in neonates have also shown inconsistent results. A systematic review[7] of studies of phenobarbital for prophylaxis of intraventricular haemorrhage in preterm neonates concluded that postnatal use cannot be recommended either, and is associated with an increased need for mechanical ventilation.

1. Kaempf JW, *et al.* Antenatal phenobarbital for the prevention of periventricular and intraventricular hemorrhage: a double-blind, randomized, placebo-controlled, multihospital trial. *J Pediatr* 1990; **117:** 933–8.
2. Barnes ER, Thompson DF. Antenatal phenobarbital to prevent or minimize intraventricular hemorrhage in the low-birthweight neonate. *Ann Pharmacother* 1993; **27:** 49–52.
3. Thorp JA, *et al.* Antepartum vitamin K and phenobarbital for preventing intraventricular hemorrhage in the premature newborn: a randomized, double-blind, placebo-controlled trial. *Obstet Gynecol* 1994; **83:** 70–6.
4. Shankaran S, *et al.* The effect of antenatal phenobarbital therapy on neonatal intracranial hemorrhage in preterm infants. *N Engl J Med* 1997; **337:** 466–71.
5. Shankaran S, *et al.* Neurodevelopmental outcome of premature infants after antenatal phenobarbital exposure. *Am J Obstet Gynecol* 2002; **187:** 171–7.
6. Crowther CA, Henderson-Smart DJ. Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 09/06/08).
7. Whitelaw A, Odd D. Postnatal phenobarbital for the prevention of intraventricular hemorrhage in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 09/06/08).

Neonatal seizures. Some consider phenobarbital to be the mainstay of treatment for all types of neonatal seizures (p.471). In a study[1] in 120 neonates with clinical seizure activity of varying aetiology, 48 were controlled by an initial intravenous loading dose of phenobarbital 15 to 20 mg/kg over 10 to 15 minutes, and a further 37 were controlled by sequential bolus doses of phenobarbital 5 to 10 mg/kg every 20 to 30 minutes up to a serum concentration of 40 micrograms/mL. Of the remaining 35 neonates only 7 responded when the serum-phenobarbital concentration was increased to 100 micrograms/mL, 13 required addition of a second antiepileptic (phenytoin or lorazepam) and 4 were controlled by addition of a third drug. Phenobarbital alone can effectively control seizures in the majority of neonates with recurrent seizure activity.

Phenobarbital given prophylactically as a single dose of about 40 mg/kg intravenously over one hour has also been shown to be effective in reducing the incidence of seizures in 15 infants with severe perinatal asphyxia compared with a control group who only received phenobarbital if there was clinical evidence of seizures.[2] Subsequent follow-up over 3 years suggested that prophylactic phenobarbital might also improve later neurological outcome.[2] However, a later retrospective cohort study[3] found no significant difference in the rate of seizure recurrence and developmental outcome between infants who were discharged with prophylactic phenobarbital (33 patients) and those who were discharged without any antiepileptics (99).

1. Gilman JT, *et al.* Rapid sequential phenobarbital treatment of neonatal seizures. *Pediatrics* 1989; **83:** 674–8.

2. Hall RT, *et al*. High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: a randomized, prospective study with three-year follow-up. *J Pediatr* 1998; **132:** 345–8.
3. Guillet R, Kwon J. Seizure recurrence and developmental disabilities after neonatal seizures: outcomes are unrelated to use of phenobarbital prophylaxis. *J Child Neurol* 2007; **22:** 389–95.

Status epilepticus. Phenobarbital given intravenously is an alternative to intravenous phenytoin in the management of status epilepticus (p.469). It should not be used in patients who have recently received oral phenobarbital or primidone.

Although one study[1] suggested that phenobarbital might be at least as effective, safe, and practical as diazepam with phenytoin for the initial treatment of convulsive status epilepticus, it tends to be reserved for patients who do not respond to benzodiazepines or phenytoin.

1. Shaner DM, *et al*. Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988; **38:** 202–7.

Preparations

BP 2008: Paediatric Phenobarbital Oral Solution; Phenobarbital Elixir; Phenobarbital Injection; Phenobarbital Sodium Tablets; Phenobarbital Tablets; ***USP 31:*** Phenobarbital Elixir; Phenobarbital Sodium for Injection; Phenobarbital Sodium Injection; Phenobarbital Tablets; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Alepsal; Gardenal; Luminal; Luminaletas; Neurogabaf; ***Belg.:*** Gardenal; ***Braz.:*** Barbitron; Carbital; Edhanol; Fenocris; Garbital; Gardenal; Unifenobarb; ***Cz.:*** Gardenal†; Luminal; Phenaemal; Phenaemaletten; ***Denm.:*** Fenemal; ***Fr.:*** Aparoxal; Gardenal; Kaneuron; ***Ger.:*** Luminal; Luminaletten; ***Gr.:*** Gardenal; Kaneuron; Lumidrops†; ***Hung.:*** Sevenal; Sevenaletta; ***India:*** Gardenal; Luminal; Luminalettes†; Phenetone; ***Indon.:*** Sibital; ***Israel:*** Luminal†; ***Ital.:*** Comizial†; Gardenale; Luminale; Luminalette; Neurobiol†; ***Mex.:*** Alepsal; Fenabbott; Sevenal†; ***Norw.:*** Fenemal; ***NZ:*** Gardenal†; ***Philipp.:*** Luminal; ***Pol.:*** Luminalum; ***Port.:*** Bialminal; Luminal; Luminaletas; ***S.Afr.:*** Gardenal†; Lethyl; ***Spain:*** Gardenal; Gratusminal; Luminal; Luminaletas; ***Swed.:*** Fenemal; ***Switz.:*** Aphenylbarbit; Luminal; ***Thai.:*** Gardenal; Menobarb; Phenobarb†; Phenotal; ***Turk.:*** Luminal; Luminaletten; ***UK:*** Gardenal†; ***USA:*** Luminal; ***Venez.:*** Gardenal.

Multi-ingredient: ***Arg.:*** Cumatil L; Lotoquis; Trixol†; ***Belg.:*** Epipropane; Vethoine; ***Braz.:*** Espasmalgon†; Gamibetal Complex†; Vagostesyl; ***Canad.:*** Bellergal; ***Chile:*** Abalgin; Baldmin; Bellergal Retardado†; Belupan†; Bufacyl; Dispasmol†; Ergobelan; Immediat†; Sinpasmon; Valpin; ***Cz.:*** Alnagon; Bellaspon†; Contraspan†; Sanepil; Spasmoveralgin Neo†; ***Fr.:*** Alepsal; ***Gr.:*** Diphenal; ***Hung.:*** Atrium†; Germicid-C; Meristin; Radipon; Troparinum; ***India:*** Alergin; Asmapax; Asthmino†; Broncofol†; Cadiphylate; Dilantin with Phenobarbital; Epilan; Garoin; ***Indon.:*** Bellapheen; Ditalin; Piptal; ***Israel:*** Pacetal; Philinal; Philinet; ***Ital.:*** Gamibetal Complex; Metinal-Idantoina L; ***Jpn:*** Trancolon P†; ***Mex.:*** Alepsal Compuesto; Gamibetal Complex; Paliatil; ***Pol.:*** Bellergot; Milocardin; ***Port.:*** Anti-Asmatico; Cosmaxil†; Hidantina Composta†; Prelus†; ***Rus.:*** Pentalgin-N (Пенталгин-Н); Sedal-M (Седал-М); Sedalgin-Neo (Седальгин-Нео); ***S.Afr.:*** Adco-Phenobarbitone Vitalet; Analgen-SA†; Donnatal; Millerspas; Natrophylline Compound; Propain Forte; ***Spain:*** Epilantin†; Equidan†; Redutona; ***Thai.:*** Bellergal†; Benera; Donnatal†; Neuramizone; ***Turk.:*** Bellergal; Para-Nox; Pedimat; ***UAE:*** Alinal†; ***USA:*** Alkabel; Antispasmodic Elixir; Barbidonna†; Bel-Phen-Ergot S; Bellacane; Bellamine; Bellatal; Bellergal-S; Donnatal; Folergot-DF; Hyosophen; Lufyllin-EPG†; Phenerbel-S; Quadrinal; Susano; Tedrigen; Theodrine; ***Venez.:*** Ervostal; Fedratal†; Fenopol†; Frevag†; Metilfedrin†; Teofedril†; Traveget; Tropifen†.

Phensuximide *(BAN, rINN)*

Fensuksimidi; Fensuximid; Fensuximida; Phensuximidum. *N*-Methyl-2-phenylsuccinimide.

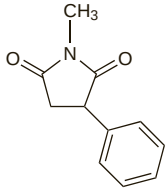
Фенсуксимид

$C_{11}H_{11}NO_2$ = 189.2.

CAS — 86-34-0.

ATC — N03AD02.

ATC Vet — QN03AD02.



Pharmacopoeias. In *US*.

USP 31 (Phensuximide). A white to off-white crystalline powder. Is odourless or has not more than a slight odour. Slightly soluble in water; soluble in alcohol; very soluble in chloroform. Store in airtight containers.

Profile

Phensuximide is a succinimide antiepileptic with actions similar to those of ethosuximide (p.479), but it is reported to be less effective.

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

Preparations

USP 31: Phensuximide Capsules.

Phenytoin *(BAN, USAN, rINN)*

Difenilhidantoína; Diphenylhydantoin; Fanantina; Fenantoína; Fenitoin; Fenitoína; Fenitoinas; Fenytoiini; Fenytoin; Fenytoina; Phenantoinum; Phénytoïne; Phenytoinum. 5,5-Diphenylhydantoin; 5,5-Diphenylimidazolidine-2,4-dione.

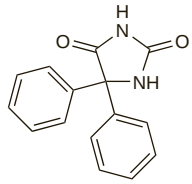
Фенитоин

$C_{15}H_{12}N_2O_2$ = 252.3.

CAS — 57-41-0.

ATC — N03AB02.

ATC Vet — QN03AB02.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Phenytoin). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; very slightly soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Phenytoin). A white, odourless powder. Practically insoluble in water; soluble in hot alcohol; slightly soluble in cold alcohol, in chloroform, and in ether. Store in airtight containers.

Phenytoin Sodium *(BANM, rINNM)*

Diphenin; Fenitoin Sodyum; Fenitoína sódica; Fenitoin-nátrium; Fenitoino natrio druska; Fenytoiininatrium; Fenytoin sodná sůl; Fenytoina sodowa; Fenytoinnatrium; Natrii Phenytoinum; Phénytoïne sodique; Phenytoinum natricum; Soluble Phenytoin.

Натрий Фенитоин

$C_{15}H_{11}N_2NaO_2$ = 274.2.

CAS — 630-93-3.

ATC — N03AB02.

ATC Vet — QN03AB02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Phenytoin Sodium). A white or almost white, slightly hygroscopic, crystalline powder. Soluble in water and in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

USP 31 (Phenytoin Sodium). A white, odourless powder. Is somewhat hygroscopic and on exposure to air gradually absorbs carbon dioxide. Freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Incompatibility. Phenytoin sodium only remains in solution when the pH is considerably alkaline (about 10 to 12) and there have been reports of loss of clarity or precipitation of phenytoin crystals when solutions of phenytoin sodium for injection have been mixed with other drugs[1-6] or added to intravenous infusion fluids,[7-10] while binding has been reported after addition to enteral nutrition solutions.[11] A phenytoin precipitate has blocked implanted central venous access devices after the inadvertent admixture of phenytoin sodium with glucose 5% or glucose in sodium chloride (pH 4);[12,13] the blockage can be successfully cleared by the local instillation of sodium bicarbonate 8.4% to increase the pH of the medium.

1. Misgen R. Compatibilities and incompatibilities of some intravenous solution admixtures. *Am J Hosp Pharm* 1965; **22:** 92–4.
2. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23:** 409–11.
3. Klamerus KJ, *et al*. Stability of nitroglycerin in intravenous admixtures. *Am J Hosp Pharm* 1984; **41:** 303–5.
4. Hasegawa GR, Eder JF. Visual compatibility of dobutamine hydrochloride with other injectable drugs. *Am J Hosp Pharm* 1984; **41:** 949–51.
5. Gayed AA, *et al*. Visual compatibility of diltiazem injection with various diluents and medications during simulated Y-site injection. *Am J Health-Syst Pharm* 1995; **52**: 516–20.
6. Trissel LA, *et al*. Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1287–92.
7. Bauman JL, *et al*. Phenytoin crystallization in intravenous fluids. *Drug Intell Clin Pharm* 1977; **11:** 646–9.
8. Bauman JL, Siepler JK. Intravenous phenytoin (concluded). *N Engl J Med* 1977; **296:** 111.
9. Cloyd JC, *et al*. Concentration-time profile of phenytoin after admixture with small volumes of intravenous fluids. *Am J Hosp Pharm* 1978; **35:** 45–8.
10. Giacona N, *et al*. Crystallization of three phenytoin preparations in intravenous solutions. *Am J Hosp Pharm* 1982; **39:** 630–4.
11. Miller SW, Strom JG. Stability of phenytoin in three enteral nutrient formulas. *Am J Hosp Pharm* 1988; **45:** 2529–32.
12. Akinwande KI, Keehn DM. Dissolution of phenytoin precipitate with sodium bicarbonate in an occluded central various access device. *Ann Pharmacother* 1995; **29:** 707–9.
13. Tse CST, Abdullah R. Dissolving phenytoin precipitate in central venous access device. *Ann Intern Med* 1998; **128:** 1049.

Adverse Effects

Adverse effects are fairly frequent in patients receiving phenytoin, but some remit with dose reduction or continued use. Often reported are CNS-related effects (such as headache, dizziness, tremor, transient nervousness, and insomnia), and gastrointestinal disturbances including nausea, vomiting, and constipation. Tenderness and hyperplasia of the gums often occur, particularly in younger patients. Acne, hirsutism, and coarsening of the facial features may be associated with phenytoin therapy, and may be particularly undesirable in adolescents and women.

Phenytoin toxicity may be manifested as a syndrome of cerebellar, vestibular, and ocular effects, notably nystagmus, diplopia, slurred speech, and ataxia. Mental confusion, sometimes severe, may occur, and dyskinesias and exacerbations of seizure frequency have been noted. Hyperglycaemia has been associated with toxic concentrations.

Overdosage may result in hypotension, coma, and respiratory depression. Hypotension and CNS depression may also follow intravenous dosage, if too rapid, as may cardiac arrhythmias and impaired cardiac conduction. Solutions for injection are very alkaline and may result in irritation at the injection site or phlebitis. A syndrome of distal limb oedema, discoloration, and pain ('purple glove syndrome') has been reported occasionally.

Prolonged therapy may produce subtle effects on mental function and cognition, especially in children. In addition there is some evidence that phenytoin interferes with vitamin D and folate metabolism. Rickets and osteomalacia have occurred in a few patients not exposed to adequate sunlight, although the causal role of phenytoin is debatable. A proportion of patients develop peripheral neuropathies, usually mild, and occasional cases of megaloblastic anaemia have been seen.

Mild hypersensitivity reactions are common, with skin rashes, often morbilliform, sometimes accompanied by fever. Bullous, exfoliative, or purpuric rashes may be symptoms of rare but severe reactions such as lupus erythematosus, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Eosinophilia, lymphadenopathy, hepatitis, polyarteritis nodosa, and blood disorders such as aplastic anaemia, leucopenia, thrombocytopenia, and agranulocytosis, have occurred rarely; some of these conditions may also represent hypersensitivity reactions.

Hypoprothrombinaemia of the newborn after use of phenytoin during pregnancy has been reported. Congenital malformations have been seen in the offspring of mothers receiving phenytoin during pregnancy (see under Precautions, below).

Effects on the blood. ***AGRANULOCYTOSIS.*** Fatal agranulocytosis has been reported[1] in a patient 17 years after starting therapy with phenytoin and primidone. In the report it was stated that since 1963 the UK CSM had received reports of 3 previous cases of fatal agranulocytosis associated with phenytoin and none associated with primidone. The most likely cause was considered to be a direct toxic effect of phenytoin although other possible mechanisms included the ability of both drugs to produce folate deficiency. For a discussion of the effect of antiepileptics on serum folate, see below.

1. Laurenson IF, *et al*. Delayed fatal agranulocytosis in an epileptic taking primidone and phenytoin. *Lancet* 1994, **344:** 332–3.

FOLIC ACID DEFICIENCY. Antiepileptic therapy has long been associated with folate deficiency: early studies suggested that more than half of all patients on long-term therapy with drugs such as phenytoin, phenobarbital, and primidone had subnormal serum-folate concentrations.[1,2] Megaloblastic haematopoiesis is often present,[3] but clinical megaloblastic anaemia appears to be rare.

The relative importance of individual antiepileptics in causing folate deficiency and macrocytosis has been difficult to establish, because of the tendency to use combination regimens; with greater emphasis on single drug therapy there is evidence that monotherapy may produce less significant changes.[4,5] Despite suggestions that carbamazepine has relatively little effect on folic acid concentrations, its effects have been found to be comparable with those of phenytoin;[5] however, valproate had little or no effect on red cell folate concentrations.