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.

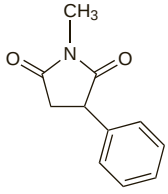
Фенсуксимид

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

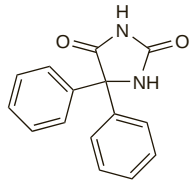
Фенитоин

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