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.

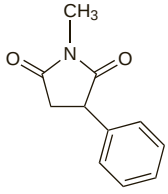
Фенсуксимид

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

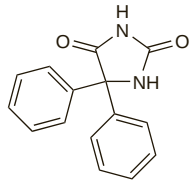
Фенитоин

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

The mechanism by which phenytoin and similar antiepileptics reduce serum folate is uncertain; there is good evidence for a reduction in absorption of glutamate both *in vitro*[6] and *in vivo*,[7] but the drugs associated with subnormal serum folate are all enzyme inducers and it has been suggested that enzyme induction and enhanced folate metabolism may also play a role.[2,5,8] Adverse blood changes also result from hypersensitivity (see below).

1. Horwitz SJ, *et al.* Relation of abnormal folate metabolism to neuropathy developing during anticonvulsant drug therapy. *Lancet* 1968; **i:** 563–5.
2. Maxwell JD, *et al.* Folate deficiency after anticonvulsant drugs: an effect of hepatic enzyme induction? *BMJ* 1972; **1:** 297–9.
3. Wickramasinghe SN, *et al.* Megaloblastic erythropoiesis and macrocytosis in patients on anticonvulsants. *BMJ* 1975; **4:** 136–7.
4. Dellaportas DI, *et al.* Chronic toxicity in epileptic patients receiving single-drug treatment. *BMJ* 1982; **285:** 409–10.
5. Goggin T, *et al.* A comparative study of the relative effects of anticonvulsant drugs and dietary folate on the red cell folate status of patients with epilepsy. *Q J Med* 1987; **NS65** (247): 911–9.
6. Hoffbrand AV, Necheles TF. Mechanism of folate deficiency in patients receiving phenytoin. *Lancet* 1968; **ii:** 528–30.
7. Rosenberg IH, *et al.* Impairment of intestinal deconjugation of dietary folate. *Lancet* 1968; **ii:** 530–2.
8. Kishi T, *et al.* Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy. *J Neurol Sci* 1997; **145:** 109–12.

Effects on bone. The effects of phenytoin and other antiepileptics on the skeletal system are a matter of some debate. There are numerous reports indicating effects on bone and on calcium and vitamin D metabolism. Therapy with *carbamazepine*, *phenobarbital*, or *phenytoin* has been associated with reduction in serum-calcium concentration to hypocalcaemic values, significant reduction in 25-hydroxycholecalciferol concentrations, and elevated alkaline phosphatase.[1] In this study, involving 226 outpatients with epilepsy, the association was not seen with *valproate*. The effects were significantly greater in the group of patients receiving polytherapy, and there was limited evidence that these biochemical changes were exacerbated by reduced exposure to sunlight. In contrast, measurements of bone mineral density (BMD) found that children treated for epilepsy have reduced BMD during the first 1 to 5 years of therapy and that this progressively deteriorates thereafter.[2] Studies[3-5] of children receiving antiepileptic monotherapy revealed a reduction in density in those taking *valproate*; no reduction was found with *carbamazepine*.[3,4] The authors of one study[5] concluded that longer duration of therapy and higher doses resulted in lower BMD, and that this effect appeared to be more prominent in children under 5 years of age. A study[6] in 54 male patients followed for 12 to 29 months revealed that treatment with antiepileptics was associated with bone loss at the hip in the absence of vitamin D deficiency. There was no evidence that any particular drug produced more bone loss than another. Risk factors appear to include treatment duration of more than 2 years, age of over 40 years, and use of enzyme-inducing antiepileptics; the greatest rate of bone loss occurred in those with a combination of risk factors.[7] In a large cohort study[8] of women aged 65 years and older, continuous use of antiepileptics, particularly *phenytoin*, almost doubled the rate of bone loss.

A review[9] stated that there have been no significant reports of altered bone metabolism associated with the newer antiepileptics (*gabapentin*, *lamotrigine*, *topiramate*, and *vigabatrin*). However, short stature, low BMD, and reduced bone formation have been reported with long-term *lamotrigine* treatment, particularly when used with *valproate*;[10] further study is needed. *Oxcarbazepine* was found to have[11] similar effects on bone and vitamin D metabolism to *carbamazepine*; both drugs were associated with a reduction in 25-hydroxycholecalciferol serum concentrations and an increased bone turnover.

A more recent literature review[12] considered that most studies to date have been limited by factors such as small sample size, possible selection bias, lack of appropriate controls, and not adjusting for potential confounders. Nevertheless, long-term antiepileptic therapy was found to have an adverse effect on BMD and to increase fracture risk in some patients; there was little information regarding the relative risk with different types of antiepileptics. The authors suggested monitoring indices of bone health, optimising lifestyle factors, maintaining vitamin D and calcium status, and preventing falls in patients on long-term therapy.

Despite these alterations in bone metabolism reports of clinical osteomalacia associated with antiepileptics are rare.[13] A study in 20 epileptic outpatients who had received antiepileptic therapy for a mean of 14 ⁄ years failed to show any clinical evidence of osteomalacia although there was some evidence of altered calcium metabolism.[14] Similarly osteomalacia was seen in only 1 of 19 elderly inpatients in another study,[15] a rate similar to that previously seen in elderly patients with acute illness not receiving antiepileptic therapy.

1. Gough H, *et al.* A comparative study of the relative influence of different anticonvulsant drugs, UV exposure and diet on vitamin D and calcium metabolism in out-patients with epilepsy. *Q J Med* 1986; **NS59** (230): 569–77.
2. Sheth RD, *et al.* Progressive bone deficit in epilepsy. *Neurology* 2008; **70:** 170–6.
3. Sheth RD, *et al.* Effect of carbamazepine and valproate on bone mineral density. *J Pediatr* 1995; **127:** 256–62.
4. Kafalı G, *et al.* Effect of antiepileptic drugs on bone mineral density in children between ages 6 and 12 years. *Clin Pediatr (Phila)* 1999; **38:** 93–8.
5. Öner N, *et al.* Bone mineral metabolism changes in epileptic children receiving valproic acid. *J Paediatr Child Health* 2004; **40:** 470–3.
6. Andress DL, *et al.* Antiepileptic drug-induced bone loss in young male patients who have seizures. *Arch Neurol* 2002; **59:** 781–6.
7. Petty SJ, *et al.* Effect of antiepileptic medication on bone mineral measures. *Neurology* 2005; **65:** 1358–63.
8. Ensrud KE, *et al.* Antiepileptic drug use increases rates of bone loss in older women: a prospective study. *Neurology* 2004; **62:** 2051–7.
9. Pack AM, Morrell MJ. Adverse effects of antiepileptic drugs on bone structure: epidemiology, mechanisms and therapeutic indications. *CNS Drugs* 2001; **15:** 633–42.
10. Guo C-Y, *et al.* Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. *Epilepsia* 2001; **42:** 1141–7.
11. Mintzer S, *et al.* Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. *Epilepsia* 2006; **47:** 510–15.
12. Petty SJ, *et al.* Anti-epileptic medication and bone health. *Osteoporos Int* 2007; **18:** 129–42.
13. Beghi E, *et al.* Adverse effects of anticonvulsant drugs: a critical review. *Adverse Drug React Acute Poisoning Rev* 1986; **2:** 63–86.
14. Fogelman I, *et al.* Do anticonvulsant drugs commonly induce osteomalacia? *Scott Med J* 1982; **27:** 136–42.
15. Harrington MG, Hodkinson HM. Anticonvulsant drugs and bone disease in the elderly. *J R Soc Med* 1987; **80:** 425–7.

Effects on the endocrine system and metabolism. Although it may be difficult to separate from the effects of the disease itself, there is some evidence that antiepileptics can diminish *sexual potency* and *fertility* in male epileptics. Phenytoin is excreted in human semen in small quantities and might affect sperm morphology and motility. Reduced plasma concentrations of free testosterone have been detected in male epileptic patients receiving one or more of the following: carbamazepine, phenytoin, primidone, and sodium valproate.[1] There is, however, some evidence[2] that some of the changes in sex hormone concentrations induced by antiepileptics in men and women are reversible. A higher frequency of sperm abnormalities has been found[3] in men given carbamazepine, oxcarbazepine, or valproate monotherapy when compared with healthy controls; those on valproate also had reduced testicular volume. Women may also have altered reproductive function and impaired fertility associated with antiepileptic therapy, particularly with the enzyme-inducing antiepileptics and valproate.[4]

Gynaecomastia has been reported[5] in 5 men receiving long-term antiepileptic treatment; one also complained of impotence but libido was stated to be normal in all 5. Phenytoin was a component of therapy in all patients and was the sole drug used in one.

Phenytoin may cause reversible *hyperglycaemia* at toxic doses but it does not appear to produce long-term effects on glucose tolerance when used in therapeutic doses.[6] Paradoxically, phenytoin has also been reported to improve insulin resistance in some patients. There has been a case report[7] of severe *hypoglycaemia* in a patient who was given intravenous phenytoin for the treatment of status epilepticus; symptoms resolved when glucose 5% was infused and no further episodes of hypoglycaemia occurred after phenytoin infusion was stopped.

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

1. Dana-Haeri J, *et al.* Reduction of free testosterone by antiepileptic drugs. *BMJ* 1982; **284:** 85–6.
2. Lossius MI, *et al.* Reversible effects of antiepileptic drugs on reproductive endocrine function in men and women with epilepsy—a prospective randomized double-blind withdrawal study. *Epilepsia* 2007; **48:** 1875–82.
3. Isojärvi JI, *et al.* Effect of epilepsy and antiepileptic drugs on male reproductive health. *Neurology* 2004; **62:** 247–53.
4. Isojärvi J. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. *Seizure* 2008; **17:** 111–19.
5. Monson JP, Scott DF. Gynaecomastia induced by phenytoin in men with epilepsy. *BMJ* 1987; **294:** 612.
6. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; **174:** 659–62.
7. Di Gennaro G, *et al.* Hypoglycaemia induced by phenytoin treatment for partial status epilepticus. *J Neurol Neurosurg Psychiatry* 2002; **73:** 349–50.

Effects on the liver. There have been occasional reports of liver damage, probably due to hypersensitivity, associated with phenobarbital and phenytoin; the authors of an early study suggested that such drugs need not be withdrawn if there were merely transient elevations in transaminase values,[1] but care is needed to distinguish such effects from the early symptoms of the antiepileptic hypersensitivity syndrome (see below).

1. Aiges HW, *et al.* The effects of phenobarbital and diphenylhydantoin on liver function and morphology. *J Pediatr* 1980; **97:** 22–6.

Effects on the lungs. Pulmonary eosinophilia and acute respiratory failure requiring mechanical ventilation have been reported[1] in a patient receiving phenytoin; other pulmonary symptoms associated with phenytoin were reviewed.

1. Mahatma M, *et al.* Phenytoin-induced acute respiratory failure with pulmonary eosinophilia. *Am J Med* 1989; **87:** 93–4.

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

Effects on the skin. A retrospective analysis involving 1890 outpatients taking antiepileptics found that rates of skin reactions associated with treatment varied with different drugs, the risk being greatest with carbamazepine, lamotrigine, and phenytoin, and lowest with gabapentin, levetiracetam, and valproate.[1] Overall, the rate of skin reactions in this study was 2.8%, but as also mentioned in Hypersensitivity, below (where more details on phenytoin-associated skin reactions are given), there appeared to be cross-sensitivity; risk in this study was increased to 8.8% in those who had previously experienced rash with another antiepileptic drug.

Rare, but severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have also occurred.

For reference to cutaneous manifestations of zinc deficiency, possibly due to chelation with phenytoin, see under Valproate, p.509.

1. Arif H, *et al.* Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 2007; **68:** 1701–9.

Gingival hyperplasia. Gingival hyperplasia, characterised by inflammation and a marked fibrotic response, may affect up to 50% of patients receiving phenytoin. It usually becomes apparent within the first few months of therapy and occurs more frequently in children; there is no increase in alveolar bone loss. The mechanism underlying its development is unknown, although the main metabolite of phenytoin, 5-(4-hydroxyphenyl)-5-phenylhydantoin, has been implicated.[1-3]

1. Ball DE, *et al.* Plasma and saliva concentrations of phenytoin and 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) in relation to gingival overgrowth in epilepsy patients. *Br J Clin Pharmacol* 1995; **39:** 539P–588P.
2. Ieiri I, *et al.* Effect of 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) enantiomers, major metabolites of phenytoin, on the occurrence of chronic-gingival hyperplasia: in vivo and in vitro study. *Eur J Clin Pharmacol* 1995; **49:** 51–6.
3. Zhou LX, *et al.* Metabolism of phenytoin by the gingiva of normal humans: the possible role of reactive metabolites of phenytoin in the initiation of gingival hyperplasia. *Clin Pharmacol Ther* 1996; **60:** 191–8.

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 antiepileptic drugs including phenytoin.[1-3] Clinical manifestations may include interstitial nephritis, anaemia, interstitial pulmonary infiltrates, thrombocytopenia, eosinophilia, myopathy, and diffuse intravascular coagulation.[1,2] Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic antiepileptics,[2,3] 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. The mean interval to onset is 17 to 21 days with phenytoin. In previously sensitised individuals the reaction may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is approximately 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[2] An early review[1] of the syndrome in patients taking phenytoin commented that it occurred mainly in black male patients and should not be confused with more common mild general hypersensitivity reactions. More recent evidence does not suggest that ethnic origin predicts differences in risk.[2]

Most cases resolve spontaneously on withdrawal of the drug and symptomatic management. The use of corticosteroids in the management of severe cases remains controversial in the absence of controlled studies of their effectiveness.[1,2]

Phenytoin-induced pseudolymphoma mimicking cutaneous T-cell lymphoma has also been reported.[2,4] In most cases, symptoms resolve within 7 to 14 days of stopping the drug, and the condition is not considered premalignant.[2] However, in one report[4] the cutaneous eruption and lymphadenopathy persisted after withdrawal of phenytoin for one year when the patient eventually became asymptomatic.

In a prospective study[5] of 306 patients given phenytoin there was an overall incidence of 8.5% of morbilliform rash, but there was a marked seasonal incidence with most reactions occurring during the summer months. The results did not appear to be due to photosensitivity and might represent seasonal alterations in the immune system.

1. Flowers FP, *et al.* Phenytoin hypersensitivity syndrome. *J Emerg Med* 1987; **5:** 103–8.
2. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21:** 489–501.
3. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35:** 533–8.
4. Harris DWS, *et al.* Phenytoin-induced pseudolymphoma: a report of a case and review of the literature. *Br J Dermatol* 1992; **127:** 403–6.
5. Leppik IE, *et al.* Seasonal incidence of phenytoin allergy unrelated to plasma levels. *Arch Neurol* 1985; **42:** 120–2.

Peripheral neuropathies. Electrophysiological abnormalities after prolonged phenytoin treatment are common, but clinically significant peripheral neuropathy is rare.[1] The neuropathy usually involves sensory nerves and lesions are generally mild and asymptomatic.[2] Much of the reported clinical neuropathy has been associated with multiple drug therapy of epilepsy and with exposure to toxic concentrations of phenytoin.[1,3] Although an association with folate deficiency has been suggested, a study in 52

patients on long-term antiepileptic therapy failed to find any convincing evidence of a relationship between serum-folate concentration and peripheral neuropathy.[4]

1. Bruni J. Phenytoin and other hydantoins: adverse effects. In: Levy RH, *et al.*, eds. *Antiepileptic drugs*. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002; 605–10.
2. Argov Z, Mastaglia FL. Drug-induced peripheral neuropathies. *BMJ* 1979; **1:** 663–6.
3. Toth C, Kotecha SA. Prolonged and excessive phenytoin therapy leading to a severe and partially reversible polyneuropathy. *J Peripher Nerv Syst* 2004; **9:** 198–9.
4. Horwitz SJ, *et al.* Relation of abnormal folate metabolism to neuropathy developing during anticonvulsant drug therapy. *Lancet* 1968; **i:** 563–5.

Treatment of Adverse Effects

Treatment of poisoning with phenytoin tends to be supportive. Repeated doses of activated charcoal may be given orally to adults and children who have ingested more than 20 mg/kg; the aim is not only to prevent absorption but also to aid elimination. Gastric lavage may be considered if a very large amount has been taken within 1 hour.

◊ Multiple oral doses of activated charcoal may reduce the absorption of phenytoin[1,2] but the degree of clinical benefit is unclear.[3] The value of charcoal haemoperfusion in the management of phenytoin overdosage is debatable. A review of haemoperfusion included data from 2 patients who ingested phenytoin[4] but, although it was suggested that haemoperfusion should contribute significantly to drug removal, results are difficult to evaluate in these patients who had also ingested phenobarbital. An evaluation in a patient who had also taken primidone[5] suggested that, although initial clearance of phenytoin was promising, the system rapidly became saturated and there was little overall benefit. A review[3] of the features and management of phenytoin poisoning concluded that supportive care is the mainstay of treatment. Gastric lavage and multiple-dose activated charcoal should not be used routinely, although they might be considered for life-threatening ingestion. They were most effective when used within 1 hour of ingestion; the airway should be secured first. Extracorporeal methods of elimination (e.g. haemodialysis, haemoperfusion, peritoneal dialysis, or plasmapheresis) had not been shown to be of benefit;[3] however, some such procedures may be beneficial in patients with renal failure[3] or hypoalbuminaemia[6] in whom free phenytoin concentrations are raised.

1. Weidle PJ, *et al.* Multiple-dose activated charcoal as adjunct therapy after chronic phenytoin intoxication. *Clin Pharm* 1991; **10:** 711–14.
2. Dolgin JG, *et al.* Pharmacokinetic simulation of the effect of multiple-dose activated charcoal in phenytoin poisoning—report of two pediatric cases. *DICP Ann Pharmacother* 1991; **25:** 646–9.
3. Craig S. Phenytoin poisoning. *Neurocrit Care* 2005; **3:** 161–70.
4. Pond S, *et al.* Pharmacokinetics of haemoperfusion for drug overdose. *Clin Pharmacokinet* 1979; **4:** 329–54.
5. Baehler RW, *et al.* Charcoal hemoperfusion in the therapy for methsuximide and phenytoin overdose. *Arch Intern Med* 1980; **140:** 1466–8.
6. De Schoenmakere G, *et al.* Phenytoin intoxication in critically ill patients. *Am J Kidney Dis* 2005; **45:** 189–92.

Precautions

Phenytoin is metabolised in the liver and should be given with care to patients with impaired liver function. Caution is also advocated in diabetic patients because of the potential effects of phenytoin on blood sugar.

Protein binding may be reduced in certain disease states such as uraemia, and in certain patient populations such as neonates, pregnant women, and the elderly. Although phenytoin is extensively protein bound this may be of little clinical significance in itself, provided that hepatic function is not impaired, because the concentration of free (pharmacologically active) drug in the plasma often remains more or less unchanged, due to distribution, metabolism, and excretion. Thus, an alteration in protein binding would not necessarily require a change in dosage of phenytoin to be made although, when plasma concentrations are being monitored, relatively lower total plasma-phenytoin concentrations will be found to be effective since there is less bound (pharmacologically inactive) phenytoin available for measurement.

Intravenous phenytoin must be given slowly and extravasation and intra-arterial injection must be avoided. Phenytoin should not be given intravenously to patients with sinus bradycardia, heart block, or Stokes-Adams syndrome, and should be used with caution in patients with hypotension, heart failure, or myocardial infarction; monitoring of blood pressure and the ECG is recommended during intravenous use.

Patients or their carers should be told how to recognise signs of blood or skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Phenytoin should be stopped, if necessary under cover of a suitable alternative antiepileptic, if leucopenia which is severe, progressive, or associated with clinical symptoms develops. It should also be stopped if a skin rash develops; in the case of mild rashes phenytoin may be reintroduced cautiously, but should be stopped immediately and permanently if the rash recurs.

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

Phenytoin may interfere with some tests of thyroid function as it can reduce free and circulating concentrations of levothyroxine, mainly by enhanced conversion to tri-iodothyronine, and it may also produce lower than normal values for dexamethasone and metyrapone suppression tests.

Breast feeding. The American Academy of Pediatrics[1] considers that phenytoin is usually compatible with breast feeding, although there had been an early case report of methaemoglobinaemia in a breast-fed infant.

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 comment on antiepileptic drugs and driving, see p.468.

Infections. A 52-year-old woman previously well-controlled on phenytoin 400 mg daily suffered phenytoin toxicity after a viral infection;[1] her plasma-phenytoin concentration had increased from 16 to 51 micrograms/mL. Six weeks later she had recovered and was re-stabilised on phenytoin 400 mg daily.

1. Levine M, Jones MW. Toxic reaction to phenytoin following a viral infection. *Can Med Assoc J* 1983; **128:** 1270–1.

AIDS. Renal abnormalities or hypoalbuminaemia associated with AIDS may increase the risk of elevated free phenytoin concentrations and subsequent toxicity. Altered protein binding resulted in marked phenytoin toxicity, with lethargy and seizure-like activity, in an HIV-positive patient with profound hypoalbuminaemia and moderate renal insufficiency.[1] Therapeutic drug monitoring in 21 patients with AIDS indicated that although total serum concentrations of phenytoin were lower than in a reference population, the fraction of unbound drug was higher.[2] These changes might be attributed to hypoalbuminaemia and it was suggested that free rather than total phenytoin concentrations should be measured in HIV-infected patients with hypoalbuminaemia.

Phenytoin itself was associated with reversible hypogammaglobulinaemia in an HIV-positive patient who previously had borderline hypergammaglobulinaemia.[3]

1. Toler SM, *et al.* Severe phenytoin intoxication as a result of altered protein binding in AIDS. *DICP Ann Pharmacother* 1990; **24:** 698–700.
2. Burger DM, *et al.* Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. *Ther Drug Monit* 1994; **16:** 616–20.
3. Britigan BE. Diphenylhydantoin-induced hypogammaglobulinemia in a patient infected with human immunodeficiency virus. *Am J Med* 1991; **90:** 524–7.

Porphyria. Phenytoin 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.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including phenytoin, and a variety of syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described. Specific syndromes such as the 'fetal hydantoin syndrome' with phenytoin have been linked to individual antiepileptics. However, there is overlap between the effects seen with different antiepileptics and these are now often seen as aspects of a single 'fetal antiepileptic syndrome'. There is also a risk of neonatal bleeding with phenytoin.

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.

Since phenytoin is extensively bound to plasma proteins it can be displaced by drugs competing for protein-binding sites, thus liberating more free (pharmacologically active) phenytoin into the plasma. However, elevation of free phenytoin is reported to be of little clinical significance provided hepatic function is not impaired (see Precautions, above). A potentially more serious type of interaction may occur because phenytoin metabolism is saturable: toxic concentrations of phenytoin can develop in patients given drugs that inhibit phenytoin metabolism even to quite a minor degree. Phenytoin itself is also a potent enzyme inducer, and induces the metabolism of a number of drugs, including some antibacterials, anticoagulants, corticosteroids, quinidine, and sex hormones (notably, oral contraceptives).

The hypotensive properties of dopamine and the cardiac depressant properties of drugs such as lidocaine may be dangerously enhanced by intravenous phenytoin.

◊ General references.

1. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin. *Clin Pharmacokinet* 1990; **18:** 37–60 and 131–150.

Anaesthetics. A 10-year-old girl with epilepsy who had been treated with phenytoin 100 mg three times daily for 5 years and who had lateral nystagmus developed symptoms of phenytoin intoxication after anaesthesia with *halothane*.[1] The plasma concentration of phenytoin 72 hours after anaesthesia was 41 microgram/mL. It was suggested that temporary liver dysfunction was responsible for impaired metabolism of phenytoin.

1. Karlin JM, Kutt H. Acute diphenylhydantoin intoxication following halothane anesthesia. *J Pediatr* 1970; **76:** 941–4.

Analgesics. *Aspirin* is reported to displace phenytoin from plasma binding[1,2] but there is no evidence of any effect on metabolism and effects are unlikely to be clinically significant.[3,4] *Paracetamol* is reported to have no significant effect on serum-phenytoin concentrations.[4] (However, enzyme-inducing antiepileptics such as phenytoin affect the threshold for use of antidote in the treatment of paracetamol poisoning, see p.110.) Alterations of the pharmacokinetics of phenytoin have been reported with *bromfenac*, but it was thought unlikely that a change in phenytoin dose would be necessary.[5]

Other analgesic and anti-inflammatory drugs may have clinically significant effects. *Phenylbutazone* has been reported to cause an initial decrease in serum phenytoin, followed by an increase;[4] in addition to effects on protein binding it inhibits phenytoin metabolism[6] and severe phenytoin toxicity may result.[7] *Azapropazone* appears to be a competitive inhibitor of phenytoin metabolism and has also been implicated in interactions resulting in toxicity.[8,9] Substantial increases in serum phenytoin have been found in healthy subjects given the analgesic and muscle relaxant *fenyramidol*,[10] indicating a potential for toxicity. There is a single report of toxicity in a patient receiving *ibuprofen* with phenytoin[11] but in a study in 9 healthy subjects, ibuprofen had no effect on the pharmacokinetics of phenytoin.[12] In another report, phenytoin toxicity developed[13] in a patient who was also taking *celecoxib*.

The opioid analgesic *dextropropoxyphene* has also been reported to affect phenytoin metabolism, with the resultant development of toxic blood-phenytoin concentrations;[14] however, the patient in this case was taking relatively high doses of dextropropoxyphene (650 mg daily). For the effect of phenytoin on *methadone* and *pethidine*, see p.84 and p.114, respectively.

1. Fraser DG, *et al.* Displacement of phenytoin from plasma binding sites by salicylate. *Clin Pharmacol Ther* 1980; **27:** 165–9.
2. Paxton JW. Effects of aspirin on salivary and serum phenytoin kinetics in healthy subjects. *Clin Pharmacol Ther* 1980; **27:** 170–8.
3. Leonard RF, *et al.* Phenytoin-salicylate interaction. *Clin Pharmacol Ther* 1981; **29:** 56–60.
4. Neuvonen PJ, *et al.* Antipyretic analgesics in patients on antiepileptic drug therapy. *Eur J Clin Pharmacol* 1979; **15:** 263–8.
5. Gumbhir-Shah K, *et al.* Evaluation of pharmacokinetic interaction between bromfenac and phenytoin in healthy males. *J Clin Pharmacol* 1997; **37:** 160–8.
6. Andreasen PB, *et al.* Diphenylhydantoin half-life in man and its inhibition by phenylbutazone: the role of genetic factors. *Acta Med Scand* 1973; **193:** 561–4.
7. Kristensen MB. Drug interactions and clinical pharmacokinetics. *Clin Pharmacokinet* 1976; **1:** 351–72.
8. Roberts CJC, *et al.* Anticonvulsant intoxication precipitated by azapropazone. *Postgrad Med J* 1981; **57:** 191–2.
9. Geaney DP, *et al.* Interaction of azapropazone with phenytoin. *BMJ* 1982; **284:** 1373.
10. Solomon HM, Schrogie JJ. The effect of phenyramidol on the metabolism of diphenylhydantoin. *Clin Pharmacol Ther* 1967; **8:** 554–6.
11. Sandyk R. Phenytoin toxicity induced by interaction with ibuprofen. *S Afr Med J* 1982; **62:** 592.
12. Townsend RJ, *et al.* The effects of ibuprofen on phenytoin pharmacokinetics. *Drug Intell Clin Pharm* 1985; **19:** 447–8.
13. Keeling KL, *et al.* Prolonged elimination half-life of phenytoin in an elderly patient also on celecoxib. *Clin Chem* 2002; **48** (suppl): A52–A53.
14. Kutt H. Interactions between anticonvulsants and other commonly prescribed drugs. *Epilepsia* 1984; **25** (suppl 2): S118–S131.

Anthelmintics. For report of an interaction between phenytoin and *levamisole* with fluorouracil, see Antineoplastics, below. For the effect of phenytoin on *mebendazole* and *praziquantel*, see p.149 and p.154, respectively.

Antiarrhythmics. There have been reports of phenytoin toxicity associated with substantial rises in serum-phenytoin concentrations after addition of *amiodarone* to the therapeutic regimen.[1,2] For the effect of phenytoin on amiodarone, see p.1212.

For the effect of phenytoin on other antiarrhythmics, see p.1270 (disopyramide), p.1340 (mexiletine), p.1384 (quinidine), and p.1863 (lidocaine).

1. Gore JM, *et al.* Interaction of amiodarone and diphenylhydantoin. *Am J Cardiol* 1984; **54:** 1145.
2. McGovern B, *et al.* Possible interaction between amiodarone and phenytoin. *Ann Intern Med* 1984; **101:** 650.

Antibacterials. Interactions, some clinically significant, may occur between phenytoin and various antibacterials. Giving *chloramphenicol* with phenytoin has resulted in moderate[1] to marked[2] elevation of serum-phenytoin concentrations due to inhibition of phenytoin metabolism;[2] toxicity has resulted.[3,4] In turn, phenytoin may affect serum concentrations of chloramphenicol (see p.240).

Phenytoin may enhance the metabolism of *doxycycline*.[5]

There is limited evidence that *erythromycin* decreases phenytoin clearance[6] but this was subject to considerable interindividual variation and is of unknown clinical significance. Results from another study[7] suggested that *clarithromycin* might also raise phenytoin levels.

The interaction with *isoniazid* is well documented and potentially significant in slow acetylators of isoniazid who may develop raised phenytoin concentrations and signs of toxicity;[8,9] in at least one case, death has resulted.[10] Plasma-isoniazid concentrations may become sufficiently raised in slow acetylators of isoniazid to produce marked inhibition of the hepatic microsomal enzymes responsible for the metabolism of phenytoin.

There have been conflicting reports of the effect of *ciprofloxacin* on serum concentrations of phenytoin. While some report no effect[11] others have reported reduced[12-16] or increased[17,18] concentrations of phenytoin in patients given ciprofloxacin. A fall in serum-phenytoin concentrations, and resultant loss of seizure control has been reported in a patient in whom *nitrofurantoin* was added to therapy.[19] The mechanism of this interaction is unknown although a combination of impaired absorption and increased metabolism of the phenytoin was suggested. Something similar was reported in a patient given *oxacillin* in whom plasma-phenytoin concentrations dropped markedly and status epilepticus developed.[20] This effect was thought to be due to impaired phenytoin absorption.

Rifampicin can also reduce plasma-phenytoin concentrations and markedly increase its clearance;[21,22] this is in marked contrast to the effects of isoniazid, and when given together it overrides the effects of isoniazid on phenytoin, even in slow acetylators.[22]

Various sulfonamides are reported to interact with phenytoin, reducing clearance and prolonging half-life: *sulfaphenazole* is reportedly the strongest inhibitor of phenytoin metabolism but *sulfamethizole* also inhibits phenytoin metabolism and the latter has been implicated in producing phenytoin toxicity.[23] *Co-trimoxazole* reportedly inhibits phenytoin metabolism to a modest degree; a case of phenytoin toxicity in a child given co-trimoxazole has been reported[24] but the role of the co-trimoxazole is uncertain since the patient was also receiving sultiame. Fatal acute fulminant hepatic failure in a 60-year-old patient was suggested[25] to be due to phenytoin-induced hepatitis exacerbated by addition of co-trimoxazole to her drug regimen.

See also Antiprotozoals, below.

1. Koup JR, *et al.* Interaction of chloramphenicol with phenytoin and phenobarbital. *Clin Pharmacol Ther* 1978; **24:** 571–5.
2. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; **ii:** 1397–9.
3. Ballek RE, *et al.* Inhibition of diphenylhydantoin metabolism by chloramphenicol. *Lancet* 1973; **i:** 150.
4. Rose JQ, *et al.* Intoxication caused by interaction of chloramphenicol and phenytoin. *JAMA* 1977; **237:** 2630–1.
5. Neuvonen PJ, *et al.* Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* 1975; **9:** 147–54.
6. Bachmann K, *et al.* Single dose phenytoin clearance during erythromycin treatment. *Res Commun Chem Pathol Pharmacol* 1984; **46:** 207–17.
7. Burger DM, *et al.* Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. *Ther Drug Monit* 1994; **16:** 616–20.
8. Brennan RW, *et al.* Diphenylhydantoin intoxication attendant to slow inactivation of isoniazid. *Neurology* 1970; **20:** 687–93.
9. Kutt H, *et al.* Diphenylhydantoin intoxication: a complication of isoniazid therapy. *Am Rev Respir Dis* 1970; **101:** 377–84.
10. Johnson J, Freeman HL. Death due to isoniazid (INH) and phenytoin. *Br J Psychiatry* 1976; **129:** 511.
11. Slavich IL, *et al.* Grand mal epileptic seizures during ciprofloxacin therapy. *JAMA* 1989; **261:** 558–9.
12. Dillard ML, *et al.* Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* 1992; **26:** 263.
13. Pollak PT, Slayter KL. Hazards of doubling phenytoin dose in the face of an unrecognized interaction with ciprofloxacin. *Ann Pharmacother* 1997; **31:** 61–4.
14. Brouwers PJ, *et al.* Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* 1997; **31:** 498.
15. McLeod R, Trinkle R. Unexpectedly low phenytoin concentration in a patient receiving ciprofloxacin. *Ann Pharmacother* 1998; **32:** 1110–11.
16. Otero M-J, *et al.* Interaction between phenytoin and ciprofloxacin. *Ann Pharmacother* 1999; **33:** 251–2.
17. Schroeder D, *et al.* Effect of ciprofloxacin on serum phenytoin concentrations in epileptic patients. *Pharmacotherapy* 1991; **11:** 276.
18. Hull RL. Possible phenytoin-ciprofloxacin interaction. *Ann Pharmacother* 1993; **27:** 1283.
19. Heipertz R, Pilz H. Interaction of nitrofurantoin with diphenylhydantoin. *J Neurol* 1978; **218:** 297–301.
20. Fincham RW, *et al.* Use of phenytoin serum levels in a case of status epilepticus. *Neurology* 1976; **26:** 879–81.
21. Wagner JC, Slama TG. Rifampin-phenytoin drug interaction. *Drug Intell Clin Pharm* 1984; **18:** 497.
22. Kay L, *et al.* Influence of rifampicin and isoniazid on the kinetics of phenytoin. *Br J Clin Pharmacol* 1985; **20:** 323–6.
23. Siersbaek-Nielsen K, *et al.* Sulfamethizole-induced inhibition of diphenylhydantoin and tolbutamide metabolism in man. *Clin Pharmacol Ther* 1973; **14:** 148.
24. Gillman MA, Sandyk R. Phenytoin toxicity and co-trimoxazole. *Ann Intern Med* 1985; **102:** 559.
25. Ilario MJ-M, *et al.* Acute fulminant hepatic failure in a woman treated with phenytoin and trimethoprim-sulfamethoxazole. *Arch Pathol Lab Med* 2000; **124:** 1800–3.

Anticoagulants. Serum-phenytoin concentrations have been reported to be markedly elevated by *dicoumarol*[1,2] and elevated to a lesser extent by *phenprocoumon*;[2] however, although *warfarin* has been implicated in a report of phenytoin toxicity,[3] other evidence suggests that it has no effect on serum-phenytoin concentrations in most patients.[2]

For the effect of phenytoin on anticoagulants such as dicoumarol and warfarin, see p.1429.

1. Hansen JM, *et al.* Dicoumarol-induced diphenylhydantoin intoxication. *Lancet* 1966; **ii:** 265–6.
2. Skovsted L, *et al.* The effect of different oral anticoagulants on diphenylhydantoin and tolbutamide metabolism. *Acta Med Scand* 1976; **199:** 513–5.
3. Rothermich NO. Diphenylhydantoin intoxication. *Lancet* 1966; **ii:** 640.

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

Plasma-phenytoin concentrations rose in 2 epileptic patients also receiving *imipramine* 75 mg daily for about 3 months for depression.[1] In one patient the concentration gradually increased over several weeks to more than twice the pretreatment figure and he showed mild signs of phenytoin intoxication, which remitted after imipramine was stopped. Increased serum-phenytoin concentration and phenytoin toxicity possibly precipitated by addition of *trazodone* has been described;[2] licensed product information for trazodone recommends monitoring serum-phenytoin concentrations in patients receiving these two drugs. Elevated plasma-phenytoin concentrations, in some cases accompanied by signs and symptoms of phenytoin toxicity, have also been reported with *fluoxetine*,[3] *fluvoxamine*,[4,5] *sertraline*,[6] and *viloxazine*.[7] Product information for *mianserin* also recommends that plasma concentrations of phenytoin should be monitored carefully when both are given.

St John's wort has been shown to induce several drug metabolising enzymes (see p.423) and consequently it might reduce the blood concentrations of phenytoin leading to an increased risk of seizure.[8] Some licensed product information for phenytoin in the UK therefore recommends that phenytoin should not be used with St John's wort and warns that the effects of St John's wort may persist for at least 2 weeks after it was last used.

For the effects of phenytoin on antidepressants, see under Amitriptyline (p.380), Fluoxetine (p.396), and Lithium (p.404).

1. Perucca E, Richens A. Interaction between phenytoin and imipramine. *Br J Clin Pharmacol* 1977; **4:** 485–6.
2. Dorn JM. A case of phenytoin toxicity possibly precipitated by trazodone. *J Clin Psychiatry* 1986; **47:** 89–90.
3. Nightingale SL. Fluoxetine labeling revised to identify phenytoin interaction and to recommend against use in nursing mothers. *JAMA* 1994; **271:** 1067.
4. Feldman D, *et al.* Cas clinique d'interaction médicamenteuse entre phénytoïne et fluvoxamine. *J Pharm Clin* 1995; **14:** 296–7.
5. Mamiya K, *et al.* Phenytoin intoxication induced by fluvoxamine. *Ther Drug Monit* 2001; **23:** 75–7.
6. Haselberger MB, *et al.* Elevated serum phenytoin concentrations associated with coadministration of sertraline. *J Clin Psychopharmacol* 1997; **17:** 107–9.
7. Pisani F, *et al.* Elevation of plasma phenytoin by viloxazine in epileptic patients: a clinically significant interaction. *J Neurol Neurosurg Psychiatry* 1992; **55:** 126–7.
8. 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)

Antidiabetics. Transient rises in the amount of non-protein-bound phenytoin were observed in 17 patients when *tolbutamide* was given in addition to phenytoin, but none developed signs of intoxication.[1] Toxic symptoms were reported in another patient given phenytoin with tolbutamide, although she had tolerated this combination on a previous occasion.[2]

Symptoms of phenytoin toxicity are known to have occurred[1] in one patient receiving *tolazamide* and phenytoin.

1. Wesseling H, Mols-Thürkow I. Interaction of diphenylhydantoin (DPH) and tolbutamide in man. *Eur J Clin Pharmacol* 1975; **8:** 75–8.
2. Beech E, *et al.* Phenytoin toxicity produced by tolbutamide. *BMJ* 1988; **297:** 1613–14.

Antiepileptics. Interactions may occur when phenytoin is used with other antiepileptics, but these are often variable in their effect and difficult to predict.

For a discussion of the effect of *benzodiazepines* on plasma concentrations of phenytoin, see Benzodiazepines, below.

Carbamazepine has been generally reported to lower serum-phenytoin concentrations,[1,2] although reports exist of elevated serum-phenytoin concentrations when the two were given concurrently.[3] It should be noted that phenytoin also reduces serum-carbamazepine values—see p.474. These studies have not indicated any loss of seizure control due to this interaction.

For the effects of phenytoin on *ethosuximide*, see p.480.

Felbamate has caused increases in serum-phenytoin concentrations, and in some cases toxicity requiring a reduction in phenytoin dose.[4,5]

Increased plasma concentrations of phenytoin with symptoms of toxicity have been reported in a patient receiving phenytoin, carbamazepine, and clobazam after *gabapentin* was added to treatment.[6]

Phenytoin reduces plasma concentrations of *lamotrigine* as described on p.486.

Phenytoin plasma concentrations may be increased by high doses of *oxcarbazepine*;[7] licensed product information for oxcarbazepine suggests that doses of phenytoin may need to be reduced when high doses of oxcarbazepine are given.

Phenobarbital both induces the metabolism of phenytoin and competes with it for metabolism by the same enzyme system; in practice there is rarely sufficient alteration for a change in phenytoin dosage to be necessary.[8-10] For the effect of phenytoin on phenobarbital, see p.493. Phenytoin has also been reported to enhance the metabolism of *primidone* to phenobarbital, see p.503.

The GABA agonist *progabide* increased blood-phenytoin concentrations[11] and *stiripentol* appears to produce a dose-dependent reduction in phenytoin clearance.[12]

Sultiame causes substantial increases in plasma-phenytoin concentrations, in some cases resulting in phenytoin toxicity;[13] the dose of phenytoin may therefore require adjustment if these drugs are given together.

Modest increases in plasma-phenytoin concentrations have been observed in some patients when *topiramate* was added to therapy, but it was considered that dosage adjustments were unlikely to be necessary.[14] For the effect of phenytoin on topiramate, see p.506.

The interaction between phenytoin and *valproate* is complex. Valproate displaces phenytoin from serum binding sites and may inhibit its metabolism;[15] the former effect increases the concentration of free drug but reduces total serum phenytoin.[16,17] Most studies seem to suggest that the dose of phenytoin need only rarely be adjusted, but the possibility of loss of seizure control, or phenytoin toxicity, does exist.[15] Interestingly there is some evidence that the interactions may be affected by circadian variations in valproate concentrations.[18] Total plasma-phenytoin concentrations rose significantly in 9 of 11 patients, 2 of whom developed toxic symptoms, when the formulation of sodium valproate that they were taking with phenytoin was changed from a standard tablet to a slow-release form.[19] The authors hypothesised that reduced diurnal fluctuations in plasma-valproate concentrations due to the use of slow-release tablets reduced the displacement interaction between phenytoin and valproate, thereby increasing total plasma-phenytoin concentrations. Phenytoin may also cause a fall in serum concentrations of valproate—see p.511.

Gradual or delayed reductions in plasma-phenytoin concentrations have been seen in several studies in patients given *vigabatrin*;[20] a review[20] states that concentrations have been reduced by 20 to 30%. The manufacturer of vigabatrin considers that this is unlikely to be of clinical significance although in a study the reduction was considered to compromise seizure control.[21]

1. Hansen JM, *et al.* Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* 1971; **12:** 539–43.
2. Windorfer A, Sauer W. Drug interactions during anticonvulsant therapy in childhood: diphenylhydantoin, primidone, phenobarbitone, clonazepam, nitrazepam, carbamazepin, and dipropylacetate. *Neuropadiatrie* 1977; **8:** 29–41.
3. Zielinski JJ, *et al.* Carbamazepine-phenytoin interaction: elevation of plasma phenytoin concentrations due to carbamazepine comedication. *Ther Drug Monit* 1985; **7:** 51–3.
4. Sheridan PH, *et al.* Open pilot study of felbamate (ADD03055) in partial seizures. *Epilepsia* 1986; **27:** 649.
5. Wilensky AJ, *et al.* Pharmacokinetics of W-554 (ADD 03055) in epileptic patients. *Epilepsia* 1985; **26:** 602–6.
6. Tyndel F. Interaction of gabapentin with other antiepileptics. *Lancet* 1994; **343:** 1363–4.
7. Hossain M, *et al.* Drug-drug interaction profile of oxcarbazepine in children and adults. *Neurology* 1999; **52** (suppl 2): A525.
8. Morselli PL, *et al.* Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. *Ann N Y Acad Sci* 1971; **179:** 88–107.
9. Cucinell SA, *et al.* Drug interactions in man: 1. lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin). *Clin Pharmacol Ther* 1965; **6:** 420–9.
10. Booker HE, *et al.* Concurrent administration of phenobarbital and diphenylhydantoin: lack of an interference effect. *Neurology* 1971; **21:** 383–5.
11. Bianchetti G, *et al.* Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia* 1987; **28:** 68–73.

12. Levy RH, *et al.* Stiripentol kinetics in epileptic patients: nonlinearity and interactions. *Epilepsia* 1984; **25:** 657.
13. Hansen JM, *et al.* Sulthiame (Ospolot) as inhibitor of diphenylhydantoin metabolism. *Epilepsia* 1968; **9:** 17–22.
14. Bourgeois BFD. Drug interaction profile of topiramate. *Epilepsia* 1996; **37** (suppl 2): S14–S17.
15. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.
16. Monks A, Richens A. Effect of single doses of sodium valproate on serum phenytoin levels and protein binding in epileptic patients. *Clin Pharmacol Ther* 1980; **27:** 89–95.
17. Perucca E, *et al.* Interaction between phenytoin and valproic acid: plasma protein binding and metabolic effects. *Clin Pharmacol Ther* 1980; **28:** 779–89.
18. Riva R, *et al.* Time-dependent interaction between phenytoin and valproic acid. *Neurology* 1985; **35:** 510–15.
19. Suzuki Y, *et al.* Interaction between valproate formulation and phenytoin concentrations. *Eur J Clin Pharmacol* 1995; **48:** 61–3.
20. Grant SM, Heel RC. Vigabatrin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. *Drugs* 1991; **41:** 889–926.
21. Browne TR, *et al.* Vigabatrin for refractory complex partial seizures: multicenter single-blind study with long-term follow-up. *Neurology* 1987; **37:** 184–9.

Antifungals. There have been several reports of interactions, sometimes resulting in phenytoin toxicity, between imidazole antifungals and phenytoin. The drug most frequently implicated is *miconazole*.[1-3] The related triazole antifungals *fluconazole*[4-6] and *voriconazole*[7] are also reported to interact with phenytoin,[4-6] possibly due to dose-related inhibition of cytochrome P450 isoenzymes by these antifungals.[4,7]

Phenytoin can decrease plasma concentrations of azole antifungals such as *ketoconazole*, voriconazole, and *itraconazole*.

1. Bourgoin B, *et al.* Interaction pharmacocinétique possible phénytoïne-miconazole. *Therapie* 1981; **36:** 347–9.
2. Loupi E, *et al.* Interactions médicamenteuses et miconazole. *Therapie* 1982; **37:** 437–41.
3. Rolan PE, *et al.* Phenytoin intoxication during treatment with parenteral miconazole. *BMJ* 1983; **287:** 1760.
4. Mitchell AS, Holland JT. Fluconazole and phenytoin: a predictable interaction. *BMJ* 1989; **298:** 1315.
5. Howitt KM, Oziemski MA. Phenytoin toxicity induced by fluconazole. *Med J Aust* 1989; **151:** 603–4.
6. Cadle RM, *et al.* Fluconazole-induced symptomatic phenytoin toxicity. *Ann Pharmacother* 1994; **28**: 191–5.
7. Purkins L, *et al.* Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. *Br J Clin Pharmacol* 2003; **56** (suppl 1): 37–44.

Antigout drugs. Licensed product information for *sulfinpyrazone* states that it displaces phenytoin from its protein-binding sites, and also inhibits microsomal liver enzymes. The net result is an increase in plasma-phenytoin concentrations and a prolonged half-life, which is potentially hazardous.

Reduced doses of phenytoin were necessary to avoid toxicity when *allopurinol* was added to the therapy of a child with the Lesch-Nyhan syndrome.[1] Although the authors thought caution was advisable in using these two drugs together, they did emphasise that overgeneralisation may be dangerous since the child also received other antiepileptics and the role his disease may have played was unknown.

1. Yokochi K, *et al.* Phenytoin-allopurinol interaction: Michaelis-Menten kinetic parameters of phenytoin with and without allopurinol in a child with Lesch-Nyhan syndrome. *Ther Drug Monit* 1982; **4:** 353–7.

Antihistamines. A young woman developed drowsiness, ataxia, diplopia, tinnitus, and episodes of occipital headaches associated with vomiting after taking phenytoin sodium and *chlorphenamine*.[1] Chlorphenamine might have delayed the hepatic metabolism of phenytoin thereby increasing the plasma concentrations.

1. Pugh RNH, *et al.* Interaction of phenytoin with chlorpheniramine. *Br J Clin Pharmacol* 1975; **2:** 173–5.

Antihypertensives. In 2 patients with hypoglycaemia associated with hyperinsulinism, therapeutic serum-phenytoin concentrations could not be achieved while they were also receiving *diazoxide*.[1] It was suggested that an increased rate of metabolism, and possibly a decreased binding, of phenytoin induced by diazoxide might have been responsible.

1. Roe TF, *et al.* Drug interaction: diazoxide and diphenylhydantoin. *J Pediatr* 1975; **87:** 480–4.

Antimalarials. Antimalarials may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold.

Antineoplastics. There have been reports of decreased plasma-phenytoin concentrations associated with cancer chemotherapy,[1-4] resulting in some cases in loss of seizure control.[2-4] The effect appears to be due to impaired absorption of phenytoin arising from antineoplastic damage to the gastrointestinal mucosa. In a patient a mean of 32% of an oral dose of phenytoin was absorbed after therapy with *cisplatin*, *vinblastine*, and *bleomycin*; this compared with a reported oral bioavailability of 80% or more.[3] *Trabectedin* may also reduce phenytoin absorption leading to an exacerbation of seizures.

Licensed product information for *levamisole* reports that increased plasma-phenytoin concentrations have been seen in patients taking phenytoin with levamisole given as an adjuvant to *fluorouracil* therapy. Treatment with fluorouracil (alone or with folinic acid) has also led to phenytoin toxicity in patients on long-term antiepileptic therapy.[5-7] Similar interactions have occurred with *doxifluridine*[8] and *capecitabine*[7] (both prodrugs of fluorouracil), and a combination preparation containing *tegafur* (a prodrug of fluorouracil) with *uracil* . However, a decrease in phenytoin serum concentrations has been seen when such a preparation was given with folinic acid to a patient receiving the antiepileptic.[9] For the effect of phenytoin on *busulfan* see Effects on the Nervous System under Adverse Effects of Busulfan, p.690. For the effect of phenytoin on the use of *streptozocin* and on *teniposide* see p.771 and p.778, respectively.

1. Fincham RW, Schottelius DD. Decreased phenytoin levels in antineoplastic therapy. *Ther Drug Monit* 1979; **1:** 277–83.
2. Bollini P, *et al.* Decreased phenytoin level during antineoplastic therapy: a case report. *Epilepsia* 1983; **24:** 75–8.
3. Sylvester RK, *et al.* Impaired phenytoin bioavailability secondary to cisplatinum, vinblastine, and bleomycin. *Ther Drug Monit* 1984; **6:** 302–5.
4. Grossman SA, *et al.* Decreased phenytoin levels in patients receiving chemotherapy. *Am J Med* 1989; **87:** 505–10.
5. Gilbar PJ, Brodribb TR. Phenytoin and fluorouracil interaction. *Ann Pharmacother* 2001; **35:** 1367–70.
6. Rosemergy I, Findlay M. Phenytoin toxicity as a result of 5-fluorouracil administration. *N Z Med J* 2002; **115:** U124.
7. Brickell K, *et al.* Phenytoin toxicity due to fluoropyrimidines (5FU/capecitabine): three case reports. *Br J Cancer* 2003; **89:** 615–16.
8. Konishi H, *et al.* Probable metabolic interaction of doxifluridine with phenytoin. *Ann Pharmacother* 2002; **36:** 831–4.
9. Veldhorst-Janssen NML, *et al.* Oral tegafur/folinic acid chemotherapy decreases phenytoin efficacy. *Br J Cancer* 2004; **90:** 745.

Antiprotozoals. Conflicting results have been reported with *metronidazole*: while one study has suggested only minimal effects on phenytoin concentrations and metabolism,[1] another has indicated inhibition of the metabolism of phenytoin.[2] For the effect of phenytoin on metronidazole, see p.838.

1. Jensen JC, Gugler R. Interaction between metronidazole and drugs eliminated by oxidative metabolism. *Clin Pharmacol Ther* 1985; **37:** 407–10.
2. Blyden GT, *et al.* Metronidazole impairs clearance of phenytoin but not of alprazolam or lorazepam. *Clin Pharmacol Ther* 1986; **39:** 181.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold. Two cases of phenytoin toxicity and elevated plasma-phenytoin concentrations associated with the phenothiazine *thioridazine* have been reported;[1] but another study indicated that *thioridazine*, *chlorpromazine*, or *mesoridazine* reduced serum-phenytoin concentrations.[2]

The non-phenothiazine antipsychotic *loxapine* has also been implicated as producing a fall in serum-phenytoin concentration.[3]

For the effect of phenytoin on antipsychotics in general, see under Chlorpromazine, p.974. For the effect of phenytoin on *clozapine*, see p.984.

1. Vincent FM. Phenothiazine-induced phenytoin intoxication. *Ann Intern Med* 1980; **93:** 56–7.
2. Haidukewych D, Rodin EA. Effect of phenothiazines on serum antiepileptic drug concentrations in psychiatric patients with seizure disorder. *Ther Drug Monit* 1985; **7:** 401–4.
3. Ryan GM, Matthews PA. Phenytoin metabolism stimulated by loxapine. *Drug Intell Clin Pharm* 1977; **11:** 428–9.

Antivirals. *Zidovudine* may possibly reduce or increase plasma concentrations of phenytoin. There has been a report[1] of markedly decreased serum-phenytoin concentrations resulting in a recurrence of seizure activity in an epileptic patient after starting *nelfinavir* as part of antiretroviral therapy. Serum concentrations of phenytoin and valproate decreased[2,3] in 2 reports in children after the addition of *aciclovir*. *Ritonavir-boosted lopinavir* was reported[4] to increase the clearance of phenytoin in healthy subjects, probably due to hepatic enzyme induction; phenytoin similarly increased the clearance of the protease inhibitor. A case report[5] described the inhibition of phenytoin clearance by *efavirenz* resulting in elevated phenytoin plasma concentrations, and subtherapeutic levels of efavirenz resulting from hepatic enzyme induction by phenytoin.

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

1. Honda M, *et al.* A generalized seizure following initiation of nelfinavir in a patient with human immunodeficiency virus type 1 infection, suspected due to interaction between nelfinavir and phenytoin. *Intern Med* 1999; **38:** 302–3.
2. Parmeggiani A, *et al.* Possible interaction between acyclovir and antiepileptic treatment. *Ther Drug Monit* 1995; **17:** 312–15.
3. Iglesias Iglesias A-A, *et al.* Disminución de la concentración sérica de antiepilépticos durante el tratamiento con aciclovir. *Med Clin (Barc)* 2005; **124:** 355–6.
4. Lim ML, *et al.* Coadministration of lopinavir/ritonavir and phenytoin results in two-way drug interaction through cytochrome P-450 induction. *J Acquir Immune Defic Syndr* 2004; **36:** 1034–40.
5. Robertson SM, *et al.* A potentially significant interaction between efavirenz and phenytoin: a case report and review of the literature. *Clin Infect Dis* 2005; **41:** e15–e18.

Anxiolytics. See Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced as a result of induction of hepatic drug-metabolising enzymes after long-term use of phenytoin. In comparison with healthy subjects, half-lives have been shorter and clearance increased.[1,2]

There are sporadic reports of interactions between phenytoin and benzodiazepines, but the evidence is conflicting. Elevated plasma concentrations of phenytoin have been reported in patients given *diazepam*[3,4] or *chlordiazepoxide*[3] but, in contrast, another study suggested that these drugs produced a significant fall in serum-phenytoin concentrations.[5] It has been suggested that phenytoin intoxication could result from the impaired metabolism associated with the combination[3,4,6] but in practice this seems to be uncommon. There are similar conflicting reports for *clonazepam*.[7-9]

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; **12:** 841–4.
2. Scott AK, *et al.* Oxazepam pharmacokinetics in patients with epilepsy treated long-term with phenytoin alone or in combination with phenobarbitone. *Br J Clin Pharmacol* 1983; **16:** 441–4.
3. Vajda FJE, *et al.* Interaction between phenytoin and the benzodiazepines. *BMJ* 1971; **1:** 346.
4. Murphy A, Wilbur K. Phenytoin-diazepam interaction. *Ann Pharmacother* 2003; **37:** 659–63.
5. Houghton GW, Richens A. The effect of benzodiazepines and pheneturide on phenytoin metabolism in man. *Br J Clin Pharmacol* 1974; **1:** 344P–345P.
6. Kutt H, McDowell F. Management of epilepsy with diphenylhydantoin sodium: dosage regulation for problem patients. *JAMA* 1968; **203:** 969–72.
7. Eeg-Oloffson O. Experiences with Rivotril® in treatment of epilepsy—particularly minor motor epilepsy—in mentally retarded children. *Acta Neurol Scand* 1973; **49** (suppl 53): 29–31.
8. Johannessen SI, *et al.* Lack of effect of clonazepam on serum levels of diphenylhydantoin, phenobarbital and carbamazepine. *Acta Neurol Scand* 1977; **55:** 506–12.
9. Saavedra IN, *et al.* Phenytoin/clonazepam interaction. *Ther Drug Monit* 1985; **7:** 481–4.

Calcium-channel blockers. Raised serum-phenytoin concentration with phenytoin toxicity developed in a patient who had been taking *nifedipine* in addition to phenytoin for 3 weeks;[1] symptoms resolved completely after nifedipine withdrawal. The mechanism of interaction appeared to be complex. Similar effects have been reported with *diltiazem*[2] and *isradipine*.[3]

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

1. Ahmad S. Nifedipine-phenytoin interaction. *J Am Coll Cardiol* 1984; **3:** 1582.
2. Bahls FH, *et al.* Interactions between calcium channel blockers and the anticonvulsants carbamazepine and phenytoin. *Neurology* 1991; **41:** 740–2.
3. Cachat F, Tufro A. Phenytoin/isradipine interaction causing severe neurologic toxicity. *Ann Pharmacother* 2002; **36:** 1399–1402.

Cardiac glycosides. For the effect of phenytoin on cardiac glycosides, see under Digoxin, p.1261.

Corticosteroids. Serum concentrations of phenytoin have been elevated[1] or reduced[2-4] by *dexamethasone* and adjustment of phenytoin dosage may be required.[2-4] For the effect of phenytoin on corticosteroids, see p.1494.

1. Lawson LA, *et al.* Phenytoin-dexamethasone interaction: a previously unreported observation. *Surg Neurol* 1981; **16:** 23–4.
2. Wong DD, *et al.* Phenytoin-dexamethasone: a possible drug-drug interaction. *JAMA* 1985; **254:** 2062–3.
3. Recuenco I, *et al.* Effect of dexamethasone on the decrease of serum phenytoin concentrations. *Ann Pharmacother* 1995; **29:** 935.
4. Lackner TE. Interaction of dexamethasone with phenytoin. *Pharmacotherapy* 1991; **11:** 344–7.

Dermatological drugs. For the effect of phenytoin on *methoxsalen*, see p.1606.

Disulfiram. A well-documented interaction exists between phenytoin and disulfiram, which may result in clinical phenytoin toxicity.[1,2] The effect appears to be due to non-competitive inhibition of the metabolism of phenytoin by disulfiram,[2] which results in a substantial increase in phenytoin half-life and a decrease in its clearance.[3]

1. Dry J, Pradalier A. Intoxication par la phénytoïne au cours d'une association thérapeutique avec le disulfirame. *Therapie* 1973; **28:** 799–802.
2. Taylor JW, *et al.* Mathematical analysis of a phenytoin-disulfiram interaction. *Am J Hosp Pharm* 1981; **38:** 93–5.
3. Svendsen TL, *et al.* The influence of disulfiram on the half-life and metabolic clearance rate of diphenylhydantoin and tolbutamide in man. *Eur J Clin Pharmacol* 1976; **9:** 439–41.

Diuretics. Severe osteomalacia in 2 previously active young women taking *acetazolamide* with phenytoin or primidone and phenobarbital has been reported.[1]

For the effect of antiepileptics such as phenytoin on *furosemide*, see p.1293.

1. Mallette LE. Anticonvulsants, acetazolamide and osteomalacia. *N Engl J Med* 1975; **293:** 668.

Dopaminergics. For the effect of phenytoin on *levodopa*, see p.807.

Enteral and parenteral nutrition. Therapeutic plasma concentrations of phenytoin may be difficult to achieve in patients receiving enteral or total parenteral nutrition.[1,2] Incompatibility studies indicate that phenytoin probably binds to components of the feed (see Incompatibility, above), which might explain this interaction when both are given together nasogastrically, but the same effect has also been reported when they were given separately by the intravenous route.[2] A review[3] of case reports and studies concluded that the exact role of enteral feeding in this interaction still remained unclear because of a lack of prospective, randomised, controlled studies performed in patients, rather

than in healthy subjects. However, because of the amount of literature describing such a phenomenon, it was considered unlikely to occur just by chance. Monitoring of serum-phenytoin concentrations to guide therapy was recommended, and measures such as staggering phenytoin and enteral feeding might be considered to minimise the occurrence of this reaction.

1. Summers VM, Grant R. Nasogastric feeding and phenytoin interaction. *Pharm J* 1989; **243:** 181.
2. Messahel FM, *et al.* Does total parenteral nutrition lower serum phenytoin levels? *Curr Ther Res* 1990; **47:** 1017–20.
3. Au Yeung SC, Ensom MH. Phenytoin and enteral feedings: does evidence support an interaction? *Ann Pharmacother* 2000 **34:** 896–905.

Gastrointestinal drugs. Evidence for an interaction between phenytoin and *antacids* is conflicting. Some studies have shown a decrease in the bioavailability of phenytoin given with various antacid mixtures[1,2] but others have failed to find any evidence of reduced absorption.[3] Furthermore even those studies that recorded decreased absorption varied in their results with regard to particular drugs, suggesting for example that calcium carbonate both does[1] and does not[2] reduce phenytoin bioavailability. The clinical significance of this data is uncertain but it has been suggested that if antacids and phenytoin are both needed, doses should be spaced several hours apart.[4,5] *Sucralfate* is also reported to reduce phenytoin absorption.[6]

A well documented interaction exists between phenytoin and *cimetidine*, which produces a dose-dependent reduction in phenytoin clearance[7] and a significant elevation of serum-phenytoin concentration.[8] There are reports of phenytoin toxicity when cimetidine was given to epileptic patients[9,10] including a report of severe granulocytopenia.[11] Although some studies have found that neither *ranitidine*[12] nor *famotidine*[13] appear to affect the pharmacokinetics of phenytoin significantly, there have been isolated reports of raised plasma concentrations of phenytoin associated with use of ranitidine[14-16] or famotidine.[17]

Omeprazole 40 mg daily can decrease the plasma clearance of phenytoin[18] and increase the area under the serum-phenytoin concentration-time curve,[19] but one study[20] suggests that the dosage of 20 mg daily usually used for peptic ulcer disease is unlikely to produce a clinically significant effect on the steady-state plasma concentrations of phenytoin in patients with epilepsy.

1. Garnett WR, *et al.* Bioavailability of phenytoin administered with antacids. *Ther Drug Monit* 1979; **1:** 435–6.
2. Kulshrestha VK, *et al.* Interaction between phenytoin and antacids. *Br J Clin Pharmacol* 1978; **6:** 177–9.
3. O'Brien LS, *et al.* Failure of antacids to alter the pharmacokinetics of phenytoin. *Br J Clin Pharmacol* 1978; **6:** 176–7.
4. Cacek AT. Review of alterations in oral phenytoin bioavailability associated with formulation, antacids, and food. *Ther Drug Monit* 1986; **8:** 166–71.
5. D'Arcy PF, McElnay JC. Drug-antacid interactions: assessment of clinical importance. *Drug Intell Clin Pharm* 1987; **21:** 607–17.
6. Smart HL, *et al.* The effects of sucralfate upon phenytoin absorption in man. *Br J Clin Pharmacol* 1985; **20:** 238–40.
7. Bartle WR, *et al.* Dose-dependent effect of cimetidine on phenytoin kinetics. *Clin Pharmacol Ther* 1983; **33:** 649–55.
8. Iteogu MO, *et al.* Effect of cimetidine on single-dose phenytoin kinetics. *Clin Pharm* 1983; **2:** 302–4.
9. Phillips P, Hansky J. Phenytoin toxicity secondary to cimetidine administration. *Med J Aust* 1984; **141:** 602.
10. Hetzel DJ, *et al.* Cimetidine interaction with phenytoin. *BMJ* 1981; **282:** 1512.
11. Sazie E, Jaffe JP. Severe granulocytopenia with cimetidine and phenytoin. *Ann Intern Med* 1980; **93:** 151–2.
12. Watts RW, *et al.* Lack of interaction between ranitidine and phenytoin. *Br J Clin Pharmacol* 1983; **15:** 499–500.
13. Sambol NC, *et al.* A comparison of the influence of famotidine and cimetidine on phenytoin elimination and hepatic blood flow. *Br J Clin Pharmacol* 1989; **27:** 83–7.
14. Bramhall D, Levine M. Possible interaction of ranitidine with phenytoin. *Drug Intell Clin Pharm* 1988; **22:** 979–80.
15. Tse CST, *et al.* Phenytoin concentration elevation subsequent to ranitidine administration. *Ann Pharmacother* 1993; **27:** 1448–51.
16. Tse CST, Iagmin P. Phenytoin and ranitidine interaction. *Ann Intern Med* 1994; **120:** 892–3.
17. Shinn AF. Unrecognized drug interactions with famotidine and nizatidine. *Arch Intern Med* 1991; **151:** 814.
18. Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism: studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. *Gastroenterology* 1985; **89:** 1235–41.
19. Prichard PJ, *et al.* Oral phenytoin pharmacokinetics during omeprazole therapy. *Br J Clin Pharmacol* 1987; **24:** 543–5.
20. Andersson T, *et al.* A study of the interaction between omeprazole and phenytoin in epileptic patients. *Ther Drug Monit* 1990; **12:** 329–33.

Ginkgo biloba. A fatal breakthrough seizure occurred[1] in a 55-year-old man who was taking phenytoin and valproate semisodium for a seizure disorder; he was also taking numerous non-prescription supplements, such as vitamin preparations and herbal medicines including ginkgo biloba extract, without the knowledge of his physician. Autopsy revealed subtherapeutic plasma concentrations of both antiepileptics. Although the exact cause was unclear, the authors postulated that hepatic enzyme induction by ginkgo biloba might have increased the clearance of phenytoin and valproate semisodium.

1. Kupiec T, Raj V. Fatal seizures due to potential herb-drug interactions with ginkgo biloba. *J Anal Toxicol* 2005; **29:** 755–8.

Immunosuppressants. Increased plasma-phenytoin concentrations were reported[1] in one patient when *tacrolimus* was added to existing therapy. Phenytoin was stopped until values were within the therapeutic range and then restarted at a lower dose, tacrolimus therapy continuing throughout; phenytoin levels remained stable thereafter.

For the effect of phenytoin on *ciclosporin*, see p.1826.

1. Thompson PA, Mosley CA. Tacrolimus-phenytoin interaction. *Ann Pharmacother* 1996; **30:** 544.

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

Muscle relaxants. An increase in serum concentrations of phenytoin has been reported[1] in a patient when *tizanidine* was added to therapy.

1. Ueno K, *et al.* Phenytoin-tizanidine interaction. *DICP Ann Pharmacother* 1991; **25:** 1273.

Neuromuscular blockers. For the effect of phenytoin on *suxamethonium*, see p.1911 and on *competitive neuromuscular blockers*, see under Atracurium, p.1904.

Sex hormones. For the effect of phenytoin on *oral contraceptives*, see p.2068. Similar effects may also be noted in patients receiving *HRT*, see p.2076.

Stimulants and anorectics. Although there has been a report of elevated phenytoin and primidone serum concentrations in a 5-year-old after addition of *methylphenidate* to therapy[1] there was no similar elevation in 2 other children receiving phenobarbital and phenytoin in the same report, nor in 11 patients of varying ages given methylphenidate with antiepileptic therapy as part of a controlled study.[2] The likelihood of an interaction seems small in the majority of patients.

1. Garrettson LK, *et al.* Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate. *JAMA* 1969; **207:** 2053–6.
2. Kupferberg HJ, *et al.* Effect of methylphenidate on plasma anticonvulsant levels. *Clin Pharmacol Ther* 1972; **13:** 201–4.

Theophylline. Although most reports of an interaction between phenytoin and theophylline concern effects on theophylline concentrations, one study in 14 healthy subjects suggested that treatment with both could lower serum-phenytoin concentrations, with a subsequent rise in concentration on stopping theophylline.[1] The mechanism was suggested to be enzyme induction by the xanthine resulting in increased phenytoin metabolism.

For the effect of phenytoin on theophylline, see p.1143.

1. Taylor JW, *et al.* The interaction of phenytoin and theophylline. *Drug Intell Clin Pharm* 1980; **14:** 638.

Ticlopidine. Acute phenytoin toxicity has been reported in a well-stabilised 44-year-old patient on introduction of ticlopidine to prevent restenosis after placement of a coronary stent.[1] The patient also took metoprolol, aspirin, and for a short period lovastatin, but inhibition of the cytochrome P450 isoenzyme CYP2C19 by ticlopidine was considered the most likely cause of the patient's elevated serum phenytoin. A later report[2] by the same authors found that ticlopidine inhibited the clearance of phenytoin in 6 patients on phenytoin monotherapy; the involvement of CYP2C19 was also supported. The authors recommended that dosage adjustment of phenytoin should be considered if ticlopidine is also given.

A similar interaction occurred in a 72-year-old patient,[3] and the authors postulated that, since steady-state plasma concentrations of ticlopidine are almost twofold higher in elderly patients than those in younger patients, the higher ticlopidine concentrations may have played a role in this drug interaction.

1. Donahue SR, *et al.* Ticlopidine inhibition of phenytoin metabolism mediated by potent inhibition of CYP2C19. *Clin Pharmacol Ther* 1997; **62:** 572–7.
2. Donahue S,*et al.* Ticlopidine inhibits phenytoin clearance. *Clin Pharmacol Ther* 1999; **66:** 563–8.
3. Klaassen SL. Ticlopidine-induced phenytoin toxicity. *Ann Pharmacother* 1998; **32:** 1295–8.

Vaccines. Contradictory results have been reported for the effects of *influenza vaccine* on serum-phenytoin concentrations. A significant elevation in total phenytoin concentration has been reported[1] after vaccination, and was suggested to be due to interferon induction and inhibition of the cytochrome P450 enzyme system. In contrast, other reports have suggested that any increase in serum-phenytoin concentration was temporary and not significant overall[2] or even that there was a slight fall in serum-phenytoin concentration.[3] One study reported a significant increase in total phenytoin concentration two days after vaccination, followed by a return to previous values but this was accompanied by evidence of a gradual and prolonged fall in free phenytoin concentrations.[4] The possibility of either phenytoin toxicity or loss of seizure control may exist in some epileptic patients given influenza vaccine during phenytoin therapy.[5]

1. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* 1986; **5:** 817–20.
2. Levine M, *et al.* Increased serum phenytoin concentration following influenza vaccination. *Clin Pharm* 1984; **3:** 505–9.
3. Sawchuk RJ, *et al.* Effect of influenza vaccination on plasma phenytoin concentrations. *Ther Drug Monit* 1979; **1:** 285–8.
4. Smith CD, *et al.* Effect of influenza vaccine on serum concentrations of total and free phenytoin. *Clin Pharm* 1988; **7:** 828–32.
5. Grabenstein JD. Drug interactions involving immunologic agents, part 1. vaccine-vaccine, vaccine-immunoglobulin, and vaccine-drug interactions. *DICP Ann Pharmacother* 1990; **24:** 67–81.

Vitamins. *Pyridoxine* given in large doses produced a reduction in serum-phenytoin concentrations in 7 patients,[1] perhaps reflecting increased activity by pyridoxal phosphate-dependent enzymes involved in phenytoin metabolism.

Correction of antiepileptic-associated folate deficiency with *folic acid* has been reported to result in a decrease in serum-phenytoin concentrations and an increase in seizure frequency.[2-4] The effect has been reported to be most marked in subjects with high initial serum-phenytoin concentrations[5] and is associated with an increased phenytoin metabolism.[4,6] However, in the majority of patients the effect is unlikely to assume clinical significance,[2,5] and there is some evidence that very low doses of folic acid may be used to maintain normal serum-folate values without an increase in seizure frequency.[3] Information regarding the dual and interdependent interaction between phenytoin and folic acid has been reviewed.[7] Although limited numbers of patients and healthy subjects were involved, evaluation of the data suggested that starting phenytoin and folic acid at the same time prevents decreased folate levels and steady-state concentrations of phenytoin are reached sooner. Plasma concentrations of phenytoin are also possibly reduced by *folinic acid* (see also Antineoplastics, above).

For the effect of antiepileptics, including phenytoin, on *vitamin D* concentrations, see Effects on Bone under Adverse Effects, above.

1. Hansson O, Sillanpaa M. Pyridoxine and serum concentration of phenytoin and phenobarbitone. *Lancet* 1976; **i:** 256.
2. Baylis EM, *et al.* Influence of folic acid on blood-phenytoin levels. *Lancet* 1971; **i:** 62–4.
3. Inoue F. Clinical implications of anticonvulsant-induced folate deficiency. *Clin Pharm* 1982; **1:** 372–3.
4. Steinweg DL, Bentley ML. Seizures following reduction in phenytoin level after orally administered folic acid. *Neurology* 2005; **64:** 1982.
5. Furlanut M, *et al.* Effects of folic acid on phenytoin kinetics in healthy subjects. *Clin Pharmacol Ther* 1978; **24:** 294–7.
6. Berg MJ, *et al.* Phenytoin and folic acid interaction: a preliminary report. *Ther Drug Monit* 1983; **5:** 389–94.
7. Lewis DP, *et al.* Phenytoin-folic acid interaction. *Ann Pharmacother* 1995; **29:** 726–35.

Pharmacokinetics

Phenytoin is slowly but almost completely absorbed from the gastrointestinal tract. It is largely insoluble at the acid pH of the stomach, most being absorbed from the upper intestine; the rate of absorption is variable and is reported to be affected by the presence of food. Absorption after intramuscular injection is slower than that from the gastrointestinal tract.

Phenytoin is extensively metabolised in the liver to inactive metabolites, chiefly 5-(4-hydroxyphenyl)-5-phenylhydantoin. The rate of metabolism appears to be subject to genetic polymorphism and may also be influenced by racial characteristics; it is reported to be increased during pregnancy and menstruation and to decrease with age. Phenytoin hydroxylation is saturable and is therefore readily inhibited by drugs that compete for its metabolic pathways; this is also the reason why small increments in dose may produce large rises in plasma concentration. Phenytoin undergoes enterohepatic recycling and is excreted in the urine, mainly as its hydroxylated metabolite, in either free or conjugated form.

Phenytoin is widely distributed throughout the body. It is about 90% bound to plasma proteins, although this may be reduced in certain disease states and in certain patient populations (see Precautions, above). It has a very variable, dose-dependent half-life, but the mean plasma half-life appears to be about 22 hours at steady state; because phenytoin inhibits its own metabolism it may sometimes be several weeks before a steady-state plasma-phenytoin concentration is attained.

Monitoring of plasma concentrations may be performed as an aid in assessing control, and the therapeutic range of total plasma-phenytoin concentrations is usually quoted as 10 to 20 micrograms/mL (40 to 80 micromoles/litre); some patients, however, achieve control at concentrations outside this range. It has been suggested that, because of differences in protein binding, measurement of free phenytoin concentrations in plasma may prove more reliable; measurement of concentrations in saliva, which contains only free phenytoin, has also been performed.

Phenytoin crosses the placental barrier and small amounts are distributed into breast milk.

The pharmacokinetics of phenytoin are affected by other antiepileptics (see Interactions, above).

Uses and Administration

Phenytoin is a hydantoin antiepileptic used to control partial and generalised tonic-clonic seizures. It is also used as part of the emergency treatment of status epilepticus and has been used for the prevention and treatment of seizures associated with neurosurgery or severe traumatic injury to the head. Phenytoin has also been used in the treatment of trigeminal neuralgia. It is a class Ib antiarrhythmic and has been used to treat cardiac arrhythmias.

Doses may be expressed in terms of phenytoin or phenytoin sodium; although phenytoin 92 mg is equivalent to about 100 mg of phenytoin sodium these molecular equivalents are not necessarily biologically equivalent. In the UK an oral suspension of phenytoin 90 mg in 15 mL may be considered about equivalent in therapeutic effect to capsules or tablets containing phenytoin sodium 100 mg. In the USA a suspension containing phenytoin 125 mg in 5 mL is available.

For **epilepsy** the dose of phenytoin should be adjusted to the needs of the individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations; in many patients control requires total plasma-phenytoin concentrations of 10 to 20 micrograms/mL (40 to 80 micromoles/litre), but some are controlled at concentrations outside this range. A suggested initial oral dose of phenytoin or phenytoin sodium given as a single dose or in divided doses is 3 to 4 mg/kg daily or 150 to 300 mg daily progressively increased with care to 600 mg daily if necessary; the suggested minimum interval between increments has ranged from about 7 to 10 days. Particular care is needed at higher doses, where saturation of metabolism may mean that a small increment produces a large rise in plasma concentrations. A usual maintenance dose is 200 to 500 mg daily.

The practice of starting phenytoin therapy with initial small doses means that more than a week may be required before therapeutic plasma concentrations are attained; it has been reported that it may even be several weeks before a steady-state concentration is established. An initial loading dose may therefore be given, with the usual maintenance dosage being instituted 24 hours after the loading dose. Once the patient is stabilised the long half-life of phenytoin may permit the total daily dose to be given in two daily divisions or as a single dose, usually at night.

Although clinical evidence is lacking, different brands of phenytoin, as well as different formulations from the same manufacturer, may vary in their bioavailability and patients may need to be restabilised in the event of a change.

In order to lessen gastric irritation, phenytoin should be taken with or after food. The time and manner of taking phenytoin should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations.

As with other antiepileptics, withdrawal of phenytoin 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.

Treatment of tonic-clonic **status epilepticus** is usually begun with a benzodiazepine such as diazepam or lorazepam given intravenously or rectally, and followed by phenytoin sodium intravenously. A suggested dose of phenytoin sodium is 10 to 15 mg/kg given by slow intravenous injection or by intermittent infusion at a uniform rate of not more than 50 mg/minute. Thereafter maintenance doses of 100 mg orally or intravenously are given every 6 to 8 hours; the rate and dose should be reduced according to body-weight. For doses in children, see below.

Deaths have been caused by the over-rapid intravenous injection of phenytoin sodium and continuous monitoring of the ECG and blood pressure is recommended whenever phenytoin sodium is given intravenously.

Phenytoin sodium is absorbed slowly and erratically from the intramuscular site and therefore intramuscular injections are not appropriate for the emergency arrest of status epilepticus. They may, however, be used in certain situations to maintain or establish therapeutic plasma concentrations of phenytoin in patients who are unconscious or otherwise unable to take phenytoin orally. Owing to the slower absorption of phenytoin from intramuscular sites, patients stabilised on the oral route require an increase in the intramuscular dose of about 50%; it is recommended that, if possible, intramuscular injections of phenytoin sodium should not be continued for longer than one week. On transfer back to the oral route the patient should receive 50% of the original oral dose for the same period of time as intramuscular injections were given, to allow for continued absorption of the residual phenytoin in the intramuscular sites. For the **prevention and treatment of seizures associated with neurosurgery** in patients who have not previously taken phenytoin sodium, a suggested intramuscular dose is 100 to 200 mg given at 4-hourly intervals during surgery and continued postoperatively for 48 to 72 hours. Thereafter, the dose should be reduced to a maintenance dose of 300 mg and adjusted according to plasma-phenytoin concentrations.

Administration in children. Phenytoin may be given to children for the control of partial and generalised tonic-clonic seizures. It is also used as part of the emergency treatment of status epilepticus and has been used for the prevention and treatment of seizures associated with neurosurgery or severe traumatic injury to the head.

For **epilepsy** the dose of phenytoin should be adjusted to the needs of the individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations; young children may require a higher dose per kg body-weight than adults due to more rapid metabolism. In many patients control requires total plasma-phenytoin concentrations of 10 to 20 micrograms/mL (40 to 80 micromoles/litre), but some are controlled at concentrations outside this range; the *BNFC* suggests concentrations of 6 to 15 micrograms/mL (25 to 60 micromoles/litre) in neonates and those aged up to 3 months. The recommended initial oral dose for children is 5 mg/kg daily in 2 or 3 divided doses up to a maximum of 300 mg daily; the usual maintenance dose is 4 to 8 mg/kg daily in divided doses. Alternatively, the *BNFC* suggests the following doses given according to age:

- neonates: an initial loading dose of 18 mg/kg by slow intravenous injection, over 20 to 30 minutes, followed by oral doses of 2.5 to 5 mg/kg twice daily adjusted as necessary to a usual maximum of 7.5 mg/kg twice daily
- 1 month to 12 years: an initial oral dose of 1.5 to 2.5 mg/kg twice daily followed by 2.5 to 5 mg/kg twice daily adjusted as necessary to a usual maximum of 7.5 mg/kg twice daily or 300 mg daily
- 12 years and older: usual adult doses (see above)

For **status epilepticus** and for the **prevention and treatment of seizures associated with neurosurgery or trauma** an initial loading dose of 15 to 20 mg/kg given by slow intravenous injection may be followed by usual adult doses (see above). Alternatively, the *BNFC* suggests the following doses given by slow intravenous injection or infusion according to age:

- neonates and children up to 12 years: a loading dose of 18 mg/kg followed by 2.5 to 5 mg/kg twice daily
- 12 to 18 years: a loading dose of 18 mg/kg followed by up to 100 mg 3 or 4 times daily

Intravenous injections and infusions of phenytoin should be given at a rate not exceeding 1 mg/kg per minute (a maximum of 50 mg per minute).

A comparison of methods[1] for the prediction of required phenytoin dosage in paediatric patients indicated that all methods produced a sizeable number of predictions with an error of more than 10% and that close monitoring of serum concentrations and clinical status was recommended regardless of the method chosen to adjust dosage. Similar conclusions have been made regarding the need to monitor plasma concentrations of phenytoin in the newborn and young infants.[2]

1. Yuen GJ, *et al.* Phenytoin dosage predictions in paediatric patients. *Clin Pharmacokinet* 1989; **16:** 254–60.
2. Loughnan PM, *et al.* Pharmacokinetic observations of phenytoin disposition in the newborn and young infant. *Arch Dis Child* 1977; **52:** 302–9.

Administration in the elderly. Pharmacokinetic studies in elderly patients have shown reduced binding to plasma proteins which was not itself an indication for dosage change,[1] but a study showing a decreased metabolism[2] did indicate that elderly patients may need lower doses of phenytoin than younger adults to maintain similar serum concentrations.

1. Patterson M, *et al.* Plasma protein binding of phenytoin in the aged: in vivo studies. *Br J Clin Pharmacol* 1982; **13:** 423–5.
2. Bauer LA, Blouin RA. Age and phenytoin kinetics in adult epileptics. *Clin Pharmacol Ther* 1982; **31:** 301–4.

Cardiac arrhythmias. Phenytoin has been given intravenously in the treatment of ventricular arrhythmias (p.1160), especially those caused by overdosage with cardiac glycosides. Although this use now appears to be obsolete, in the UK the licensed dose of phenytoin sodium is 3.5 to 5 mg/kg given by slow intravenous injection at a uniform rate of not more than 50 mg/minute, repeated once if necessary.

Eclampsia and pre-eclampsia. Phenytoin has been used for eclampsia but now treatment with magnesium sulfate is preferred, see p.470.

Epidermolysis bullosa. There have been reports[1-3] of a favourable but variable clinical response to phenytoin in patients with some variants of epidermolysis bullosa (p.1579), a condition for the severe forms of which there is no truly effective treatment. However, a double-blind placebo-controlled study[4] concluded that phenytoin was not an effective treatment for the recessive dystrophic variant, and offered no overall benefit when compared with placebo.

1. Bauer EA, *et al.* Phenytoin therapy of recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1980; **303:** 776–81.
2. Cooper TW, Bauer EA. Therapeutic efficacy of phenytoin in recessive dystrophic epidermolysis. *Arch Dermatol* 1984; **120:** 490–5.
3. Scheinfeld N. Phenytoin in cutaneous medicine: its uses, mechanisms and side effects. *Dermatol Online J* 2003; **9:** 6.
4. Caldwell-Brown D, *et al.* Lack of efficacy of phenytoin in recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1992; **327:** 163–7.

Epilepsy. Phenytoin has long been used in the treatment of partial seizures with or without secondary generalisation and in primarily generalised tonic-clonic seizures, although other drugs may be better tolerated and easier to use (see p.465). It is also effective in other forms of epilepsy with the exception of absence and myoclonic seizures.

Hiccup. Phenytoin may be of value for the treatment of intractable hiccups,[1] especially those of neurogenic origin. For the management of intractable hiccups see under Chlorpromazine, p.976.

1. Petroski D, Patel AN. Diphenylhydantoin for intractable hiccups. *Lancet* 1974; **i:** 739.

Myotonia. A review[1] of myotonia congenita, a hereditary muscular disorder characterised by symptoms of muscle stiffness especially after rest and on starting to move. Where treatment is necessary it is usually with phenytoin or procainamide, the former being preferred as being better tolerated.

1. Gutmann L, *et al.* Myotonia congenita. *Semin Neurol* 1991; **11:** 244–8.

Neonatal seizures. Phenytoin is one of the antiepileptics that may be used in the management of neonatal seizures (p.471).

Neuropathic pain. Phenytoin is used alone or added to treatment in trigeminal neuralgia (p.9) in patients unresponsive to or intolerant of carbamazepine. It has also been used in the treatment of painful diabetic neuropathy (p.6).

Post-traumatic seizures. About 12% of patients with severe traumatic brain injury develop seizures and the rate may be more than 50% for those with penetrating missile injuries.[1] The use of antiepileptics to treat such seizures is standard but there has been some debate about prophylactic use. Evidence suggests that prophylaxis with phenytoin (and perhaps carbamazepine) is effective in preventing early seizures (arbitrarily defined as those occurring up to 7 days after trauma), but prophylaxis with these or other antiepileptics such as phenobarbital valproate, has not been shown to be effective for preventing late seizures, disability, or death.[1-6] Guidelines and recommendations for such use have been issued.[1,7,8] Children with severe, acute neurotrauma were found to have markedly altered protein binding and phenytoin metabolism, and therefore may require increased doses.[9]

1. Chang BS, Lowenstein DH. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003; **60:** 10–16. Also available at: http://www.neurology.org/cgi/reprint/60/1/10.pdf (accessed 09/06/08)
2. Schierhout G, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 09/06/08).
3. Chadwick D. Seizures and epilepsy after traumatic brain injury. *Lancet* 2000; **355:** 334–5.
4. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia* 2001; **42:** 515–24.
5. Agrawal A, *et al.* Post-traumatic epilepsy: an overview. *Clin Neurol Neurosurg* 2006; **108:** 433–9.
6. Beghi E. Overview of studies to prevent posttraumatic epilepsy. *Epilepsia* 2003; **44** (suppl 10): 21–6.
7. Meek PD, *et al.* Guidelines for nonemergency use of parenteral phenytoin products. *Arch Intern Med* 1999; **159:** 2639–44.

8. Bratton SL, *et al.* Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, and Joint Section on Neuotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury—XIII: antiseizure prophylaxis. *J Neurotrauma* 2007; **24** (suppl 1): S-83–S-86. Also available at: http://www.braintrauma.org/site/DocServer/Management_3rd_Edition.pdf?docID=222 (accessed 01/09/08)
9. Stowe CD, *et al.* Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. *J Clin Pharmacol* 2000; **40:** 1452–61.

Status epilepticus. A benzodiazepine is the usual choice to abort an attack of status epilepticus (p.469). If this fails to control the seizures or the seizures recur, then intravenous phenytoin may be given.

Once seizures have been brought under control, maintenance antiepileptic therapy may be started.

Syndrome of inappropriate ADH secretion. Phenytoin has been used occasionally to inhibit pituitary antidiuretic hormone (ADH) secretion in patients with the syndrome of inappropriate ADH secretion (SIADH), the management of which is discussed on p.2182.

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

Withdrawal syndromes. Phenytoin has little place in the management of seizures associated with the *alcohol withdrawal syndrome* (p.1626). Prophylaxis with phenytoin has been shown[1,2] to be ineffective for prevention of recurrent alcohol-related seizures and therefore drugs such as the benzodiazepines or clomethiazole, which are effective both for the treatment and prophylaxis of such seizures, are preferred.

Results from a double-blind study[3] indicated that phenytoin was associated with a reduction in *cocaine abuse* compared with placebo. The abuse of cocaine is discussed on p.1858 and treatment of cocaine withdrawal on p.1860.

1. Chance JF. Emergency department treatment of alcohol withdrawal seizures with phenytoin. *Ann Emerg Med* 1991; **20:** 520–2.
2. Rathlev NK, *et al.* The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. *Ann Emerg Med* 1994; **23:** 513–8.
3. Crosby RD, *et al.* Phenytoin in the treatment of cocaine abuse: a double-blind study. *Clin Pharmacol Ther* 1996; **59:** 458–68.

Wounds and ulcers. Phenytoin has been used to promote wound healing (p.1585). Topical application of phenytoin has produced encouraging results in the healing of various types of ulcers[1-7] and large abscess cavities.[8] It has been suggested that phenytoin may reduce bacterial colonisation by changing the pH or by a direct antibacterial effect.[2] The enhanced wound healing may also be due to increased fibroblast proliferation and increased collagen content.[2] Limited absorption from the wound site may occur[9,10] and patients may need to be monitored for signs of toxicity. A systematic review,[11] which included some of these studies, found evidence to support the use of phenytoin in the treatment of leg ulcers, leprosy wounds, chronic wounds, and diabetic foot ulcers despite the poor methodological quality in the majority of studies.

1. Muthukumarasamy MG, *et al.* Topical phenytoin in diabetic foot ulcers. *Diabetes Care* 1991; **14:** 909–11.
2. Pendse AK, *et al.* Topical phenytoin in wound healing. *Int J Dermatol* 1993; **32:** 214–17.
3. Anstead GM, *et al.* Phenytoin in wound healing. *Ann Pharmacother* 1996; **30:** 768–75.
4. Adjei O, *et al.* Phenytoin in the treatment of Buruli ulcer. *Trans R Soc Trop Med Hyg* 1998; **92:** 108–9.
5. Rhodes RS, *et al.* Topical phenytoin treatment of stage II decubitus ulcers in the elderly. *Ann Pharmacother* 2001; **35:** 675–81.
6. Bhatia A, *et al.* Topical phenytoin suspension and normal saline in the treatment of leprosy trophic ulcers: a randomized, double-blind, comparative study. *J Dermatolog Treat* 2004; **15:** 321–7.
7. Younes N, *et al.* Wound bed preparation with 10 percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. *Dermatol Online J* 2006; **12:** 5. Available at: http://dermatology.cdlib.org/126/pearls/phenytoin/younes.html (accessed 09/06/08)
8. Lodha SC, *et al.* Role of phenytoin in healing of large abscess cavities. *Br J Surg* 1991; **78:** 105–8.
9. Gore R, *et al.* Topical phenytoin. *Pharm J* 1991; **247:** 620.
10. Lewis WG, Rhodes RS. Systemic absorption of topical phenytoin sodium. *Ann Pharmacother* 1994; **28:** 961.
11. Shaw J, *et al.* The clinical effect of topical phenytoin on wound healing: a systematic review. *Br J Dermatol* 2007; **157:** 997–1004.

Preparations

BP 2008: Phenytoin Capsules; Phenytoin Injection; Phenytoin Oral Suspension; Phenytoin Tablets;
USP 31: Extended Phenytoin Sodium Capsules; Phenytoin Oral Suspension; Phenytoin Sodium Injection; Phenytoin Tablets; Prompt Phenytoin Sodium Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Epamin; Etoina; Fenigramon; Fenitenk; Lotoquis Simple; Opliphon; ***Austral.:*** Dilantin; ***Austria:*** Epanutin; Epilan-D; Phenhydan; ***Belg.:*** Diphantoine; Epanutin; ***Braz.:*** Dantalin; Epelin; Fenital; Feniton; Hidantal; Unifenitoin; ***Canad.:*** Dilantin; ***Chile:*** Epamin; ***Cz.:*** Epanutin; Epilan-D; Phenhydan†; Sodanton†; ***Fin.:*** Hydantin; ***Fr.:*** Di-Hydan; Dilantin; ***Ger.:*** Epanutin†; Phenhydan; ***Gr.:*** Epanutin; ***Hong Kong:*** Dilantin; Ditoin; ***Hung.:*** Diphedan; Epanutin; ***India:*** Dilantin; Epsolin; Eptoin; ***Indon.:*** Dilantin; Ikaphen; Kutoin; Movileps; Phenilep; ***Irl.:*** Epanutin; ***Israel:*** Dilantin; Epanutin; ***Ital.:*** Aurantin; Dintoina; ***Malaysia:*** Dilantin; Ditoin; ***Mex.:*** Biodan; Comvufen; Epamin; Fenidantoin S; Feniffler; Fenitron; Hidantoina; Nuctane†; ***Neth.:*** Diphantoine; Epanutin; ***Norw.:*** Epinat; ***NZ:*** Dilantin; ***Philipp.:*** Dilantin; Epilantin; ***Pol.:*** Epanutin; ***Port.:*** Fenitan; Hidantina; ***S.Afr.:*** Epanutin; ***Singapore:*** Dilantin; ***Spain:*** Epanutin; Neosidantoina; Sinergina; ***Swed.:*** Epanutin; Fenantoin; Lehydan; ***Switz.:*** Epanutin†; Epilantine†; Phenhydan; ***Thai.:*** Dilantin; Ditoin; Ditomed; Pepsytoin; Utoin; ***Turk.:*** Epanutin; Epdantoin; Hidantin; Phenydan; ***UK:*** Epanutin; ***USA:*** Dilantin; Phenytek; ***Venez.:*** Dantoinal; Dilantin; Epamin; Fentoinal.

Multi-ingredient: ***Arg.:*** Cumatil L; Lotoquis; ***Belg.:*** Vethoine; ***Braz.:*** Dialudon; Gamibetal Complex†; Taludon†; ***Cz.:*** Sanepil; ***Gr.:*** Diphenal; ***India:*** Dilantin with Phenobarbital; Epilan; Garoin; ***Indon.:*** Ditalin; ***Ital.:*** Dintoinale; Gamibetal Complex; Metinal-Idantoina; Metinal-Idantoina L; ***Mex.:*** Alepsal Compuesto; Gamibetal Complex; ***Port.:*** Hidantina Composta†; ***Spain:*** Epilantin†; Equidan†; Redutona.

Pregabalin *(BAN, USAN, rINN)*

CI-1008; PD-144723; Pregabalina; Prégabaline; Pregabalinum.
(*S*)-3-(Aminomethyl)-5-methylhexanoic acid.

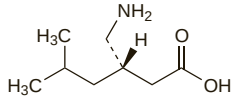
Прегабалин

$C_8H_{17}NO_2$ = 159.2.

CAS — 148553-50-8.

ATC — N03AX16.

ATC Vet — QN03AX16.



Adverse Effects and Precautions

The most common adverse effects reported during therapy with pregabalin are dizziness and somnolence. Other common adverse effects include blurred vision, diplopia, increased appetite and weight gain, dry mouth, constipation, vomiting, flatulence, euphoria, confusion, reduced libido, erectile dysfunction, irritability, vertigo, ataxia, tremor, dysarthria, paraesthesia, fatigue, and oedema. Disturbances of attention, memory, coordination, and gait also occur frequently. Syncope and congestive heart failure have been reported less frequently. Reversible renal failure, elevation of creatine kinase concentration, and rhabdomyolysis have been reported rarely. Hypersensitivity reactions have occurred shortly after starting pregabalin therapy; symptoms include rash, blisters, urticaria, dyspnoea, and wheezing. Stevens-Johnson syndrome has also been reported. An increased incidence of haemangiosarcoma was observed in *mice* that had been given high doses of pregabalin.

Licensed product information states that care is required when withdrawing pregabalin therapy, regardless of the indication—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.

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

Hypersensitivity reactions. The Australian Adverse Drug Reactions Advisory Committee[1] stated in December 2007 that 13% of all pregabalin adverse reaction reports in its database were hypersensitivity reactions. Presenting symptoms included anaphylaxis, skin rash, and angioedema. Of the 22 reports received, 6 women developed symptoms within hours of their first dose and pregabalin was the sole suspected drug in 14.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Reports of hypersensitivity reactions to pregabalin. *Aust Adverse Drug React Bull* 2007; **26:** 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0712.pdf (accessed 09/06/08)

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

Pharmacokinetics

Pregabalin is rapidly absorbed after oral doses and peak plasma concentrations are achieved within 1.5 hours. Oral bioavailability is about 90%. The rate but not the extent of absorption is reduced if given with food but this is not clinically significant. Steady state is achieved after 1 to 2 days. Pregabalin is not bound to plasma proteins and undergoes negligible metabolism. About 98% of a dose is excreted in the urine as unchanged drug. The mean elimination half-life is 6.3 hours. Pregabalin is removed by haemodialysis.

Distribution into milk has been found in studies in *rats*.

Renal impairment. References.

1. Randinitis EJ, *et al.* Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol* 2003; **43:** 277–83.

Uses and Administration

Pregabalin is an antiepileptic used as an adjunct in the treatment of partial seizures with or without secondary generalisation. It is also used in the treatment of generalised anxiety disorder, neuropathic pain, and fibromyalgia.

Pregabalin is given orally in 2 or 3 divided doses daily.

The initial dose in the treatment of **epilepsy** is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 600 mg daily after another week.

In the treatment of **generalised anxiety disorder**, the initial dose is 150 mg daily; this may be increased at weekly intervals in steps of 150 mg, to a maximum of 600 mg daily.

For **neuropathic pain** the initial dose in the UK is 150 mg daily increased after 3 to 7 days according to response to 300 mg daily and then to 600 mg daily after another 7 days. Similar doses are licensed in the USA for the treatment of neuropathic pain in diabetic neuropathy and postherpetic neuralgia, although a maximum daily dose of 300 mg is recommended in diabetic neuropathy.

For **fibromyalgia** the initial dose is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 450 mg daily if necessary.

Dosage of pregabalin should be reduced in patients with renal impairment (see below).

As with other antiepileptics, withdrawal of pregabalin therapy in epilepsy 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. Licensed drug information states that if pregabalin therapy has to be stopped, this should be done gradually over a minimum of 1 week, regardless of indication.

◊ References.

1. Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacother* 2005; **39:** 2029–37.
2. Tassone DM, *et al.* Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther* 2007; **29:** 26–48.

Administration in renal impairment. The dose of pregabalin for patients with renal impairment should be reduced according to creatinine clearance (CC):

- CC 30 to less than 60 mL/minute: starting daily dose: 75 mg; maximum daily dose: 300 mg; daily dose given in 2 or 3 divided doses
- CC 15 to less than 30 mL/minute: starting daily dose: 25 to 50 mg; maximum daily dose: 150 mg; daily dose given in 2 divided doses or once daily
- CC less than 15 mL/minute: starting daily dose: 25 mg; maximum daily dose: 75 mg; daily dose given as one dose
- haemodialysis patients should receive in addition to the daily dose a supplementary dose of 25 to 100 mg immediately after each 4-hour haemodialysis session

Anxiety disorders. Pregabalin is used for the treatment of generalised anxiety disorder (p.952); it has also been tried in social anxiety disorder (see Phobic Disorders, p.953).

References.

1. Pande AC, *et al.* Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry* 2003; **160:** 533–40.
2. Feltner DE, *et al.* A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol* 2003; **23:** 240–9.
3. Pande AC, *et al.* Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2004; **24:** 141–9.
4. Rickels K, *et al.* Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. *Arch Gen Psychiatry* 2005; **62:** 1022–30.
5. Owen RT. Pregabalin: its efficacy, safety and tolerability profile in generalized anxiety. *Drugs Today* 2007; **43:** 601–10.