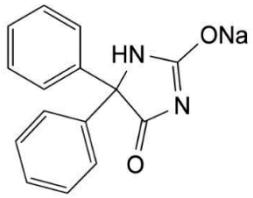
PRODUCT INFORMATION
PHENYTOIN SANDOZ® 100mg/2mL, 250mg/5mL INJECTION

NAME OF THE MEDICINE

Phenytoin sodium.

Chemical Name: 4-oxo-5,5-diphenyl-4,5-dihydro-1H-imidazol-2-olate

Chemical structure:



CAS: 630-93-3

Empirical formula: C_{15} H_{11} N_2 NaO_2 MW: 274.3

DESCRIPTION

Phenytoin sodium is a white crystalline powder, slightly hygroscopic, soluble in water and in alcohol, practically insoluble in ether and in methylene chloride.

Excipients: propylene glycol, ethanol, sodium hydroxide (to adjust pH) and water for injection.

PHARMACOLOGY

Pharmacodynamics
Phenytoin is a hydantoin derivative which inhibits the spread of seizure activity in the motor cortex. Epileptic seizures are thought to occur through the development of excessive central excitability due to post-tetanic potentiation, which is blocked by phenytoin.

The primary target of phenytoin appears to be sodium channels in depolarising neurones, where phenytoin binds and blocks sodium influx, reducing neuronal excitability and the spread of electrical activity characteristic of epileptic seizures. Phenytoin may also suppress sodium action potentials by stimulating the sodium pump. Other mechanisms possibly contributing to the antiepileptic activity of phenytoin include inhibition of neuronal calcium influx, enhancement of GABA neurotransmission, block of inotropic receptors for glutamate (a transmitter implicated in seizure activity) and an action at central sigma binding sites.

The antiarrhythmic action of phenytoin may be attributed to the normalisation of influx of sodium and calcium to cardiac Purkinje fibres. Abnormal ventricular automaticity and membrane responsiveness are decreased. It also shortens the refractory period, and therefore shortens the QT interval and the duration of the action potential.

Pharmacokinetics

Absorption

Absorption from an intravenous dose of phenytoin is immediate and bioavailability from the intravenous route is essentially 100%. The onset of action after an intravenous dose is 30 to 60 minutes and the effect persists up to 24 hours.

Distribution

Phenytoin is distributed into cerebrospinal fluid, saliva, semen, gastrointestinal fluids, bile and breast milk; also crosses the placenta, with foetal serum concentrations equal to those of the mother.

Protein binding

Phenytoin is about 90% protein bound. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal. Protein binding may be lower in neonates and hyperbilirubinaemic infants; also altered in patients with hypoalbuminaemia, uraemia or acute trauma, and in pregnancy. Therapeutic concentrations of free (unbound) phenytoin, which are frequently monitored in patients with altered protein binding, usually fall in the range of 0.8 to 2 microgram/mL (3 to 8 micromol/L).

Half-life

The plasma half-life is normally from 10 to 15 hours. Because phenytoin exhibits saturable or dose dependent pharmacokinetics, the apparent half-life of phenytoin changes with dose and serum concentration. At therapeutic concentrations of the drug, the enzyme system responsible for metabolising phenytoin becomes saturated. Thus, a constant amount of drug is metabolised and small increases in dose may cause disproportionately large increases in serum concentrations and apparent half-life, possibly causing unexpected toxicity.

Conventionally, with drugs following linear kinetics the half-life is used to determine the dose rate, drug accumulation and the time to reach steady state. Phenytoin, however, demonstrates nonlinear kinetics. Therefore, the half-life is affected by the degree of absorption, saturation of metabolic pathways, dose and degree of metabolic enzyme induction. This results in considerable interpatient and intrapatient variability in phenytoin pharmacokinetics. As a consequence the clinical relevance of reported phenytoin half-life values are limited and cannot be used in the conventional manner to estimate the dosage regimen.

Therapeutic serum concentrations

When administering phenytoin to a patient it is necessary to measure the serum levels as this provides the most accurate means of deriving a suitable dosage regimen. Serum level determinations should originally be obtained at least seven to ten days after treatment initiation, dosage change or addition or subtraction of another drug to the regimen so that equilibrium or steady state will have been achieved. Further serum level determinations may be required to further refine the dosage regimen. Trough levels provide information about the clinically effective serum level range and confirm patient compliance, and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose related side effects and are obtained at the time of expected peak concentration.

Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and 20 microgram/mL. In renal failure or hypoalbuminaemia, 5 to 12 microgram/mL or even less may be therapeutic. Occasionally a patient may have seizure

control with plasma concentrations of 6 to 9 microgram/mL. Effective treatment, therefore, should be guided by clinical response, not drug concentrations. In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolisers of phenytoin. Unusually high levels of phenytoin result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful.

Metabolism
Phenytoin is hydroxylated in the liver by a saturable enzyme system. It is metabolised in the liver primarily by CYP2C9 (major) and CYP2C19 (minor), and the major inactive metabolite is 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH). The rate of metabolism is increased in younger children, pregnant women, in women during menses and in patients with acute trauma. The rate decreases with advancing age. Phenytoin may be metabolised slowly in a small number of individuals due to genetic polymorphism, which may cause isoenzyme mutations (e.g. CYP2C9/19), limited enzyme availability and lack of induction (e.g. CYP3A4).

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly by glomerular filtration but more importantly by tubular secretion.

INDICATIONS

Control of status epilepticus, tonic-clonic (grand mal), psychomotor seizures and the prevention of seizures occurring during or following neurosurgery. Phenytoin will prevent or effectively decrease the incidence and severity of convulsive seizures in a high percentage of cases, with patients exhibiting little tendency to become resistant to its action. Besides its effectiveness in controlling seizures, phenytoin frequently improves the mental condition and outlook of epileptic patients.

It has also been used in the treatment of certain cardiac arrhythmias, particularly in those patients who do not respond to conventional antiarrhythmic agents or to cardioversion. Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Known hypersensitivity to phenytoin or other hydantoins.
Sinus bradycardia, sinoatrial block, second and third degree atrioventricular block or Stokes-Adams syndrome (due to the effect of phenytoin on ventricular automaticity).
Coadministration of phenytoin is contraindicated with delavirdine due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors

PRECAUTIONS

The mixing of phenytoin sodium with other drugs or with intravenous infusion solutions is not recommended because the solubility of phenytoin sodium is such that crystallisation or precipitation may result if the special vehicle is altered or the pH is lowered.

Soft tissue irritation and inflammation, varying from slight tenderness to extensive necrosis and sloughing, have been noted at the site of injection, with and without the extravasation of intravenous phenytoin. Each injection of phenytoin should be followed by an injection of sodium chloride intravenous infusion 0.9% through the same needle or catheter to avoid irritation caused by the alkalinity of the solution.

This drug must be administered slowly, at a rate not exceeding 50mg/minute in adults. Administration at faster rates may result in cardiac arrhythmias, impaired cardiac conduction, hypotension, cardiovascular collapse or CNS depression, related to the propylene glycol diluent. In children and neonates, the drug should be administered at a rate not exceeding 1 to 3mg/kg/minute (maximum of 50mg/minute). The response to phenytoin may be significantly altered by the concomitant use of other drugs (see INTERACTION WITH OTHER MEDICINES).

Phenytoin should be used with caution in patients with hypotension and severe myocardial insufficiency. Hypotension usually occurs when the drug is administered rapidly by the intravenous route.

In patients with cardiovascular disease, parenteral administration may result in atrial and ventricular conduction depression, ventricular fibrillation or reduced cardiac output. Intramuscular administration of phenytoin sodium is not recommended due to erratic absorption and local tissue reactions, such as tissue necrosis, caused by the alkalinity of the solution. Erratic absorption is partly caused by tissue precipitation of phenytoin.

While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy. If folic acid is added to phenytoin therapy, a decrease in seizure control may occur (see INTERACTION WITH OTHER MEDICINES).

Phenytoin and other anticonvulsants that have been shown to induce the CYP450 enzyme are thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to Vitamin D deficiency and heightened risk of osteomalacia, bone fractures, osteoporosis, hypocalcaemia and hypophosphatemia in chronically treated epileptic patients (see ADVERSE EFFECTS).

It is recommended that patients receiving long-term phenytoin therapy should undergo regular blood counts as serious adverse haematological reactions have been reported (see ADVERSE EFFECTS).

Caution should be used when administering phenytoin to patients suffering from porphyria. There have been isolated reports linking phenytoin to exacerbation of this disease.

Toxic hepatitis, liver damage and hypersensitivity syndrome have been reported and may, in rare cases, be fatal.

A small percentage of individuals, who have been treated with phenytoin, have shown to metabolise the drug slowly. Slow metabolism appears to be due to limited enzyme availability

and lack of or defective induction, which may be genetically determined (see PHARMACOLOGY, Pharmacokinetics, metabolism).

Serum levels of phenytoin sustained above the optimal range may produce encephalopathy, confusional states (delirium psychosis) or, rarely, irreversible cerebellar dysfunction. Plasma level determinations are recommended at the first signs of acute toxicity. If plasma levels are excessive, dosage reduction is indicated. Termination of phenytoin therapy is recommended if symptoms persist.

Literature reports suggest the combination of phenytoin, cranial irradiation and the gradual reduction of corticosteroids may be associated with the development of erythema multiforme and/or Stevens-Johnson syndrome and/or toxic epidermal necrolysis.

Phenytoin should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric or bullous, or if lupus erythematosus, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected, phenytoin should not be resumed. If the rash is mild (measles-like or scarlatiniform), resumption of therapy, after the rash has disappeared completely, will depend on a consideration of the risk-benefit ratio by the treating doctor. However, in the case of the rash recurring upon reinstitution of therapy, further phenytoin medication is contraindicated.

Hypersensitivity reactions
Published literature has suggested that there may be an increased, although still rare, risk of hypersensitivity reactions, including skin rash, SJS, TEN, hepatotoxicity, and Anticonvulsant Hypersensitivity Syndrome in black patients. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using another anticonvulsant, carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of drugs associated with SJS/TEN, including phenytoin, in HLA-B*1502 positive patients when alternative therapies are otherwise equally available.

Anticonvulsant Hypersensitivity Syndrome (AHS)
Anticonvulsant Hypersensitivity Syndrome (AHS) is a rare drug induced, multiorgan syndrome which is potentially fatal and occurs in some patients taking anticonvulsant medication. It is characterized by fever, rash, lymphadenopathy, and other multiorgan pathologies, often hepatic. The mechanism is unknown. The interval between first drug exposure and symptoms is usually 2-4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. Patients at higher risk for developing AHS include black patients, patients who have a family history of or who have experienced this syndrome in the past, and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals. If a patient is diagnosed with AHS, discontinue the phenytoin and provide appropriate supportive measures.

General
Phenytoin should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus, hence any need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication should be implemented gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of an alternative therapy

may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally caution should be exercised if using structurally similar compounds (e.g. barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Phenytoin can cause rare, serious skin adverse events such as exfoliative dermatitis, SJS, and TEN, which can be fatal. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. The physician should advise the patient to discontinue treatment if the rash appears. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Suicidal Behaviour and Ideation
Antiepileptic drugs (AED), including phenytoin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/ or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43% compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5- 100 years) in the clinical trials analysed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo patients with events/1000 patients	Drug patients with Events/1000 patients	Relative Risk: Incidence of events in Drug patients/ incidence in Placebo patients	Risk Difference: Additional Drug patients with events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing phenytoin or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

There have been a number of reports suggesting a relationship between phenytoin and the development of local or generalised lymphadenopathy, including benign lymph node hyperplasia, lymphoma, pseudolymphoma and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy requires differentiation from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms resembling serum sickness, e.g. rash, fever and liver involvement. In all cases of lymphadenopathy, seizure control should be sought using alternative antiepileptic drugs and observation of patients for an extended period is recommended.

Phenytoin is not effective for absence (petit mal) seizures as it may increase the frequency of these seizures. Therefore, combined therapy is required if both tonic-clonic (grand mal) and absence (petit mal) seizures are present.

Diabetes

Phenytoin should be used with caution in diabetic patients, as hyperglycaemia may be potentiated. There have been isolated reports of hyperglycaemia occurring in patients receiving phenytoin, resulting from the drug's inhibitory effects on insulin release. Phenytoin may also raise the serum glucose in diabetic patients. Patients with impaired renal function appear to be more susceptible to this effect.

Phenytoin is not indicated for the treatment of seizures due to hypoglycaemia or other metabolic causes. The appropriate diagnostic tests should be performed as indicated.

Caution should also be used in patients with hypoalbuminaemia as this condition can lead to potential toxicity through its effect on increasing unbound phenytoin levels (see PHARMACOLOGY, Pharmacokinetics).

Impaired renal function
Patients with renal function impairment should be carefully observed, as excretion and protein binding of phenytoin may be altered.

Impaired hepatic function
As the main site of biotransformation for phenytoin is in the liver, patients with impaired liver function may show early signs of toxicity on standard dosage. Care should be exercised with dosage adjustment in these patients.

Use in the elderly
Severe complications are most commonly encountered in elderly or gravely ill patients. In these patients, the drug should be administered at a rate not exceeding 25mg/minute, and if necessary, at a slow rate of 5 to 10mg/minute. Elderly patients have an increased frequency of toxicity due to their slower rate of phenytoin metabolism and decreased serum albumin concentration, which decreases the degree of protein binding of phenytoin. Therefore, lower doses and subsequent dosage adjustment may be necessary.

Carcinogenicity, Mutagenicity and Effects on Fertility
In two studies in mice, increased incidences of hepatic adenoma were seen when phenytoin sodium was administered at dietary doses of 45 and 90mg/kg/day. The incidence of hepatic carcinoma was also increased in one of these studies. These effects were seen at plasma phenytoin concentrations slightly lower than the human therapeutic range. In rats, the incidence of hepatic adenoma was marginally increased at 240mg/kg/day in one study, but was not affected at 100mg/kg/day in another. In the latter study, plasma concentrations of phenytoin were slightly lower than the human therapeutic range. In two other studies, no carcinogenic effects were seen at low doses (16mg/kg/day in mice and 20mg/kg/day in rats). Phenytoin induced hepatic tumours in rodents may be secondary to hepatic enzyme induction, and are of uncertain clinical relevance.

In genotoxicity studies with phenytoin sodium, negative results were obtained in assays for chromosomal damage in mammalian cells in vitro and in vivo and in a sister chromatid exchange assay in vivo. The potential for phenytoin sodium to cause gene mutations has not been investigated.

In studies in which phenytoin sodium was administered orally to female mice and rats for two weeks before breeding, and throughout gestation and lactation, no pregnancies occurred at respective doses of 90mg/kg/day and 240mg/kg/day; there were no adverse effects at respective doses of 30 and 80mg/kg/day.

Use in pregnancy (Category D)
The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy. It is recommended that:

- Women on antiepileptic drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of foetal abnormalities.
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication.

- Folic acid supplementation (5mg) should be commenced four weeks prior to and continue for 12 weeks after conception.
- Specialist pre-natal diagnosis including detailed mid-trimester ultrasound should be offered.

Phenytoin sodium taken during pregnancy has been associated with craniofacial defects, fingernail hypoplasia, developmental disability and growth retardation, and less frequently, oral clefts and cardiac anomalies. This clinical pattern is sometimes called the 'foetal hydantoin syndrome'. Phenytoin can also cause coagulation defects with consequent risk of haemorrhage in the foetus and the newborn infant that may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.

The risk of a mother with epilepsy and taking anticonvulsants giving birth to a baby with an abnormality is about three times that of the normal population. Some of this risk is due to the anticonvulsant drugs taken.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo and foetus. The prescribing physician will wish to weigh these considerations in treating and counselling epileptic women of childbearing potential.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated. Some patients may experience a rapid reduction in maternal hepatic phenytoin metabolism at the time of delivery, requiring the dosage to be reduced within 12 hours postpartum.

Malignancies such as neuroblastoma have been reported rarely in children whose mothers received phenytoin during pregnancy.

Use in lactation
Breastfeeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in breast milk.

Effects on Ability to Drive and Use Machines
Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that this medication does not affect their ability to engage in these activities.

Drug enteral feeding/nutrition preparations interaction
Patients who must receive continuous enteral feedings should probably receive phenytoin intravenously as enteral feeds may reduce the absorption of oral phenytoin.

Effect on Laboratory tests

Phenytoin increases blood glucose levels due to inhibition of insulin secretion. Raised serum levels of alkaline phosphatase, hypocalcaemia and osteomalacia have been linked with altered vitamin D metabolism. Elevated serum levels of gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase may be related to hepatic enzyme induction. Phenytoin may also produce lower than normal values for dexamethasone or metyrapone.

Folic acid, calcium and free thyroxine concentrations and protein bound iodine (PBI) test values may all be reduced.

INTERACTION WITH OTHER MEDICINES

Mechanisms of drug interactions with phenytoin may be complex. In assessing drug interactions, serum phenytoin concentrations and the clinical status of the patient will be helpful.

In general, phenytoin is an inducer of the hepatic cytochrome P450 microsomal enzymes including CYP3A4, CYP2D6, CYP1A2, CYP2C9 and CYP2C19 isoenzymes. However, a patient's susceptibility to enzyme induction interactions may be influenced by factors such as age, cigarette smoking or the presence of liver disease (see PHARMACOLOGY, Pharmacokinetics, metabolism). Phenytoin is metabolised primarily by CYP2C9 (major) and CYP2C19 (minor), thus several drugs may inhibit or induce the metabolism of phenytoin. The activities of some enzymes such as CYP P450 isoenzymes, the uridine diphosphate glucuronosyl transferase (UDPGT) system and epoxide hydrolase enzymes are significantly increased by phenytoin therapy, which in turn enhances the metabolism of many drugs.

In addition, phenytoin is highly plasma-protein bound and may be displaced by other drugs, increasing unbound ('free') phenytoin levels.

Drugs that may increase phenytoin serum levels:
Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with capecitabine or its metabolite fluorouracil (5-FU). Formal interaction studies between phenytoin and capecitabine have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine. Serum levels of phenytoin sustained above the optimal range may produce encephalopathy, or confusional states (delirium psychosis), or rarely irreversible cerebellar dysfunction. Patients taking phenytoin concomitantly with capecitabine or fluorouracil should be regularly monitored for increased phenytoin plasma levels.

Analgesics/anti-inflammatory agents: phenylbutazone, salicylates.
Anaesthetics: halothane.
Antibacterial agents: chloramphenicol, erythromycin, isoniazid, sulfonamides (e.g. sulfamethizole, sulfaphenazole, sulfadiazine, sulfamethoxazole-trimethoprim).
Anticonvulsants: felbamate, succinimides (ethosuximide, methsuximide and phensuximide), mephenytoin, oxcarbazepine, topiramate.
Antifungal agents: amphotericin B, azoles (fluconazole, itraconazole, ketoconazole, miconazole, voriconazole).
Benzodiazepines/psychotropic agents: chlordiazepoxide, diazepam, methylphenidate, phenothiazines.
Calcium channel antagonists/cardiovascular agents: amiodarone, diltiazem, nifedipine.
H2-Antagonists/ proton pump inhibitors: cimetidine, omeprazole, ranitidine.
Hormones: oestrogens.

Oral hypoglycaemic agents: tolbutamide.
Serotonin reuptake inhibitors: fluoxetine, sertraline.
Other: azapropazone, clopidogrel, coumarin anticoagulants, dicumarol, disulfiram, fluvoxamine, ticlopidine, trazodone, viloxazine, warfarin, fluvastatin.

Drugs which may decrease serum levels of phenytoin:
Anticonvulsants: carbamazepine, vigabatrin.
Antibacterial agents: fluoroquinolones (e.g. ciprofloxacin), rifampicin.
Cardiovascular agents: diazoxide.
Cytotoxic agents: bleomycin, carboplatin, carmustine, cisplatin, methotrexate, vinblastine, doxorubicin.
Dietary supplements: calcium folinate, folic acid.
Other: antacids and preparations containing calcium ions, nelfinavir, reserpine, ritonavir, fosemprenavir, sucralfate, theophylline, St John's wort (*Hypericum perforatum*).

Calcium ions may interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

Phenytoin levels may be reduced by 20 to 30% when coadministered with vigabatrin; in some patients this may require a dosage adjustment.

Drugs that may either increase or decrease phenytoin serum levels:
Anticonvulsants: carbamazepine, barbiturates (e.g. phenobarbitone), primidone, sodium valproate, valproic acid.
Antineoplastic agents.
Benzodiazepines: chlordiazepoxide.
Cytotoxic agents.
Psychotropic agents: diazepam.
Other: ciprofloxacin.

Acute alcohol intake may increase serum levels of phenytoin sodium while chronic alcohol use may decrease them.

Drugs whose blood levels and/or effects may be altered by phenytoin:
Drugs that should not be coadministered with phenytoin: delavirdine (see CONTRAINDICATIONS).

Antibacterial agents: doxycycline, praziquantel, rifampicin, tetracycline.
Anticonvulsants: lamotrigine, succinimide, felbamate, oxcarbazepine, topiramate, carbamazepine.
Antifungal agents.
Calcium channel antagonists/cardiovascular agents: diazoxide, digoxin, disopyramide, frusemide, lignocaine, mexiletine, nicardipine, nifedipine, nimodipine, quinidine, nisoldipine, simvastatin, verapamil.
Cytotoxic agents: dacarbazine.
Hormones: oestrogens, oral contraceptives.
Neuromuscular blocking drugs: alcuronium, pancuronium, vecuronium, rocuronium, cisatracurium.
Opioid analgesics: methadone.
Oral hypoglycaemic agents: glibenclamide, tolbutamide.

Other: corticosteroids, coumarin anticoagulants, chlorpropamide, cyclosporin, HIV antivirals (amprenavir, efavirenz, lopinavir/ritonavir, indinavir, nelfinavir, ritonavir, saquinavir), levodopa, sertraline, teniposide, vitamin D, warfarin, xanthines (e.g. theophylline), atorvastatin, albendazole, fluvastatin.
Dietary supplements : folic acid
Psychotropic agents: clozapine, quetiapine, paroxetine.

The plasma clearance of lamotrigine is doubled and its elimination half-life is reduced by 50% when given in combination with phenytoin, this requires dosage adjustment.
Tricyclic antidepressants, haloperidol, MAO inhibitors and thioxanthenes may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.
Caution is advised when nifedipine or verapamil are used concurrently with phenytoin. All are highly protein bound medications; therefore, changes in serum concentrations of the free, unbound medications may occur.

Phenytoin sodium, especially in large doses, may increase serum glucose levels; therefore, dosage adjustments for insulin or oral antidiabetic agents may be necessary.
Concurrent use of phenytoin and oral diazoxide may decrease the efficacy of phenytoin and the hyperglycaemic effect of diazoxide and is not recommended.

Use of intravenous phenytoin in patients maintained on dopamine may produce sudden hypotension and bradycardia. This appears to be dose rate dependent. If anticonvulsant therapy is necessary during administration of dopamine, an alternative to phenytoin should be considered.

Concurrent use of intravenous phenytoin with lignocaine or beta-blockers may produce additive cardiac depressant effects. Phenytoin may also increase the metabolism of lignocaine.
Concomitant use of fluoxetine in patients stabilised on phenytoin has resulted in elevated plasma phenytoin concentrations and signs and symptoms of phenytoin toxicity. Plasma phenytoin concentrations should be monitored closely during concomitant use of fluoxetine, and the dose of phenytoin adjusted if necessary.

Coadministration of phenytoin and topiramate reduces topiramate levels by 59% and has the potential to increase phenytoin levels by 25% in some patients.

ADVERSE EFFECTS

The most notable signs of toxicity are cardiovascular collapse and/or central nervous system (CNS) depression. Nystagmus is the most frequently reported clinical finding of toxicity and tends to occur when the serum phenytoin concentration exceeds 20 microgram/mL. Toxicity should be minimised by following the appropriate directions (see DOSAGE AND ADMINISTRATION).

Body as a whole: Anaphylactoid reaction and anaphylaxis.

Cardiovascular: Periarteritis nodosa has been reported. Severe cardiotoxic reactions and fatalities have been reported, most commonly in gravely ill patients or the elderly (see PRECAUTIONS).

Central nervous system: These are the most common reactions encountered with phenytoin and include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. These side effects are usually dose related. Cases of dizziness, insomnia, transient nervousness, stuttering, trembling of hands, paresthesia, somnolence, unusual excitement, irritability, toxic amblyopia, cognitive impairment, tonic seizures, motor twitchings, vertigo, drowsiness, taste perversion and headaches have also been reported.

There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs. These may be due to sudden administration of intravenous phenytoin for status epilepticus. The effect usually lasts 24 to 48 hours after discontinuation.

A predominantly sensory peripheral polyneuropathy has been reported for patients on long-term phenytoin therapy.

Gastrointestinal: Nausea, vomiting, epigastric pain, dysphagia, loss of taste, anorexia, weight loss and constipation.

Dermatological: A measles-like rash is the most common dermatological manifestation. Rashes are sometimes accompanied by fever and are generally more common in children and young adults. Other types of rashes are more rare, and more serious forms that may be fatal include bullous, exfoliative or purpuric dermatitis, systemic lupus erythematosus, Stevens-Johnson syndrome, scarlatiniform or morbilliform rashes and toxic epidermal necrolysis (see PRECAUTIONS).

*Immunological**:*** Hypersensitivity syndrome (which may include but is not limited to symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash [DRESS syndrome: drug rash with eosinophilia and systemic symptoms]), systemic lupus erythematosus and immunoglobulin abnormalities.

Hepatic: Potentially fatal cases of toxic hepatitis and liver damage may occur. This effect may be the result of a hypersensitivity reaction.

Musculoskeletal: Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with vitamin D metabolism. Some patients on high phenytoin doses with poor dietary intake of vitamin D, limited sun exposure and reduced levels of physical activity may require vitamin D supplementation. Bone fractures and osteomalacia have also been associated with long-term (>10 years) use of phenytoin by patients with chronic epilepsy. Osteoporosis and other disorders of bone metabolism such as hypocalcaemia, hypophosphatemia and decreased serum levels of Vitamin D metabolites have also been reported.

Haematological: Some fatal haemopoietic complications have occasionally been reported in association with the use of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis and pancytopenia with or without bone marrow suppression. Although macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy.

Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma and Hodgkin's Disease has also been reported (see PRECAUTIONS).

Other: Gingival hyperplasia occurs frequently, usually within the first six months, beginning as gingivitis or gum inflammation. Children and young adults do appear more susceptible to gingival hyperplasia than adults. The incidence of gum hyperplasia may be reduced by maintaining good oral hygiene, e.g. frequent brushing, gum massage and appropriate dental care.

Coarsening of the facial features, enlargement or thickening of the lips, widening of the nasal tip, protrusion of the jaw, gynaecomastia, Dupuytren's contracture, hypertrichosis, immunoglobulin abnormalities, hirsutism and Peyronie's disease may occur.

Younger patients appear more susceptible to bleeding, tender and enlarged gums. Unusual and excessive body hair growth may be more pronounced in young patients. Local irritation, inflammation, tenderness, necrosis and sloughing at the injection site have been reported with or without extravasation of intravenous phenytoin.

Rare reports of pulmonary infiltrates or fibrosis, with symptoms including fever, troubled or quick shallow breathing, unusual tiredness or weakness, weight loss, loss of appetite and chest discomfort, have also occurred.

DOSAGE AND ADMINISTRATION

Phenytoin Sandoz must be administered slowly. Intravenous administration should not exceed 50mg/minute in adults. In neonates and children, the drug should be administered at a rate not exceeding 1 to 3mg/kg/minute, maximum of 50mg/minute.

Dilution of Phenytoin Sandoz into intravenous infusion is not recommended due to lack of solubility and resultant precipitation.

The solution is suitable for use as long as it remains free of haziness and precipitate. A precipitate might form if the product has been kept in a refrigerator or freezer. This precipitate will dissolve if allowed to stand at room temperature. The product will then be suitable for use.

Phenytoin Sandoz should be injected slowly and directly into a large vein through a large gauge needle or intravenous catheter. Each injection should be followed by an injection of sodium chloride intravenous infusion 0.9% through the same needle or catheter to avoid local venous irritation due to the alkalinity of the solution. Continuous infusion should be avoided. Product is for one dose in one patient only. Discard any remaining contents.

<u>Status epilepticus</u>
Adults: For the control of status epilepticus in adults, a loading dose of 10 to 15mg/kg should be administered slowly intravenously, at a rate not exceeding 50mg/minute. This will require approximately 20 minutes in a 70 kg patient. The loading dose should be followed by maintenance doses of 100mg orally or intravenously every six to eight hours.
Neonates, children: For neonates and children, a loading dose of 10 to 20mg/kg intravenously will usually provide a plasma concentration of phenytoin within the generally accepted therapeutic range (10 to 20 microgram/mL). The drug should be administered intravenously at a rate not exceeding 1 to 3mg/kg/minute, maximum of 50mg/minute (see PRECAUTIONS). Children tend to metabolise phenytoin more rapidly than adults, which may affect dosage regimens. Therefore, serum level monitoring may be particularly beneficial in such cases.

In the treatment of status epilepticus, an intravenous benzodiazepine, e.g. diazepam or an intravenous short acting barbiturate, is usually given initially for the rapid control of seizures and is then followed by the slow intravenous administration of phenytoin.

Intramuscular administration of phenytoin is unsuitable for the emergency treatment of status epilepticus due to very slow and erratic absorption from the intramuscular site.

Intra-arterial administration must be avoided in view of the high pH of the preparation. Dosage should be individualised to obtain maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments. Serum levels between 10 and 20 microgram/mL (40 to 80 micromol/L) are considered to be clinically effective. With the recommended dosage, a period of at least seven to ten days may be required to achieve therapeutic blood levels of phenytoin unless therapy is initiated with a loading dose. After the initial dose has been prescribed, plasma levels should be determined and the dosage adjusted if necessary to obtain a level in the therapeutic range; 10 to 20 microgram/mL, (40 to 80 micromol/L).

When serum levels are in the upper range, small incremental doses may increase the half-life of phenytoin and produce large increases in serum levels, as hydroxylation in the liver enzyme system is saturable.

Neurosurgery
For the prevention of seizures during or following neurosurgery, cautious intravenous administration of 250mg every six to twelve hours is recommended until oral dosage is possible. Plasma levels should be monitored to ensure optimal efficacy and to minimise toxicity. Phenytoin should not be given by intramuscular injection for the prevention of seizures following neurosurgery.

Cardiac arrhythmias
Phenytoin sodium can be useful in ventricular arrhythmias, especially those due to digitalis. Although not a cardiac depressant, it has a positive inotropic effect and enhances conduction, though it generally decreases automaticity. The recommended dosage is one intravenous injection of Phenytoin Sandoz 3 to 5mg/kg bodyweight initially, repeating if necessary. Because there is approximately an 8% increase in drug content in the free form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt or vice versa.

Continuous monitoring of the electrocardiogram and blood pressure is essential. The patient should be observed for signs of respiratory depression. Determination of phenytoin plasma levels is advised when using phenytoin in the management of status epilepticus and the subsequent establishment of maintenance dosage. Cardiac resuscitative equipment should be available.

OVERDOSAGE

Symptoms
The mean lethal dose in adults is considered to be phenytoin 2 to 5g. The lethal dose in children is not known. The initial symptoms are nystagmus, ataxia and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea and vomiting. The patient may become comatose, hypotensive, severely confused, dizzy or drowsy, unusually tired or weak.

The patient's pupils may become unresponsive and blurred vision or double vision may also occur. Other manifestations of accidental intravenous overdosages of phenytoin are bradycardia and heart block. Death is due to respiratory and circulatory depression and apnoea.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus or lateral gaze usually appears at 20 microgram/mL, ataxia at 30 microgram/mL, dysarthria and lethargy appear when the plasma concentration is over 40 microgram/mL, but as high a concentration as 50 microgram/mL has been reported without evidence of toxicity.

Treatment
Treatment is non-specific since there is no known antidote. If the gag reflex is absent, the airway should be supported. Oxygen, vasopressors and assisted ventilation may be necessary for central nervous system, respiratory and cardiovascular depression. Haemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been utilised in the treatment of severe intoxication in children. In acute overdose the possibility of other CNS depressants, including alcohol, should be borne in mind.

PRESENTATION AND STORAGE CONDITIONS

Phenytoin Sandoz 100mg/2mL and 250mg/5mL - Ready mixed ampoules (clear colourless solution, free from visible particulates). Each ampoule contains 100mg/2mL or 250mg/5mL phenytoin sodium as an active ingredient. It also contains the following excipients: propylene glycol, ethanol, sodium hydroxide (to adjust pH) and water for injections.

Phenytoin Sandoz is available in the following pack sizes:
100mg/2mL: 1 x 2mL ampoule*; 5 x 2mL ampoules and 10 x 2mL ampoules*.
250mg/5mL: 1 x 5mL ampoule*; 5 x 5mL ampoules and 10 x 5mL ampoules*.

*Not currently marketed in Australia.

Store below 25°C. Do not freeze. Do not use if the solution is hazy or contains a precipitate. The product should be visually inspected for particulate matter and discolouration prior to administration.

NAME & ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4- Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
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