

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phenytoin 100mg Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Phenytoin Sodium 100mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White, circular, sugar coated, biconvex tablets coded or uncoded.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy: control of tonic-clonic (grand mal) seizures and partial seizures (focal including temporal lobe) or a combination of these.

Treatment of seizures occurring during or following neurosurgery and/or severe head injury.

Treatment of trigeminal neuralgia but only as a second line therapy if carbamazepine is ineffective or patients are intolerant of carbamazepine.

4.2 Posology and method of administration

Posology

92mg of phenytoin is equivalent to 100mg of phenytoin sodium.

Dosage should be individually titrated as there may be wide variability in phenytoin serum levels with equivalent dosage. Phenytoin should be introduced in small doses with gradual increments until control is achieved or until toxic effects appear. The clinically effective plasma phenytoin concentration is 10-20µg/ml (40-80µmol/l) but some patients are satisfactorily controlled at concentrations outside this range. With recommended dosage a period of seven to ten days may be required to achieve steady state serum levels with Phenytoin and changes in dosage should not be carried out at intervals shorter than seven to ten days. Maintenance of treatment should be the lowest dose of anticonvulsant consistent with control of seizures.

Adults: Initially 3 to 4mg/kg/day with subsequent dosage adjustment as necessary. For most adults a satisfactory maintenance dose will be 200 to 500 mg daily in single or divided doses. Exceptionally, a daily dose outside this range may be indicated. Dosage should normally be adjusted according to serum levels where assay facilities exist.

Children and Infants: Initially 5mg/kg/day in 2 or 3 divided doses. A suggested maintenance dose is 4 to 8mg/kg daily in divided doses. Maximum dosage is 300mg daily.

Neonates: In neonates the absorption of phenytoin following oral administration is variable and the metabolism of phenytoin may be depressed. It is therefore very important to monitor serum levels in the neonate.

Administration in liver disorders: A reduced dose should be used to avoid toxicity.

Elderly: As with adults the dosage of phenytoin should be titrated to the patient's individual requirements using the same guidelines. The usual adult dose unless serum albumin is low or hepatic or renal dysfunction is present. As older people tend to receive multiple drug therapies, the possibility of drug interactions should be borne in mind.

If it is necessary to transfer a patient from phenytoin to other anticonvulsant therapy, this is best effected over a period of one week with gradual withdrawal of phenytoin.

Method of administration

Oral

4.3 Contraindications

Hypersensitivity to phenytoin, other hydantoin, or any of the excipients listed in section 6.1.

Acute intermittent porphyria.

Co-administration of phenytoin is contraindicated with delavirdine due to the potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

4.4 Special warnings and precautions for use

General

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence seizures are present together, combined drug therapy is needed.

Phenytoin is not indicated for seizures due to hypoglycaemia or other metabolic causes.

Phenytoin may precipitate or aggravate absence seizures and myoclonic seizures.

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative anti-epileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anti-epileptic drug not belonging to the hydantoin chemical class.

Acute alcohol intake may increase phenytoin serum levels while chronic alcoholism may decrease serum levels.

Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used while taking phenytoin due to the risk of decreased plasma concentrations and reduced clinical effects of phenytoin (see section 4.5).

Suicide

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for phenytoin sodium.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms (HSS/DRESS)

Hypersensitivity Syndrome (HSS) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking anticonvulsant drugs, including phenytoin. Some of these events have been fatal or life threatening.

HSS/DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, haematological abnormalities, myocarditis, myositis or pneumonitis. Initial symptoms may resemble an acute viral infection. Other common manifestations include arthralgias, jaundice, hepatomegaly, leucocytosis, and eosinophilia. The interval between first drug exposure and symptoms is usually 2 to 4 weeks but has been reported in individuals receiving anticonvulsants for 3 or more months. If such signs and symptoms occur, the patient should be evaluated immediately. Phenytoin should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

Patients at higher risk for developing HSS/DRESS include black patients, patients who have experienced this syndrome in the past with phenytoin or other anticonvulsant drugs, patients who have a family history of this syndrome and immuno-suppressed patients. The syndrome is more severe in previously sensitized individuals.

Serious Skin Reactions

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Phenytoin. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, phenytoin treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of Phenytoin, Phenytoin must not be re-started in this patient at any time.

If a rash is of the milder type (measles-like or scarlatiniform), phenytoin therapy may be resumed after the rash has completely disappeared. If the rash recurs further phenytoin medication is contraindicated. The risk of serious skin reactions and other hypersensitivity reactions to phenytoin may be higher 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 human leukocyte antigen HLA-B*1502, an inherited allelic variant of the HLAB gene, in patients using carbamazepine.

HLA-B*1502 may be associated with an increased risk of developing Stevens Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) in patients of Thai and Han Chinese ancestry taking drugs associated with SJS/TEN, including phenytoin. If these patients are known to be positive for HLA-B*1502, the use of phenytoin should only be considered if the benefits are thought to exceed risks.

In the Caucasian and Japanese population, the frequency of the HLA-B*1502 allele is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about the risk association in other ethnicities is currently not available.

Hepatic Injury

Phenytoin is highly protein bound and extensively metabolised by the liver. Reduced dosage to prevent accumulation and toxicity may therefore be required in patients with impaired liver function. Where protein binding is reduced, as in uraemia, total serum phenytoin levels will be reduced accordingly. However, the pharmacologically active free drug concentration is unlikely to be altered. Therefore, under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range of 10 mcg/ml to 20 mcg/ml (40-80 micromoles/l). Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents usually within the first 2 months of treatment and may be associated with HSS/DRESS (see section 4.4). Patients with impaired liver function, elderly patients or those who are gravely ill may show early signs of toxicity.

The risk of hepatotoxicity and other hypersensitivity reactions to phenytoin may be higher in black patients.

Haematopoietic System

Haematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local and generalised) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling HSS/DRESS (see section 4.4). In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy.

Central Nervous System Effect

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium", "psychosis", or "encephalopathy", or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum drug level determinations are recommended. Dose reduction of phenytoin therapy is indicated if serum levels are excessive; if symptoms persist, termination of therapy with phenytoin is recommended.

Musculoskeletal Effect

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, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients.

Metabolic Effect

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using the medication in patients suffering from this disease.

Phenytoin may affect glucose metabolism and inhibit insulin release. Hyperglycaemia has been reported in association with toxic levels.

Endocrine disorders

There have been reports of secondary hyperparathyroidism associated with phenytoin use.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions:

Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome (CYP) P450 enzymes CYP2C9 and CYP2C19 and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity.

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes and may reduce the levels of drugs metabolized by these enzymes.

There are many drugs which may increase or decrease serum phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

The most commonly occurring drug interactions are listed below.

Drugs that may increase phenytoin serum levels

Table 1 summarizes the drug classes which may potentially increase phenytoin serum levels.

Table 1. Drugs that may potentially *increase* phenytoin serum levels

Drug Classes	Drugs in each Class (such as)
Alcohol (acute intake)	
Analgesics/Anti-inflammatories	azapropazone phenylbutazone salicylates
Anaesthetics	halothane
Antibacterials	chloramphenicol erythromycin isoniazid sulfadiazine sulfamethizole sulfamethoxazole-trimethoprim sulfaphenazole sulfisoxazole sulfonamides
Anticonvulsants	felbamate oxcarbazepine sodium valproate succinimides topiramate
Antifungals	amphotericin B fluconazole itraconazole ketoconazole miconazole voriconazole
Antineoplastics	capecitabine fluorouracil

Benzodiazepines/Psychotropic agents	chlordiazepoxide diazepam disulfiram methylphenidate trazodone viloxazine
Calcium channel blockers/Cardiovascular agents	amiodarone dicoumarol diltiazem nifedipine ticlopidine
H2-antagonists	cimetidine
HMG-CoA reductase inhibitors	fluvastatin
Hormones	oestrogens
Immunosuppressant drugs	tacrolimus
Oral hypoglycemic agents	tolbutamide
Proton pump inhibitors	omeprazole
Serotonin re-uptake inhibitors	fluoxetine fluvoxamine sertraline

Drugs that may decrease phenytoin serum levels

Table 2 summarizes the drug classes which may potentially decrease phenytoin plasma levels.

Table 2. Drugs that may *decrease* phenytoin plasma levels

Drug classes	Drugs in each class (such as)
Alcohol (chronic intake)	
Antibacterials	ciprofloxacin rifampicin
Anticonvulsants	vigabatrin
Antineoplastic agents	bleomycin carboplatin cisplatin doxorubicin methotrexate
Antiulcer agents	sucralfate
Antiretrovirals	fosamprenavir nelfinavir ritonavir
Bronchodilators	theophylline
Cardiovascular agents	reserpine
Folic acid	folic acid

Hyperglycemic agents	diazoxide
St. John's Wort	St. John's wort

Serum levels of phenytoin can be reduced by concomitant use of the herbal preparations containing St. John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes by St. John's wort. Herbal preparations containing St. John's wort should therefore not be combined with phenytoin. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort. If a patient is already taking St. John's wort check the phenytoin levels and stop St. John's wort. Phenytoin levels may increase on stopping St. John's wort. The dose of phenytoin may need adjusting.

Drugs that may either increase or decrease phenytoin serum levels

Table 3 summarizes the drug classes which may either increase or decrease phenytoin serum levels.

Table 3. Drugs that may either *increase* or *decrease* phenytoin serum levels

Drug Classes	Drugs in each Class (such as)
Antibacterial agents	ciprofloxacin
Anticonvulsants	carbamazepine phenobarbital sodium valproate valproic acid
Antineoplastics	
Psychotropic agents	chlordiazepoxide diazepam phenothiazines

Drugs whose serum levels and/or effects may be altered by phenytoin

Table 4 summarizes the drug classes whose serum levels and/or effects may be altered by phenytoin.

Table 4. Drugs whose serum levels and/or effects may be *altered* by phenytoin

Drug class	Drugs in each class
Antibacterial agents	doxycycline rifampicin tetracycline
Anticonvulsants	carbamazepine lamotrigine phenobarbital sodium valproate valproic acid

Antifungal agents	azoles posaconazole voriconazole
Anthelmintics	albendazole praziquantel
Antineoplastics	teniposide
Antiretrovirals	delavirdine* efavirenz fosamprenavir indinavir lopinavir/ritonavir nelfinavir ritonavir saquinavir
Bronchodilators	theophylline
Calcium channel blockers/Cardiovascular agents	digitoxin digoxin mexiletine nicardipine nimodipine nisoldipine quinidine verapamil
Corticosteroids	
Coumarin anticoagulants	warfarin
Cyclosporin	
Diuretics	furosemide
HMG-CoA reductase inhibitors	atorvastatin fluvastatin simvastatin
Hormones	oestrogens oral contraceptives
Hyperglycemic agents	diazoxide
Immunosuppressant drugs	
Neuromuscular blocking agents	alcuronium cisatracurium pancuronium rocuronium vecuronium
Opioid analgesics	methadone
Oral hypoglycemic agents	chlorpropamide glyburide tolbutamide
Psychotropic agents/Antidepressants	clozapine quetiapine

Vitamin D	vitamin D
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* Coadministration of phenytoin is contraindicated with delavirdine due to the potential to decrease delavirdine plasma concentration due to enzyme induction by phenytoin, and for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors (see section 4.3).

Although not a true pharmacokinetic interaction, tricyclic antidepressants and phenothiazines may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

Drug/Laboratory Test Interactions:

Phenytoin may cause a slight decrease in serum levels of total and free thyroxine, possibly as a result of enhanced peripheral metabolism. These changes do not lead to clinical hypothyroidism and do not affect the levels of circulating TSH. The latter can therefore be used for diagnosing hypothyroidism in the patient on phenytoin. Phenytoin does not interfere with uptake and suppression tests used in the diagnosis of hypothyroidism. It may, however, produce lower than normal values for dexamethasone or metapyrone tests. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that serum folate concentrations be measured at least once every 6 months, and folic acid supplements given if necessary. Phenytoin may affect blood sugar metabolism tests

4.6 Fertility, Pregnancy and lactation

Pregnancy

Specialist advice should be given to women who are of childbearing potential. If pregnancy is planned, the risks of phenytoin must be compared to the risk of discontinuing treatment. Phenytoin crosses the placenta.

In view of the increased risk of neural tube defects and other congenital malformations associated with phenytoin, women taking antiepileptic drugs who intend to become pregnant or become pregnant should be counselled and offered antenatal screening. To counteract the risk of neural tube defects, adequate folate supplements are advised for women before and during the first trimester.

Other reported congenital abnormalities include the fetal hydantoin syndrome symptoms of which include intrauterine growth retardation, microcephaly, underdeveloped nails on fingers and toes, developmental delay and craniofacial abnormalities). Congenital heart defects, urogenital defects, cleft lip and/or palate have also been reported. The features of foetal hydantoin syndrome are all interrelated and are frequently associated with intrauterine growth retardation from other causes. Phenytoin should only be used during pregnancy, especially early pregnancy, if in the judgement of the physician the potential benefits clearly outweigh the risk.

The frequency of seizures may increase during pregnancy in some women. This may be due to altered phenytoin absorption or metabolism. During pregnancy, caution is needed in interpreting plasma concentrations as total plasma concentrations of phenytoin may fall, particularly in the later stages, but free plasma concentrations may remain the same or even rise. Periodic measurement of serum phenytoin levels is valuable in the management of a pregnant epileptic patient as a guide to adjustment of dose. However, postpartum restoration of the original dose will probably be indicated.

Genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. 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 disorders 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 or foetus.

Exposure to phenytoin prior to delivery may lead to an increased risk of haemorrhage in the neonate, usually within 24 hours of the birth. Phenytoin may also produce a deficiency of vitamin K in the mother causing increased maternal bleeding during delivery. Risk of maternal and infant bleeding may be reduced by administration of vitamin K prophylactically to the mother one month prior to and during delivery and to the neonate intravenously immediately after birth.

Neuroblastoma as well as other neuroectodermal and non-ectodermal tumours have been seen in neonates and children exposed to phenytoin prenatally. It is possible that there is an increased risk of neuroblastoma in children with fetal hydantoin syndrome.

Breast-feeding

Phenytoin is excreted in breast milk. Infant breast-feeding is not recommended. The benefits of breast-feeding should be weighed against the possibility of an adverse effect occurring in the infant.

4.7 Effects on ability to drive and use machines

Phenytoin causes dizziness and drowsiness. Patients should not drive or operate machinery if affected. Driving by patients with epilepsy is legally regulated and restricted to those whose seizures are adequately controlled.

4.8 Undesirable effects

The following adverse reactions have been reported with phenytoin (frequency unknown-cannot be estimated from available data):

Immune system reactions:

Anaphylactoid reaction and anaphylaxis.

Central Nervous System:

Adverse reactions in this body system are common and are usually dose-related. Reactions include nystagmus, ataxia, slurred speech, decreased co-ordination and mental confusion. Cerebellar atrophy has been reported, and appears more likely in settings of elevated phenytoin levels and/or long-term phenytoin use (see section 4.4). Dizziness, insomnia, transient nervousness, motor twitchings, taste perversion, headaches paraesthesia, somnolence and vertigo have also been observed.

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. There are occasional reports of irreversible cerebellar dysfunction associated with severe phenytoin overdosage. A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System:

Acute hepatic failure, toxic hepatitis, liver damage, vomiting, nausea, constipation (see section 4.4).

Dermatological System:

Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash is the most common; dermatitis is seen more rarely. Other more serious and rare forms have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus. Severe cutaneous adverse reactions (SCARs): SJS and TEN have been reported very rarely (see section 4.4).

Connective Tissue System:

Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hirsutism, hypertrichosis, Peyronie's Disease and Dupuytren's contracture may occur rarely.

Haematopoietic System:

Haematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, and aplastic anaemia. While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy.

Frequent blood counts should be carried out during treatment with phenytoin.

Immune System:

Hypersensitivity syndrome/Drug reaction with eosinophilia and systemic symptoms (HSS/DRESS) (see section 4.4) has been reported and may in rare cases be fatal (the syndrome may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, polyarteritis nodosa, and immunoglobulin abnormalities may occur.

Several individual case reports have suggested that there may be an increased, although still rare, incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in black patients.

Other:

Polyarthropathy, interstitial nephritis, pneumonitis.

Musculoskeletal System:

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with phenytoin. The mechanism by which phenytoin affects bone metabolism has not been identified. However, phenytoin has been shown to induce the CYP450 enzyme, which can 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, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients.

Endocrine Disorders:

Secondary hyperparathyroidism.

Paediatric population:

The adverse event profile of phenytoin is generally similar between children and adults. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

a) Symptoms

The lethal dose in children is not known. The mean lethal dose in adults is estimated to be 2 g to 5g. The initial symptoms are nystagmus, ataxia, dysarthria. The patients then becomes comatose, the pupils are unresponsive and hypotension occurs followed by respiratory depression and apnoea. Death is due to respiratory and circulatory depression.

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

b) Treatment

Treatment is non-specific since there is no antidote. If ingested within the previous 4 hours the stomach should be emptied. If the gag reflex is absent, the airway should be supported. Oxygen and assisted ventilation may be necessary for central nervous system (CNS), 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 overdosage the possibility of the presence of other CNS depressants, including alcohol, should be borne in mind.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptic, hydantoin derivative, ATC Code: N03AB02

Phenytoin is a hydantoin anticonvulsant structurally related to the barbiturates but having a five membered ring. The mechanism of anticonvulsant action is not completely understood but it is thought to be due to a neuronal membrane stabilising effect at the cell body, axon and synapse. In neurones phenytoin decreases sodium and calcium ion influx, in non-neuronal cell types it increases sodium ion efflux and potassium uptake and at the synapse it decreases post tetanic potentiation and repetitive after-discharge. Phenytoin has an excitatory effect on the cerebellum activating inhibitory cerebellar pathways, this may reduce the seizure activity that is associated with an increased cerebellar discharge.

The antineuralgic action of phenytoin is also not understood but it is thought that phenytoin may act in the CNS to decrease synaptic transmission leading to neuronal discharge. Phenytoin raises the threshold of facial pain and shortens the duration of attacks by diminishing self maintenance of excitation and repetitive firing.

5.2 Pharmacokinetic properties

Phenytoin is slowly and irregularly absorbed from the gastro-intestinal tract. Absorption is poor in neonates. Phenytoin is metabolised in the liver. The rate is increased in young children, pregnant or menstruating women and after trauma. The rate decreases with age. The major inactive metabolite of phenytoin is 5 (p-hydroxyphenyl)-5-phenylhydantoin. Phenytoin is primarily eliminated in the urine as metabolites, but is also excreted in faeces, breast milk and in small quantities in the saliva. Phenytoin excretion is enhanced by alkaline urine. Phenytoin is highly protein bound (90%) this may be lower in neonates (84%) and in hyperbilirubinaemic infants (80%), and is also altered in patients with hypoalbuminaemia and in uraemic patients.

The therapeutic serum concentration of phenytoin is usually within the range 10-20µg/ml, this is usually achieved after 5-10 days of daily oral dosage of 300mg phenytoin. Higher concentrations (23 µg/ml or more) may be needed to control simple or complex partial seizures with or without tonic-clonic seizures than are necessary for control of tonic-clonic seizures alone. The time to peak plasma concentration after a single oral phenytoin dose is 1½ to 3 hours. The half life of phenytoin is about 22 hours but with wide inter-individual variation (range 7 to 42 hours).

5.3 Preclinical safety data

There is some controversy as to whether chronic phenytoin overdosage in experimental animals and humans causes cerebellar Purkinje cell degeneration. Overdosage in humans has been reported to cause computerised topographic appearances of cerebellar atrophy. There is no evidence of significant mutagenicity from phenytoin given to rats and mice between the 10th and the 14th day of pregnancy causes an increased incidence of fetal malformation (fetal resorption, cleft lip and cleft palate, hydronephrosis, hydrocephalus and abdominal haemorrhages). In humans phenytoin very occasionally causes a reversible pseudo-lymphoma syndrome in which the enlarged lymph nodes have a histological appearance resembling that of Hodgkin's disease. There have been suggestions that the drug may occasionally be responsible for the development of malignant lymphomas and leukaemia. However, one study found no association between phenytoin intake and neoplasia in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Icing sugar

Calcium hydrogen phosphate (Caliment)

Sucrose

Purified water

Magnesium stearate

Byco - C (Gelatin)

Titanium dioxide

Sucrose

Talc

Opaglos 6000P (IMS74 OP, shellac USNF/DAB, beeswax-white. carnauba wax-yellow)

6.2 Incompatibilities

None.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container in order to protect from moisture.

Place 2 desiccants on top of tablets

6.5 Nature and contents of container

Polypropylene or polyethylene containers containing 28, 100, 250, 500, 1000 or 5000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

SNIGD (UK Limited)
Office Gold,
Building 3 Chiswick Park,
566 Chiswick High Road,
London, England,
W4 5YA

8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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