mg and adjusted according to plasma-phenytoin concentrations.

INTERACTIONS

There are complex interactions between antiepileptic's, 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 freer (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). 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.

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.

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. Over dosage 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.

WARNINGS

Cardiovascular Risk You will receive Phenytoin Sodium Injection USP through injection into the vein or muscle. If your doctor injects this medication into the vein too fast, your blood pressure may drop quickly, and you may experience irregular heartbeat. This can be serious. Therefore, your doctor should observe you closely while you are receiving PHENYTOIN SODIUM INJECTION USP and after.

Alcohol Use

Acute alcohol intoxication may increase Phenytoin serum levels while chronic alcoholism may decrease it. Alcohol should be avoided during treatment with phenytoin.

Overdose:

The lethal dose in paediatric patients is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Most patients experience blurred vision and nystagmus at serum phenytoin concentrations of 20 µg/ml, ataxia and unsteady gait at 30 µg/ml and lethargy at more than 40 µg/ml. As high a concentration as 50 µg/ml has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 µg/ml with complete recovery.

Nursing Mothers:

Infant breast feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

Storage: - Protected from light at temperature not exceeding 30°C. Protect from freezing.

Improper Storage may deteriorate the product.

Keep the medicine out of reach of children.

Presentation: - Each pack contain 2 ml Ampoule of Phenytoin Sodium Injection USP

Manufactured by:

AMERICAN REMEDIES ©
Care & Cure with Research
American Remedies Healthcare Pvt. Ltd.
(An ISO 9001-2015 Certified Company)
ICO: American Remedies LLC, DE, USA
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Scan for Batch Certificate

For the use only of a Registered Medical Practitioner or a hospital or a laboratory

℞ Phenytoin Sodium Injection

AMERICAN
Eptocan

FOR I.M./I.V. USE ONLY.

Composition :

Each ml contains :

Phenytoin Sodium	I.P.	50 mg.
Water for Injections	I.P.	q.s.

DESCRIPTION

Phenytoin sodium Injection USP is solution of phenytoin sodium in a vehicle containing propylene glycol and in water for injection. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is sodium 5, 5-diphenyl-2, 4- imidazolidinedione represented by the following structural formula:



Phenytoin sodium

PHARMACOLOGY

Pharmacokinetics

Phenytoin Sodium 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 is affected by other antiepileptic's.

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. 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 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