PHENYTOIN

SRIPHEN-100 Rx

100 mg Capsule

ANTICONVULSANT / ANTI-EPILEPTIC

Formulation:
Each capsule contains:
Phenytoin (as sodium)..... 100 mg

PRODUCT DESCRIPTION:
Orange and Ivory coloured hard getalin capsule size "3" with printed "SITI" and "Pharma" on capsule containing white powder.

PHARMACOLOGICAL ACTION:
Phenytoin is an antiepileptic drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post tetanic potentiation at synapses. Loss of post tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

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

INDICATIONS:
It is used to control partial and generalized tonic-clonic seizures. It is also used as part of the emergency treatment of status epilepticus and has been used for the prophylactic control of seizures associated with neurosurgery or severe traumatic injury to the head.

DOSAGE AND ADMINISTRATION:
Serum concentrations should be monitored in changing from extended phenytoin sodium capsules, USP, to prompt phenytoin sodium capsules, USP, and from the sodium salt to the free acid form.
Extended phenytoin sodium capsules are formulated with the sodium salt of phenytoin. Because there is approximately an 8% increase in drug content with the free acid 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 and vice versa.

General
Dosage should be individualized to provide maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments - the clinically effective serum level is usually 10 to 20 mcg/mL. With recommended dosage, a period of 7 to 10 days may be required to achieve steady-state blood levels with phenytoin and changes in dosage (increase or decrease) should not be carried out at intervals shorter than 7 to 10 days.

Adult Dosage

Divided Daily Dosage
Patients who have received no previous treatment may be started on one 100 mg extended phenytoin sodium capsule three times daily and the dosage then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be one capsule three to four times a day. An increase up to two capsules three times a day may be made, if necessary.

Once-a-Day Dosage
In adults, if seizure control is established with divided doses of three 100 mg extended phenytoin sodium capsules daily, once-a-day dosage with 300 mg of extended phenytoin sodium capsules may be considered. Studies comparing divided doses of 300 mg with a single daily dose of this quantity indicated absorption, peak plasma levels, biologic half-life, difference between peak and minimum values, and urinary recovery were equivalent. Once-a-day dosage offers a convenience to the individual patient or to nursing personnel for institutionalized patients and is intended to be used only for patients requiring this amount of drug daily. A major problem in motivating noncompliant patients may also be lessened when the patient can take this drug once-a-day. However, patients should be cautioned not to miss a dose, inadvertently.
Only extended phenytoin sodium capsules are recommended for once-a-day dosing. Inherent differences in dissolution characteristics and resultant absorption rates of phenytoin due to different manufacturing procedures and/or dosage forms preclude such recommendation for other phenytoin products. When a change in the dosage form or brand is prescribed, careful monitoring of phenytoin serum levels should be carried out.

Loading Dose
Some authorities have advocated use of an oral loading dose of phenytoin in adults who require rapid steady-state serum levels and where intravenous administration is not desirable. This dosing regimen should be reserved for patients in a clinic or hospital setting where phenytoin serum levels can be closely monitored. Patients with a history of renal or liver disease should not receive the oral loading regimen.
Initially, one gram of extended phenytoin sodium capsules is divided into three doses (400 mg, 300 mg, and 300 mg) and administered at 2 hour intervals. Normal maintenance dosage is then instituted 24 hours after the loading dose, with frequent serum level determinations.

Dosing inSpecial Populations

Patients with Renal or Hepatic Disease
Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution. Unbound phenytoin concentrations may be more useful in these patient populations.

Elderly Patients
Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.

Pediatric
Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years old and adolescents may require the minimum adult dose (300 mg/day)

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. Hyperglycemia has been associated with toxic concentrations.
Overdosage may result in hypotension, coma, and respiratory depression. Hypotension and CNS depression may also follow intravenous dosage, if too rapid, as may cardiac arrhythmias and impaired cardiac conduction. Solutions for injection are very alkaline and may result in irritation at the injection site or phlebitis. A syndrome of distal limb edema, 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 anemia 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-John- son syndrome, or toxic epidermal necrolysis. Eosinophilia, lymphadenopathy, hepatitis, polyarteritis nodosa, and blood disorders such as aplastic anemia, leucopenia, thrombocytopenia, and agranulocytosis, have occurred rarely; some of these conditions may also represent hypersensitivity reactions.
Hypoprothrombinemia 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.

OVERDOSAGE
The lethal dose in pediatric 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. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL; dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/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 mcg/mL with complete recovery.

TREATMENT
Treatment is nonspecific since there is no known antidote.
The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in pediatric patients.
In acute overdosage, the possibility of other CNS depressants, including alcohol, should be borne in mind.

REPORTING OF SUSPECTED ADVERSE REACTIONS:
To allow continued monitoring of the benefit/risk balance of the medicinal product, reporting of suspected adverse reaction is necessary. Healthcare professionals are encouraged to report any suspected adverse reactions directly to the importer/distributor and/or to FDA: www.fda.gov.ph. Patients are advised to seek immediate medical attention at the first sign/s of adverse reactions.

DRUG INTERACTIONS:
There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.
Since phenytoin is extensively bound to plasma proteins it can be displaced by drugs competing for protein-binding sites, thus liberating more free (pharmacologically active) phenytoin into the plasma. However, elevation of free phenytoin is reported to be of little clinical significance provided hepatic function is not impaired (see Precautions, above). A potentially more serious type of interaction may occur because phenytoin metabolism is saturable: toxic concentrations of phenytoin can develop in patients given drugs that inhibit phenytoin metabolism even to quite a minor degree. Phenytoin itself is also a potent enzyme inducer, and induces the metabolism of a number of drugs, including some antibacterials, anticoagulants, corticosteroids, quinidine, and sex hormones (notably, oral contraceptives).
The hypotensive properties of dopamine and the cardiac depressant properties of drugs such as lidocaine may be dangerously enhanced by intravenous phenytoin.

CONTRAINDICATIONS:
Phenytoin sodium capsules are contraindicated in those patients with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins.
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.

WARNINGS AND PRECAUTIONS:
Phenytoin is metabolized 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 uremia, 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, pro- vided 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 al- though, 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 recognize signs of blood or skin toxicity and they should be ad- vised 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. 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 test

Storage Condition: Store at temperature not exceeding 30°C.
Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Availability: Wide mouth Amber Bottle x 100's.

FDA Registration No.: DRP-5579
D.L.No.: G/849
Date of renewal of Authorization: 28/03/2018
Date of revision of package insert: 02/02/2022

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