PRESCRIBING INFORMATION

[Pr]PHENYTOIN SODIUM INJECTION, USP

50 mg/mL

STERILE

Anticonvulsant agent

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[Pr]PHENYTOIN SODIUM INJECTION, USP

50 mg/mL

THERAPEUTIC CLASSIFICATION

Anticonvulsant agent

INDICATIONS AND CLINICAL USE

- Phenytoin Sodium Injection, USP is an anticonvulsant used to control tonic-clonic (grand mal) and psychomotor or partial (focal) seizures.

- Phenytoin Sodium Injection, USP may be used for the prevention and treatment of seizures occurring during neurosurgery.

CONTRAINDICATIONS

Phenytoin is contraindicated in patients who are hypersensitive to the drug or to other hydantoins.

IV use of phenytoin is contraindicated in patients with sinus bradycardia, sino-atrial block, second or third degree AV block, and Adams-Stokes syndrome.

WARNINGS

a) Intravenous injection should be administered **SLOWLY** in order to avoid extravasation; the injection rate should not exceed 50 mg per minute.

b) Edema, discolouration, and pain of the distal limb (described as “purple glove syndrome") have been reported following peripheral intravenous phenytoin sodium injection. This may or may not be associated with extravasation. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting and amputation. See DOSAGE AND ADMINISTRATION for suggested IV administration of PHENYTOIN SODIUM INJECTION, USP.

c) Abrupt withdrawal of phenytoin may precipitate status epilepticus. If the dosage has to be reduced or if Phenytoin has to be discontinued or substituted by another antiepileptic drug, the change should be done gradually (except in case of hypersensitivity or allergy).

d) Phenytoin is NOT recommended for seizures with hypoglycaemic or other imbalances of metabolic origin.

e) Phenytoin should be used with caution in patients with hypotension or severe myocardial insufficiency.

f) The intramuscular route is not recommended for the treatment of status epilepticus (See Dosage and Administration).

g) Acute alcohol intoxication may increase Phenytoin serum levels while chronic alcoholism may decrease it.

Psychiatric

Suicidal Ideation and Behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour 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. An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behavior reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

PRECAUTIONS

1. Pregnancy and the neonate:

Risks due to antiepileptic drugs: Considering all antiepileptic drugs, it has been shown that among newborns delivered by women under antiepileptic treatment, the proportion of child defects is two to three times (about 3%) more elevated than among the general population. However the relationship between antiepileptic treatment and the occurrence of these abnormalities is not clearly established.

The child defects mostly reported are cleft lip and palate and heart malformations. With the use of phenytoin or other hydantoins, microcephaly, prenatal growth deficiency and mental deficiency, have also been encountered. These features are often associated with retarded intrauterine growth due to other causes. Animal experimentations did not report any drug related teratogen effect.

However, the great majority of mothers on antiepileptic medications deliver normal babies and it is up to the prescribing physician to appreciate these considerations in treating or counseling epileptic women of childbearing potential. But when the drug is administered to prevent major seizures the treatment should not be discontinued because of the strong possibility of precipitating status epilepticus. When the severity and the frequency of the seizures are less important, discontinuation of the medication may be considered prior to and during pregnancy although one has to keep in mind that even minor seizures may be hazardous to the developing embryo or fetus.

In pregnant women, altered phenytoin absorption and metabolism have been detected resulting in increased seizure frequency. Dosage adjustments should be considered in pregnant, phenytoin-treated women.

Coagulation defects have been reported within the first 24 hours in the neonates born from epileptic mothers receiving phenobarbital and /or phenytoin. Resulting bleeding stopped soon after administration of vitamin K_1. Treatment of the mother, during pregnancy, with vitamin K_1 is the best form of prophylaxis.

2. Lactation: Not recommended because of the secretion of phenytoin into the mother's milk.

3. In patients on long term phenytoin therapy, vitamin D and folic acid are given to prevent side effects respectively affecting bones and hematopoiesis.

4. As the liver is the main site of biotransformation of phenytoin; the drug should be given with precaution to patients with hepatic impairment.

5. In case of appearance of skin rash, phenytoin should be discontinued. If the rash is of milder type (measles like) therapy may be resumed after the drug has completely disappeared. If the

rash is of a more severe type, treatment must be discontinued and alternate therapy considered. The patient must be warned to call his physician in case of skin rash.

6. A poor metabolism of phenytoin in patients might be due to genetic abnormalities such as limited enzyme availability.

7. Lymphadenopathy, including pseudolymphoma, lymphoma and Hodgkin's disease have been reported in relation to phenytoin administration.

8. Poly-therapy is necessary in patients suffering from both tonic-clonic and absence seizures.

9. Plasma level determinations are recommended to adjust dosage (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

10. Blood count (including platelets) and hemogram should be checked before and during treatment.

11. Alcohol should be avoided during treatment.

12. Patients should be aware of the importance of a good dental hygiene in order to prevent gingival hyperplasia.

DRUG INTERACTIONS

Drugs increasing phenytoin serum levels (risk of overdosage and toxicity):
Chloramphenicol, dicoumarol, disulfiram, tolbutamide, phenothiazines, phenylbutazone, acute alcohol intake, salicylates, chlordiazepoxide, diazepam, estrogens, halothane, methylphenidate, isoniazid, sulfonamides, cimetidine, trazodone, ethosuximide.

Drugs decreasing phenytoin serum levels (seizures not controlled):
Carbamazepine, chronic alcohol abuse, reserpine. Antiacids preparations containing calcium.

The effects on phenytoin serum levels of phenobarbital, valproic acid and sodium valproate are unpredictable.

Conversely, effects of phenytoin on these drugs are not well established.

Drugs whose efficacy is impaired by phenytoin:
Coumarin anticoagulants, corticosteroids, oral contraceptives, quinidine, vitamin D, digitoxin, doxycycline, rifampin, estrogens, furosemide.

Incompatibility
Phenytoin sodium only remains in solution when the pH is considerably alkaline (about 10 to 12). The mixing of phenytoin sodium injection with other drugs or its addition to infusion solutions is not recommended.

ADVERSE REACTIONS

The most important signs of toxicity associated with IV use of phenytoin sodium are cardiovascular collapse and/or CNS depression (coma and respiratory depression have been observed); hypotension occurs if the drug is administered too rapidly by the IV route.

The margin between therapeutic and toxic levels of phenytoin is very narrow. Moreover, there is considerable variation from patient to patient in relation to blood and tissue concentrations.

Central Nervous System:
Progressive neurological deterioration in patients receiving long term phenytoin therapy: ataxia, impaired speech, diplopia, nystagmus, mental confusion, headache, dizziness, transient nervousness and insomnia, bizarre behavior, EEG changes. Some of these effects are dose-related and may disappear with reduced dosage. Phenytoin may cause asterixis, orofacial dyskinesia, limb chorea and dystonia in patients given excessive doses (these dyskinesias may be related to the dopamine antagonist properties of phenytoin). Mild peripheral neuropathy (essentially sensorial) may appear in patients receiving long term therapy.

Conjunctive and Bone tissues:
Rickets; osteomalacia; polyarthropathy. Thickening of the skull, facial changes or gingival hyperplasia

Skin:
Dermatological manifestations are sometimes accompanied by fever; skin rashes are common, particularly in children, and may resemble measles; Lupus erythematosus; erythema multiform; occurrence of bullous, exfoliative or purpuric rash. Lymphadenopahy may occasionally occur.

Gastrointestinal:
Nausea, vomiting, constipation.

Hematopoiesis:
Leucopenia, thrombocytopenia, pancytopenia, agranulocytosis, granulocytopenia. Megaloblastic anaemia, following prolonged use, usually responds to treatment with folic acid.

Other effects:
Hirsutism (more noticeable in young females), hepatitis, hyperglycemia (resulting from phenytoin's inhibitory effect on insulin release), liver damage (correlated to the hepatic metabolism of the drug), lymphoma, myasthenia gravis. Anticonvulsants diminish sexual potency and fertility in young male epileptics. Phlebitis, under IV administration. In some

patients high serum triglycerides and cholesterol levels have been reported (due to the effect of phenytoin on lipid metabolism).

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

Symptoms: Early symptoms of overdosage are slurred speech, digestive disturbances (nausea, vomiting), tremor, hyperflexia and lethargy. Other signs are nystagmus, ataxia, and dysarthria. Most patients experience blurred vision and nystagmus at serum phenytoin concentrations of 20 mcg per mL, ataxia and unsteady gait at 30 mcg per mL and lethargy at more than 40 mcg per mL. The lethal dose in children is unknown. In adults it is estimated to be in the order of 2 to 5 g.

Treatment: There is no known antidote; consequently the treatment is not specific. Respiratory and circulatory functions should be carefully monitored and appropriate supportive measures should be employed. The effectiveness of hemodialysis and peritoneal dialysis has been seriously questioned. As phenytoin's volume of distribution is relatively small, blood transfusion, particularly at high drug concentrations, should contribute significantly to total drug removal. Total exchange transfusion has been used in the treatment of severe intoxication in children.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

Dosage

Status Epilepticus: Usual IV adult dosage. Loading dose of 15 to 18 mg/kg. Alternatively, 150 to 250 mg at a rate not exceeding 50 mg/minute (in geriatric patients with heart disease, it has been recommended that the drug be given at a rate of 50 mg over 2-3 minutes), followed by subsequent doses of 100 to 150 mg, as required, 30 minutes later. Higher doses may be required to control seizures. The IM route should not be used.

Children may be given 250 mg/m^2 of body surface.

If the state of the patient is such that immobilization of an extremity is impossible due to convulsions, or veins are inaccessible, medication can be given IM during the attack.

If administration of phenytoin does not terminate the seizure, the use of other anticonvulsants, IV barbiturates, general anesthesia or other measures should be considered.

Oral therapy should replace parenteral administration as soon as possible.

Neurosurgery: Prophylactic control of seizures - 100 to 200 mg IM at approximately 4 hour intervals during surgery and the immediate postoperative period.

Tachycardia: For the treatment of ventricular tachycardia or paroxysmal atrial tachycardia, or arrhythmias caused by digitalis intoxication, 100 mg of phenytoin sodium can be administered by direct IV injection at 5 minute intervals until the arrhythmia is abolished or undesirable effects appear or until a total of 1 g is given.

If phenytoin is administered IM to patients unable to take the drug orally, the IM dosage should be increased by 50% over the previously established oral dosage. To avoid drug accumulation resulting from eventual absorption from IM injection site, it is recommended that for the first week, back on oral therapy, the oral dosage be reduced to one-half the original oral dosage. Monitoring of serum concentrations is also recommended. IM therapy should generally be limited to one week.

Administration

The sodium salt of phenytoin may be administered by direct IV injection for the initial treatment of status epilepticus and for prophylaxis of seizures in neurosurgery.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Phenytoin sodium injection, USP is a sterile solution of the drug containing 40% propylene glycol, 10% (v/v) ethyl alcohol in water for injection. Sodium hydroxide is added during manufacture of the injection to adjust the pH to 12.0.

Phenytoin sodium injection, USP is a clear, colourless solution contained in a clear, type I glass vial with a chlorobutyl rubber stopper and an aluminum sealwith a plastic flip-off cap. Each mL of Phenytoin Sodium Injection, USP, contains 50 mg of phenytoin sodium.

Phenytoin sodium injection, USP is available in 100 mg/2 mL and 250 mg/5 mL presentations contained within single-use vials. Vials come in boxes of 10.

STORAGE AND STABILITY

Store between 15°C and 30°C; freezing should be avoided. A precipitate may form if the injection is refrigerated or frozen; however, this will dissolve after warming to room temperature.

Slightly yellowish discolouration of the injection will not affect potency or efficacy, but the injection should not be used if the solution is not clear or if a precipitate is present.

PHARMACEUTICAL INFORMATION

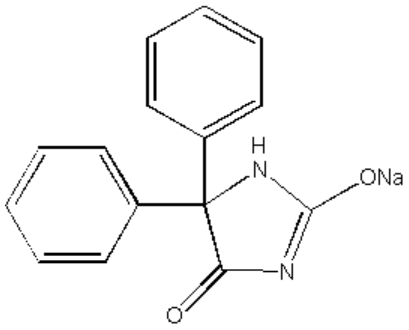
Proper Name: Phenytoin Sodium

Chemical Name: 5,5 - Diphenyl - 2,4 Imidazolidinedione Monosodium Salt,
5,5 - Diphenylhydantoin sodium salt.

Molecular Formula: $C_{15}H_{11}N_2Na0_2$

Molecular Weight: 274.25 g/mol

Structure:



phenytoin sodium

Description: Phenytoin sodium occurs as a white, odourless, hygroscopic powder and is freely soluble in water, soluble in alcohol, and freely soluble in warm propylene glycol. It is insoluble in ether and chloroform.

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