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Phenytoin: Clinical Use, Pharmacokinetics, Pharmacodynamics, Toxicology, Side Effects, Contraindication, and Drug Interactions Review

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ABSTRACT

Phenytoin is an antiepileptic drug derived from an organic compound called hydantoin. Phenytoin is an antiepileptic drug primarily used to treat seizures in people with epilepsy. Phenytoin works by targeting and blocking voltage-gated sodium channels in the nervous system, which helps reduce abnormal electrical activity in the brain that leads to seizures. Phenytoin can also be used to treat trigeminal neuralgia and ventricular tachycardia. Absorption of phenytoin depends on the route of administration. The distribution of phenytoin is affected by plasma protein binding. Phenytoin is metabolized primarily by liver enzymes, especially the cytochrome P450 enzyme system. Phenytoin excretion is influenced by the pH in the urine. Side effects of phenytoin use that can occur are sedation, fever, sedation, confusion, hallucinations, peripheral neuropathy, Stevens-Johnson syndrome, cardiovascular collapse, hypotension, purple glove syndrome, nystagmus, ataxia, nausea, coma, seizures, vomiting, hyperactivity, lethargy, fetal hydantoin syndrome (FHS), and megaloblastic anemia. Phenytoin is contraindicated in patients with hypersensitivity to phenytoin or other hydantoin, pregnant women, and lactating women. Oral phenytoin overdose causes neurotoxicity while parenteral phenytoin overdose causes cardiovascular toxicity. There is no specific antidote for phenytoin toxicity and the treatment is usually supportive. There are various drugs that can interact with phenytoin to decrease or increase phenytoin levels.

Keywords: Phenytoin, Clinical Use, Pharmacokinetics, Pharmacodynamics, Toxicology

1. BACKGROUND

Phenytoin is an antiepileptic drug derived from an organic compound called hydantoin. The compound was first developed in 1908 by a chemist named Heinrich Biltz as a food preservative. However, in 1938, further research showed that this compound had significant antiepileptic effects and it was then used as an antiepileptic drug. Today, phenytoin is produced synthetically and is available as tablets, capsules, syrup, or injection. Phenytoin is a drug to treat seizures or anticonvulsants, which commonly occur in people with epilepsy. The chemical name of this drug is

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5,5-diphenyl-2,4-imidazolidinedione. It may also be used to treat trigeminal neuralgia, a type of nerve pain that affects the face. Phenytoin is categorized as a prescription drug, so it is not sold over the counter. It comes in capsule and injectable form. It can be used by both adults and children. Use in pregnant and breastfeeding women should consult a doctor first [1].

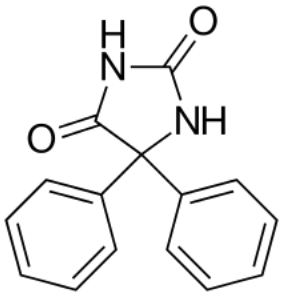

Figure 1. The Structure of Phenytoin [1].

2. CLINICAL USE

Phenytoin is used as an antiarrhythmic drug due to its effects on ion channels and receptors on myocardial cell membranes. Primarily, phenytoin shortens the action and inhibits the rapid inward sodium current. Phenytoin is considered as a potent arrhythmic agent of class IB, and may be useful in the treatment of ventricular tachycardia [2].

Phenytoin is also one of the anticonvulsant drugs commonly used to treat patients with epilepsy with hypersensitivity to antiepileptic drugs [3]. Some studies assess that phenytoin has an effect on the prevention or suppression of epileptic seizures by stabilizing the trigeminal neuralgia tract. Studies evaluating the effect of phenytoin (PHT) in preventing as well as suppressing early seizures have shown that PHT reduces the risk of seizures in the first week after surgery [4]. It also has anxiolytic properties and can be used as a mood stabilizer. Phenytoin is a drug that is sometimes used in patients with intractable trigeminal neuralgia [5].

The usual dose of single-use phenytoin as an anticonvulsant drug in oral administration for children and infants is 1,5-4 mg/kg body weight. The single-use dose of phenytoin as an anticonvulsant and antiarrhythmic drug in oral administration for adults is 100 mg. The usual dose of orally administered phenytoin for adults as an anticonvulsant drug is 300 mg and as an antiarrhythmic drug is 400 mg. The maximum single-use dose of phenytoin in oral administration for adults as an anticonvulsant drug is 400 mg and as an antiarrhythmic drug is 200mg. The maximum dose of phenytoin in oral administration for adults as an anticonvulsant drug is 800 mg and as an antiarrhythmic drug is 600 mg [6].

3. PHARMACOKINETICS

1. Absorption

Absorption of phenytoin depends on the route of administration either peroral or parenteral. Absorption of phenytoin in the stomach is very low because phenytoin is insoluble in the acidic stomach. Phenytoin is well absorbed after oral administration. The absorption of orally administered

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phenytoin is slow and sometimes incomplete [7]. Phenytoin will dissolve in solutions containing pH 6-8. When administered orally, 10% of the dose is excreted intact with the feces in the duodenum (part of the small intestine) because the duodenum has a pH of 7-7.5. Maximum absorption occurs in the duodenum while in the jejunum (small intestine) and ileum (intestinal absorption) is slower, and no absorption occurs in the rectum. The maximum concentration after oral administration is reached within 4-8 hours after administration. If the initial dose is given together with a bolus, a dose of 600-800 mg is required to be given in divided doses between 8-12 hours, with effective plasma concentrations reached within 24 hours. Intramuscular administration of phenytoin causes phenytoin to be deposited at the injection site for approximately 5 days, and absorption is slower than peroral administration. This is because its low solubility in water causes phenytoin crystals to form in the muscle. Phenytoin is distributed in different tissues at various levels in the body, after intravenous injection, concentrations in the brain, skeletal muscle and adipose tissue are lower than levels in the liver, kidneys and salivary glands [8].

2. Distribution

The distribution of phenytoin is affected by plasma protein binding. Proteins will bind phenytoin, especially plasma albumin, with approximately 90%. The distribution of the drug in different parts of the body is not correlated with the concentration of phenytoin in the brain, which is 1-3 times higher than the concentration in plasma [8].

3. Metabolism

Phenytoin is metabolized mainly by liver enzymes, especially the cytochrome P450 (CYP450) enzyme system into inactive metabolites. Phenytoin is an inducer of CYP3A4, hence responsible for many drug interactions [8].

4. Excretion

Phenytoin excretion is influenced by the pH in the urine. Changes in urine pH due to drug interactions cause changes in renal clearance by altering the volume of passive reabsorption in the renal tubules. The final metabolites of phenytoin are water soluble. Excretion through feces is only a small portion. Maximum excretion of phenytoin only occurs after 72-120 hours [8].

4. PHARMACODYNAMICS

The mechanism of action of antiepileptic drugs can be classified into four main groups. Some antiepileptics work by increasing inhibition of Gamma-Aminobutyric Acid (GABA) by acting on the GABA-A receptor, GAT-1 GABA transporter, or GABA transaminase. Others work directly at regulating synaptic release such as SV2A and α2δ. Antiepileptics also works by inhibiting synaptic excitation by ionotropic glutamate receptors, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [9].

Phenytoin is a voltage-gated sodium channel-targeting drug that stabilizes the inactive state of sodium channels and prolongs the neuronal refractory period [9,10,11]. Voltage-gated sodium channels are multimeric protein complexes composed of α and β subunits. The α subunit is larger and consists of multiple subunits, while the β subunit is smaller and consists of only one [9,11].

The drug acts on sodium channels in nervous tissue to treat epilepsy and in cardiac muscle tissue to treat arrhythmias. In the central nervous system, the drug targets neurons with high-

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frequency (epileptic) activity, with most of its effects affecting the motor cortex. This prevents enlargement of the seizure focus and reduces activity in brainstem regions responsible for the tonic phase of tonic-clonic seizures. Phenytoin also shortens the duration of cardiac action potentials and prolongs the period of unresponsiveness between cardiac muscle tissues [10].

5. TOXICOLOGY

Phenytoin is available for oral and parenteral administration. In oral administration, phenytoin is fully absorbed after ingestion and absorption is rapid. Phenytoin is poorly soluble in water, therefore parenteral administration of phenytoin should be mixed with propylene glycol and alcohol. It is only recommended for intravenous (IV) administration [10]. The symptoms of phenytoin toxicity mainly occur in the nervous system and cardiovascular system. Oral phenytoin overdose causes neurotoxicity and parenteral phenytoin overdose causes cardiovascular toxicity [12].

The 7-day LD_{50} of phenytoin in mice is 40 mg/kg (intraparenteral/ip) and 100 mg/kg (peroral/po). At a dose of ≥100 mg/kg, the side effects recorded were ataxia and convulsions. The drowsiness seen at all doses may have been largely due to the vehicle. The 72-hour LD50 of phenytoin in mice has been reported to be 200 mg/kg (ip). The lethal dose of phenytoin in adults is estimated to be 2-5 g and in children it is unknown [16].

1. Neurotoxicity

The neurotoxic effects depend on the plasma concentration of phenytoin. Neurotoxic effects can range from ataxia, tremors, nystagmus, hyperactivity, lethargy, and eventually coma and death. At high concentrations, phenytoin may cause seizures. However, this is rare, therefore it is necessary to search for other causes in patients with seizures with phenytoin overdose. The general correlation of side effects with total plasma phenytoin concentrations (values obtained through most laboratories) at a concentration of 10 mg/L is rare, at a concentration of 10-20 mg/L is mild horizontal nystagmus that occasionally occurs in lateral gaze, at a concentration of 20-30 mg/L is nystagmus, at a concentration of 30-40 mg/L is ataxia and tremors, at a concentration of 40-50 m /L is lethargy and hyperactivity, at a concentration above 50 mg/L is coma and seizures [10].

2. Cardiac Toxicity

Although it is hardly used as an antiarrhythmic medication anymore, phenytoin is a class IB antiarrhythmic medicine. In addition to SA and AV nodal obstruction, the toxic effects of phenytoin on the cardiac gated sodium channels might result in dysrhythmias. When administered intravenously (IV), these adverse effects are more common than when administered orally. In intravenous (IV) dosing, propylene glycol, the solvent for phenytoin, is thought to be hazardous. Rapid IV delivery of phenytoin can result in bradycardia, hypotension, and asystole since propylene glycol is a cardiac depressant. As a result, administering IV phenytoin at a rate greater than 50 mg per minute is not advised [10,8].

3. Others Toxicities

The unusual adverse effect known as "Purple Glove Syndrome" can happen when phenytoin is administered intravenously (IV). It is characterized by increased limb edema, discolouration, and ischemia, which can result in limb amputation and severe skin necrosis. The blood-borne crystallization of phenytoin is the cause of this condition. Phenytoin hypersensitivity, which often

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appears 1 week to 1 month after therapy starts, is another hazardous side effect. Fever, rash, and involvement of several internal organs (hepatitis, myocarditis, pneumonitis) are its defining features. Chronic phenytoin use may result in megaloblastic anemia from peripheral neuropathy, lupus-like disease, or folate insufficiency. This is an acute overdose occurrence that is not frequently documented [10,8].

4. Toxicokinetics

Phenytoin toxicity may result from increasing the dose of phenytoin or changing the frequency of administration. Phenytoin can be metabolized by the liver, namely with the liver enzyme CYP450, so that if there is a slight increase in dose, it will cause the levels to increase drastically and cause various side effects [10].

5. Management

There is no specific antidote for phenytoin toxicity and the usual treatment is supportive care [10]. The management of phenytoin toxicity is consistent with the management of overdose in general. These range from improving the airway of patients with compromised airways to checking vital signs. Hypotension can be treated with isotonic solution. If the patient does not respond to fluids, vasopressors such as norepinephrine and dopamine can be administered. Other overdose symptoms, such as nausea and vomiting, can be treated with antiemetics. If seizures occur, they can be controlled according to the usual seizure protocol using benzodiazepines as the initial drug, followed by phenobarbital or levetiracetam for persistent or recurrent seizures. Phenytoin overdose can be treated with activated charcoal and hemodialysis. Activated charcoal can bind to phenytoin and prevent its absorption, while hemodialysis can prevent plasma proteins from binding to phenytoin. However, both treatments are less recommended due to their clinical risks [10,8].

6. SIDE EFFECTS AND CONTRAINDICATIONS

Side effects of phenytoin use that can occur are sedation, hallucinations, fever, sedation, confusion, peripheral neuropathy, Stevens-Johnson syndrome, cardiovascular collapse, hypotension, purple glove syndrome, nystagmus, ataxia, nausea, coma, seizures, vomiting, hyperactivity, lethargy, fetal hydantoin syndrome (FHS), and megaloblastic anemia [10,8,13].

Contraindications to the use of phenytoin are in someone with hypersensitivity to phenytoin or other hydantoin. The use of phenytoin in pregnancy is category D, therefore pregnant women are an absolute contraindication to the use of phenytoin as it may cause fetal hydantoin syndrome (FHS). Lactating women should also be carefully considered as phenytoin can be excreted through the liver [10,8].

7. DRUG INTERACTIONS

There are various drugs that can interact with phenytoin to decrease or increase phenytoin levels. Drugs that can reduce phenytoin levels due to interactions that affect gastrointestinal absorption are antacids, calcium gluconate, and oxacillin. Drugs that can reduce plasma concentrations of phenytoin by displacing phenytoin from albumin plasma binding sites are valproic acid, phenylbutazone, aspirin, sulfafurazole, sulfamethoxypyridine, and tolbutamide. Drugs that can increase serum phenytoin levels by inhibiting phenytoin metabolism are sulthiamine, phenethurid,

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isoniazid, chloramphenicol, sulfonamides, phenobarbital, and warfarin. Drugs that can reduce phenytoin levels by inducing phenytoin metabolism are folic acid, carbamazepine, phenobarbital, benzodiazepines, dichloralphenazone, quinidine, and misonidazole [14,15].

8. CONCLUSION

Phenytoin is an antiepileptic drug derived from an organic compound called hydantoin. Phenytoin is an antiepileptic drug that is primarily used to treat seizures in people with epilepsy. Phenytoin works by targeting and blocking voltage-gated sodium channels in the nervous system, which helps reduce the abnormal electrical activity in the brain that causes seizures. Phenytoin has various side effects so its use should be considered. The use of phenytoin should also be considered in someone who is hypersensitive to phenytoin or other hydantoins, pregnant women, and lactating women. There is no specific antidote for phenytoin toxicity and the usual treatment is supportive care. There are various drugs that can interact with phenytoin to lower or increase phenytoin levels.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

AUTHOR DETAILS

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