PHENOBARBITAL TABLETS, USP

Rx only

WARNING: MAY BE HABIT-FORMING

DESCRIPTION

The barbiturates are nonselective central nervous system (CNS) depressants that primarily act as competitive inhibitors of the release of excitatory neurotransmitters, such as glutamate and aspartate, at the synapse. The barbiturates and their sodium salts are subject to control under the Federal Controlled Substance Act, 21 U.S.C. 812(b)(2).

Phenobarbital is a barbituric acid derivative and occurs as white, odorless, crystalline or slightly yellowish powder that is very slightly soluble in water; soluble in alcohol; and, in solutions of fixed alkali hydroxides and carbonates, sparingly soluble in chloroform. Phenobarbital is 5-S-barbituric acid-phenylhydrazine in which the basic structure is barbituric acid, a substance that has no CNS action. Phenobarbital is obtained by the reaction of phenylglyoxal, or any group of the pyrimidine ring. It has the following structural formula:

\[ \text{C}_6\text{H}_9\text{N}_{10}\text{O}_3 \]

M.W. = 204.24

Each phenobarbital tablet contains 10.2 mg, 32 mg, 64 mg or 92.7 mg of phenobarbital, phenobarbital sodium, lactose monophosphate, magnesium stearate, microcrystalline cellulose and starch gum.

CLINICAL PHARMACOLOGY

PHENOBARBITAL is an example of producing all levels of CNS mood alteration, from excitation to mild sedation, hypnotic, and sleep coma. Overdose can produce death. In high enough doses, phenobarbital produces profound anesthetic depression and is used medicinally in anesthesia.

Barbiturates depress the sensory cortex, decrease motor activity, alter cerebral function, and produce deep sleep. These effects can be reversed by aspiration or surgical removal of the CNS.

Barbiturate-induced sleep differs from physiologic sleep. Sleep laboratory studies have demonstrated that barbiturates reduce the amount of time spent in the rapid eye movement (REM) phase of sleep or the dreaming stage. Also, Stages III and IV sleep are decreased and the production of barbiturates used regularly, patients may experience markedly increased dreaming, nightmares, and insomnia. Therefore, withdrawal of a hypnotic medication over 3 to 4 days should be done slowly to lessen the REM rebound and disturbed sleep that can contribute to the drug withdrawal syndrome (for example, insomnia, agitation, and delirium tremens) during the first 1 to 2 days of a course. In studies, sedative-hypnotic and psychotropic barbiturates have been found to lose most of their therapeutic effect for both inducing and maintaining sleep by the end of 2 weeks of continued drug administration even with the use of multiple doses. As with sedative-hypnotic and psychotropic barbiturates (including amobarbital) might be expected to lose their effectiveness for inducing and maintaining sleep after about 2 weeks. Phenobarbital doses and - dose responses differ greatly between patients and are widely prescribed for treating insomnia. Although the clinical literature abounds with claims of increased REM sleep occurring upon withdrawal of sedative-hypnotic drugs, whereas the intermediate-acting compounds are more effective in maintaining sleep, controlled studies have failed to demonstrate these differentials in the wake-sleep relationship, so sleep industries embrace the barbiturates as being of limited value short beyond sleep-related effects.

Barbiturates have little apparent effect on the duration of sleep. Rather, in sedative-hypnotic doses, these drugs may increase the reaction to painful stimuli. All barbiturates exhibit anticonvulsant activity in anesthetic doses; however, of the drugs in this class, only phenobarbital, meprobamate, and mephobarbital are effective as oral anticonvulsants in subhuman primates.

Barbiturates are respiratory depressants, and the degree of respiratory depression is dependent upon the dose. With hypnotic doses, respiratory depression produced by barbiturates is similar to that which occurs during physiologic sleep and is accompanied by a slight decrease in blood pressure and heart rate.

Studies in laboratory animals have shown that barbiturates cause reduction in the tone and contractility of the uterus, uterine and uterine blood flow. However, the depression of the barbiturate-induced uterus is markedly less than that produced by the barbiturates used in anesthetic doses.

Barbiturates and carbon dioxide. Inhalation of carbon dioxide has been shown to produce a decrease in anticonvulsant activity as measured by the prothrombin time. Barbiturates reduce hepatic microsomal enzymes resulting in increased metabolism and decreased anticonvulsant response of oral anticonvulsants (e.g., acetylsalicylic, warfarin, dicumarol, and phenaceturin). Patients stabilized on anticonvulsant therapy may require dosage adjustments if barbiturates are added to or withdrawn from their dosage regimen.

Barbiturates and barbiturates. Barbiturates appear to enhance the metabolism of exogenous corticosteroids, probably through the induction of hepatic microsomal enzymes that metabolize the steroid. If phenobarbital and corticosteroids are administered concomitantly, phenobarbital-induced decrease in the half-life of corticosteroids should be monitored closely.

Barbiturates and phenobarbital. The effect of barbiturates on the metabolism of phenobarbital is variable. Some patients report an accelerated effect, whereas others may report no effect. The effect of barbiturates on the metabolism of phenobarbital is not predictable, phenobarbital and barbiturate blood levels should be monitored more frequently if these drugs are given concurrently. The concentration of phenobarbital serum levels should be closely monitored and appropriate dosage adjustments made accordingly.

In CNS Depressants. The concomitant use of other CNS depressants, including other sedatives or hypnotics, antihistamines, tranquilizers, or alcohol, may produce additive depressant effects.

Monoamine oxidase inhibitors (MAOIs) MAOIs prolong the effects of barbiturates, perhaps because metabolism of the barbiturate is inhibited.

Oxidase, Phenothiazines, and Other Steroids. Phenothiazines or other antihypertensive agents that can cause suppression of the sodium-retaining effect of phenobarbital serum levels; therefore, phenobarbital blood levels should be closely monitored and appropriate dosage adjustments made accordingly.

Carcinogenesis

1. Animal Data. Phenobarbital is carcinogenic in the mouse after lifetime administration. In mice, it produced benign and malignant liver tumors. In rats, benign and malignant liver tumors were observed very rarely.

2. Human Data. In a 28-year epidemiological study of 9,136 patients who were treated on an anticonvulsant protocol that included phenobarbital, results indicated a higher than normal incidence of hepatic carcinoma. Premature deaths from liver cancer had been noted. Premature death was due to liver cancer and not from hepatic carcioma. Therefore, this study did not provide sufficient evidence that phenobarbital is associated with an increased risk of hepatic tumors.

A retrospective study of 84 children with brain tumors matched to 75 normal controls and 78 cancer controls (malignant disease other than brain tumors) suggested an association between exposure to barbiturates prenatally and an increased incidence of brain tumors.

Use in Pregnancy

1. Teratogenic Effects. Pregnancy Category D – See Usage in pregnancy under WARNINGS.

2. Neonatal/Infant Effects. Reports of infants suffering from withdrawal symptoms in infants and neonates included the acute withdrawal syndrome of jaundice and hyperbilirubinemia from birth to a delayed onset of up to 14 days (see DRUG ABUSE AND DEPENDENCE).

Labor and Delivery

Hypnotic doses of barbiturates do not appear to impair uterine activity significantly during labor. Full anesthetic doses of barbiturates decrease the force and frequency of uterine contractions. Administration of sedative-hypnotic barbiturates at high doses during labor may result in respiratory depression in the newborn. Premature infants are particularly susceptible to the depressant effects of barbiturates. If barbiturates are used during labor and delivery, resuscitation equipment should be available.

Data are not available to evaluate the effect of barbiturates when formula delivery or other

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