Phenobarbital is a barbituric acid derivative and occurs as white, odorless, small crystals or crystalline powder that is very slightly soluble in water; soluble in alcohol, in ether, and in solutions of fixed alkali hydroxides and carbonates. It is sparingly soluble in chloroform.

Phenobarbital is 5-ethyl-5-phenylbarbituric acid. Phenobarbital is a substituted pyrimidine derivative in which the basic structure is barbituric acid, a substance that has no CNS activity. CNS activity is obtained by substituting alkyl, alkenyl, or aryl groups on the pyrimidine ring. It has the following structural formula:

Each phenobarbital tablet contains 16.2 mg, 32.4 mg, 64.8 mg or 97.2 mg of phenobarbital.

In addition each tablet contains: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

### General

### CLINICAL PHARMACOLOGY

Barbiturates are capable of producing all levels of CNS mood alteration, from excitement to mild sedation, hypnosis, and deep coma. Overdose can produce death. In high enough therapeutic doses, barbiturates induce anesthesia.

Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis.

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. Stages III and IV sleep are decreased. Following withdrawal of a single therapeutic dose over 5 or 6 days has been recommended to lessen the REM rebound and disturbed sleep that contribute to the drug withdrawal syndrome (for example, decrease the dose from 3 to 2 doses a day for 1 week).

In studies, secobarbital sodium and pentobarbital sodium have been found to lose most of their effectiveness 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 secobarbital sodium and phenobarbital sodium, other barbiturates (including amobarbital) might be expected to lose their effectiveness for inducing and maintaining sleep after about 2 weeks. The short-, intermediate-, and, to a lesser degree, long-acting barbiturates have been widely prescribed for treating insomnia. Although the clinical literature abounds with claims that the short-acting barbiturates are superior for producing sleep whereas the intermediate-acting compounds are more effective in maintaining sleep, controlled studies have failed to demonstrate these differential effects. Therefore, as sleep medications, the barbiturates are of limited value beyond short-term use.

Barbiturates have a highly addictive action on subanesthetic doses. Rather, in subanesthetic 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, mephobarbital, and metharbital are effective as oral anticonvulsants in subanesthetic doses.

Barbiturates are respiratory depressants, and the degree of respiratory depression is dependent on 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, ureters, and urinary bladder. However, concentrations of the drugs required to produce this effect in some persons, especially children, barbiturates repeatedly produce excitement rather than depression.

With hypnotic doses, respiratory depression produced by barbiturates is similar to that which occurs during physiologic sleep. However, the application of these data to other barbiturates appears valid and warrants serial case-controlled studies.

### Usual Doses

1. Habit Forming. Phenobarbital may be habit forming. Tolerance and psychological and physical dependence may occur with continued use (see DRUG ABUSE AND DEPENDENCE and Pharmacokinetics under CLINICAL PHARMACOLOGY). Patients who have psychologic dependence on barbiturates may increase the dosage or decrease the dosage interval without consulting a physician and may subsequently develop a physical dependence on barbiturates. In order to minimize the possibility of overdose or the development of dependence, the prescribing and dispensing of sedative-hypnotic barbiturates should be limited to the amount required for the interval until the next appointment. Discontinuation after prolonged use in a person who is dependent on the drug can produce symptoms of withdrawal, including delirium, convulsions, and possibly death. Barbiturates should be withdrawn gradually from any patient known to be taking excessive doses over long periods of time (see DRUG ABUSE AND DEPENDENCE).

2. Acute or Chronic Pain. Caution should be exercised when barbiturates are administered to patients with acute or chronic pain, because paradoxical excitement can be induced or important symptoms can be masked. However, the use of barbiturates as sedatives in the postoperative surgical period and as adjuncts to cancer chemotherapy is well established.

3. Usage in Pregnancy. Barbiturates can cause fetal damage when administered to a pregnant woman. Retrospective, case-controlled studies have suggested a connection between the maternal consumption of barbiturates and a higher than expected incidence of fetal abnormalities. Barbiturates readily cross the placental barrier and are distributed throughout fetal tissues; the highest concentrations are found in the placenta, fetal liver, and brain. Fetal blood levels approach maternal blood levels following prenatal administration.

Withdrawing symptoms occur in infants born to women who receive barbiturates throughout the last trimester of pregnancy (see DRUG ABUSE AND DEPENDENCE).

If phenobarbital is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

4. Usage in Pediatric Patients. Phenobarbital has been reported to be associated with cognitive deficits in children taking it for complicated febrile seizures.

5. Synergic Effects. The concomitant use of alcohol or other CNS depressants may produce additive CNS depressant effects.

### PRECAUTIONS

#### General

Barbiturates may be habit forming. Tolerance and psychological and physical dependence may occur with continued use (see DRUG ABUSE AND DEPENDENCE). Barbiturates should be administered with caution, if at all, to patients who are mentally depressed, have suicidal tendencies, or have a history of drug abuse.

Elderly or debilitated patients may react to barbiturates with marked excitement, depression, or confusion. In some persons, especially children, barbiturates repeatedly produce excitement rather than depression.

In patients with hepatic damage, barbiturates should be administered with caution and initially in reduced doses. Barbiturates should not be administered to patients showing the prematory signs of hepatic coma.

The systemic effects of exogenous and endogenous corticosteroids may be diminished by phenobarbital. Thus, this product should be administered with caution to patients with borderline hypoadrenal function, regardless of whether it is of pituitary or of primary adrenal origin.

#### Information for Patients

The following information and instructions should be given to patients receiving barbiturates.

1. The use of barbiturates carries with it an associated risk of psychological and/or physical dependence. The patient should be warned against increasing the dose of the drug without consulting a physician.

2. Barbiturates may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

3. Alcohol should not be consumed while taking barbiturates. The concurrent use of the barbiturates with other CNS depressants may produce additive CNS depressant effects.

#### Laboratory Tests

Prolonged therapy with barbiturates should be accompanied by periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic systems (see General under PRECAUTIONS AND ADVERSE REACTIONS).

### Drug Interactions

Most reports of clinically significant drug interactions occurring with the barbiturates have involved phenobarbital. However, the application of these data to other barbiturates appears valid and warrants serial case-controlled studies.

1. Anticoagulants. Phenobarbital lowers the plasma levels of dicumarol and causes a decrease in anticoagulant activity as measured by the prothrombin time. Barbiturates can induce hepatic microsomal enzymes which increased metabolism and decreased anticoagulant response of oral anticoagulants (e.g., acenocoumarol, warfarin, dicumarol, and phenprocoumon). Patients stabilized on anticoagulant therapy may require dosage adjustments if barbiturates are added to or withdrawn from their dosage regimen.

2. Corticosteroids. Barbiturates appear to enhance the metabolism of exogenous corticosteroids, probably through the induction of hepatic microsomal enzymes. Patients stabilized on corticosteroid therapy may require dosage adjustments if barbiturates are added to or withdrawn from their dosage regimen.

3. Griseofulvin. Phenobarbital appears to interfere with the absorption of orally administered griseofulvin, thus decreasing its blood level. The effect of the resultant decreased blood levels of griseofulvin on therapeutic response has not been established. However, it would be preferable to avoid concomitant administration of these drugs.

4. Doxycycline. Phenobarbital has been shown to shorten the half-life of doxycycline for as long as 2 weeks after barbiturate therapy is discontinued. This mechanism is probably through the induction of hepatic microsomal enzymes that metabolize the antibiotic. If phenobarbital and doxycycline are administered concurrently, the clinical response to doxycycline should be monitored closely.

5. Phenytoin, Sodium Valproate, Vigabacpine. The effect of barbiturates on the metabolism of phenytoin appears to be variable. Some investigators report an accelerating effect, whereas others report no effect. Because the effect of barbiturates on the metabolism of phenytoin is not predictable, phenytoin and barbiturate blood levels should be monitored more frequently if these drugs are given concurrently. Sodium valproate and valpric acid increase the phenytoin blood levels; therefore, phenytoin blood levels should be closely monitored and appropriate dosage adjustments made as clinically indicated.

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

7. Monoamine Oxidase Inhibitors (MAOIs). MAOIs prolong the effects of barbiturates, probably because metabolism of the barbiturate is inhibited. The patient should be warned against increasing the dose of the drug without consulting a physician.

8. Estradiol, Estrone, Progesterone, and other Steroidal Hormones. The effect of barbiturates on the metabolism of estradiol and estrone appears to be variable. Barbiturates may either inhibit or stimulate the metabolism of estradiol and estrone. The patient should be warned against increasing the dose of the drug without consulting a physician.

9. Thyroid Hormones. The effect of barbiturates on the metabolism of thyroid hormones appears to be variable. Barbiturates may either inhibit or stimulate the metabolism of thyroid hormones. The patient should be warned against increasing the dose of the drug without consulting a physician.

10. Estrogens, Progestins, and other Steroidal Hormones. Pretreatment with or concurrent administration of phenobarbital may decrease the effect of estrodiol by increasing its metabolism. There have been reports of patients treated with antiepileptic drugs (e.g., phenobarbital) who become pregnant while taking oral contraceptives. An alternate contraceptive method might be suggested to women taking phenobarbital.

### Carcinogenesis

1. Animal Data. Phenobarbital sodium is carcinogenic in mice and rats after lifetime administration. In a 29-year epidemiological study of 9,136 patients who were treated on an anticonvulsant protocol for epilepsy, no evidence of a significant increase in risk of cancers of the lungs, breast, or colon was found.

2. Human Data. In a 29-year epidemiological study of 9,136 patients who were treated on an anticonvulsant protocol for epilepsy, no evidence of a significant increase in risk of cancers of the lungs, breast, or colon was found.

A retrospective study of 84 children with brain tumors matched to 73 normal controls and 78 cancer controls with head and neck tumors had no evidence that phenobarbital was a risk factor for these cancers.
Infants who are physically dependent on barbiturates may be given phenobarbital, 3 to 10 mg/kg/day. After withdrawal symptoms (hyperactivity, disturbed sleep, tremors, and hyperreflexia) are relieved, the dosage of phenobarbital should be gradually decreased and completely withdrawn over a 2-week period.

OVERDOSAGE

Signs and Symptoms – The onset of symptoms following a toxic oral exposure to phenobarbital may not occur until several hours following ingestion. The toxic dose of barbiturates varies considerably. In general, an oral dose of 1 g of most barbiturates produces serious poisoning in an adult. Death commonly occurs after 2 to 10 g of ingested barbiturate, although, therapeutic blood levels of phenobarbital range between 0.5 to 40 mcg/mL. If the usual lethal blood level varies from 100 to 200 mcg/mL. Barbiturate intoxication may be confused with alcoholism, bromide intoxication, and various neurologic disorders. Potential tolerance must be considered when estimating the magnitude of the effects of the dose and plasma concentration.

The manifestations of a long-acting barbiturate in overdose include nystagmus, ataxia, CNS depression, respiratory depression, hypothermia, and hypotension. Other findings may include absent or depressed reflexes and erythematous or hemorrhagic blisters (primarily at pressure points). Following massive exposure to barbiturates, pulmonary edema, circulatory collapse with loss of peripheral vascular tone, cardiac arrest, and death may occur.

In extreme overdose, all electrical activity in the brain may cease, in which case a "flat EEG normally equated with clinical death should not be accepted. This effect is fully reversible only if hypoxic damage occurs.

Consideration should be given to the possibility of barbiturate intoxication even in situations that appear to involve trauma.

Complications such as pneumonia, pulmonary edema, cardiac arrhythmias, congestive heart failure, and renal failure may occur. Uremia may increase CNS sensitivity to barbiturates if renal function is impaired. Differential diagnosis should include hypoglycemia, head trauma, cerebrovascular accidents, convulsive states, and diabetic coma.

Treatment – To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are published in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Protect the patient’s airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient’s vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient’s airway when employing gastric emptying or charcoal.

Alkalization of urine hastens barbiturate excretion, but dialysis and hemoperfusion are more effective and cause less troublesome alterations in electrolyte equilibrium. If the patient has chronically abused sedatives, withdrawal reactions may be manifest following the chronic use of phenobarbital.

DOSE AND ADMINISTRATION

The dose of phenobarbital must be individualized with full knowledge of its particular characteristics. Factors of consideration are the patient’s age, weight, and condition.

Sedation: For sedation, the drug may be administered in single dose of 30 to 120 mg repeated at intervals; frequency will be determined by the patient’s response. It is generally considered that no more than 400 mg of phenobarbital should be administered during a 24-hour period.

Adults:
• Daytime Sedation: 30 to 120 mg daily in 2 to 3 divided doses.
• Oral Hypnic: 100 to 200 mg.

Anticonvulsant Use – Clinical laboratory reference values should be used to determine the therapeutic anticonvulsant level of phenobarbital in the serum. To achieve the blood levels considered therapeutic in pediatric patients, higher per-kilogram doses are generally necessary for phenobarbital and most other anticonvulsants. In children and infants, phenobarbital at a loading dose of 15 to 20 mg/kg produces blood levels of about 20 mcg/mL after administration.

Phenobarbital has been used in the treatment and prophylaxis of febrile seizures. However, it has not been established that prevention of febrile seizures influences the subsequent development of epilepsy.

Adults: 60 to 200 mg/day.

Pediatric Patients: 3 to 6 mg/kg/day.

Special Patient Population – Dosage should be reduced in the elderly or debilitated because these patients may be more sensitive to barbiturates. Dosage should be reduced for patients with impaired renal function or hepatic disease.

HOW SUPPLIED

Phenobarbital Tablets, USP 16.2 mg are white, round, biconvex, scored tablets, debossed “5011” and “V” on one side and plain on the reverse side, and supplied as follows:
- Bottles of 100 NDC 0603-5165-21
- Bottles of 1000 NDC 0603-5165-32

Phenobarbital Tablets, USP 32.4 mg are white, round, biconvex, scored tablets, debossed “9012” and “V” on one side and plain on the reverse side, and supplied as follows:
- Bottles of 100 NDC 0603-5166-21
- Bottles of 1000 NDC 0603-5166-32

Phenobarbital Tablets, USP 64.8 mg are white, round, biconvex, scored tablets, debossed “9014” and “V” on one side and plain on the reverse side, and supplied as follows:
- Bottles of 100 NDC 0603-5167-21
- Bottles of 1000 NDC 0603-5167-32

Phenobarbital Tablets, USP 97.2 mg are white, round, biconvex, scored tablets, debossed “9014” and “V” on one side and plain on the reverse side, and supplied as follows:
- Bottles of 100 NDC 0603-5168-21
- Bottles of 1000 NDC 0603-5168-32

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