PRODUCT MONOGRAPH

APO-PHENYLBUTAZONE

(Phenylbutazone)

100 mg tablets

Nonsteroidal Anti-inflammatory Agent

APOTEX INC.
150 Signet Drive
Weston, Ontario
M9L 1T9

DATE OF PREPARATION:

NAME OF DRUG

APO-PHENYLBUTAZONE

(Phenylbutazone)

100 mg tablets

PHARMACOLOGICAL CLASSIFICATION

Nonsteroidal Anti-inflammatory Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Phenylbutazone is a nonsteroidal anti-inflammatory agent with antipyretic and analgesic properties. Although phenylbutazone does not alter the course of the underlying disease, it has been found effective in relieving pain, reducing swelling and tenderness and increasing mobility in patients with rheumatic disorders.

The exact mechanism of the anti-inflammatory effects of phenylbutazone has not been elucidated, but clinical pharmacology studies have shown that phenylbutazone inhibits certain factors believed to be involved in the inflammatory process, e.g. prostaglandin synthesis.

Phenylbutazone is rapidly absorbed after oral administration and distributed partially into an extravascular compartment, with about one third remaining in plasma. About 98% of the drug in plasma is bound to human serum albumin.

Following oral administration of phenylbutazone, peak serum concentrations of the active substance are attained after approximately 2 hours. Following repeated doses of 100 mg, 200 mg, or 300 mg daily, the mean serum concentrations amount to 52, 83 and 95 mcg/mL, respectively. Measurements of the area under the serum concentration curve have shown that, of the dose administered, 63% circulates in the serum as unchanged phenylbutazone, 23% as oxyphenbutazone, and approximately 2.5% in the form of other hydroxymetabolites.

Phenylbutazone is slowly metabolized in the liver and upon cessation of administration it remains in the body in detectable quantities for 7 to 10 days. It is excreted almost entirely in the form of metabolites approximately 3/4 in the urine (approximately 40% as the C-glucuronide of phenylbutazone and approximately 10-15% as the C-glucuronide of -hydroxyphenylbutazone) and approximately 1/4 in the feces. The plasma half-life of the drug is approximately 75 hours, but is prolonged in geriatric patients to approximately 105 hours.

INDICATIONS

Because of the toxicity of this drug the indications are limited to:

Ankylosing (rheumatoid) spondylitis

Acute attacks of gout

In case of acute attacks of gout, treatment should not exceed one week. APO-PHENYLBUTAZONE (phenylbutazone) is only recommended in cases where other therapeutic measures including other nonsteroidal anti-inflammatory agents have been tried and found unsatisfactory.

CONTRAINDICATIONS

APO-PHENYLBUTAZONE (phenylbutazone) is contraindicated in patients with peptic ulcer or active inflammatory disease of the gastrointestinal system.

Phenylbutazone is contraindicated in those patients with known or suspected hypersensitivity to phenylbutazone or oxyphenbutazone. Phenylbutazone should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

APO-PHENYLBUTAZONE is contraindicated in children fourteen years of age or less and senile patients.

Phenylbutazone should not be used in patients with blood dyscrasias; haemorrhagic diathesis (thrombocytopenia, disorder of blood coagulation); hepatic, cardiac or renal dysfunction; hypertension; thyroid disease; systemic edema, Sjögren's syndrome; salivary gland enlargement due to the drug; stomatitis due to the drug, polymyalgia rheumatica; temporal arteritis or pancreatitis.

Phenylbutazone should not be used concurrently with other drugs which accentuate or show a potential for similar toxicity. It is also inadvisable to administer phenylbutazone in combination with other potent drugs because of the possibility of increased toxic reactions from phenylbutazone and other agents.

Phenylbutazone should not be given to patients on long-term oral anticoagulant therapy.

WARNINGS

Frequent and regular hematological evaluations should be performed on patients receiving phenylbutazone for periods over 1 week. Any significant change in the total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should be a signal for immediate cessation of therapy and a complete hematologic investigation. Serious, sometimes fatal blood dyscrasias, including aplastic anemia have been reported to occur with phenylbutazone. Hematology toxicity may occur suddenly or many days or weeks after cessation of treatment as manifested

by the appearance of anemia, leukopenia, thrombocytopenia or clinically significant hemorrhagic diathesis.

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti-inflammatory drugs (NSAID's) including phenylbutazone.

APO-PHENYLBUTAZONE (phenylbutazone) should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment. In addition to the gastrointestinal adverse reactions common to all NSAIDs, an incidence of bone marrow depression is associated with the use of phenylbutazone.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAID's). For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. See PRECAUTIONS for further advice.

Use in pregnancy and lactation:

Animal reproduction studies thus far, though inconclusive, exhibit evidence of embryotoxicity. Nonsteroidal anti-inflammatory drugs have been reported to cause premature closure of the ductus arteriosus in the fetus. Therefore, the use of phenylbutazone in pregnancy is not recommended. Very small quantities of the active substance pass into breast milk. Therefore, nursing mothers should either wean their infants or discontinue medication.

PRECAUTIONS

Prior to initiation of therapy, a careful history should be taken and a physical examination including a complete blood count and urinalysis should be performed.

Patients should be followed closely, especially the elderly, and warned to discontinue the drug and contact their physician immediately if any of the following signs or symptoms are observed: fever, sore throat, lesions in the mouth, spontaneous bruising, black or tarry stools, jaundice, skin reactions, a sudden weight gain, or persistent or severe dyspepsia.

From age 40 on, the possibility of adverse reactions increases, and therefore APO-PHENYLBUTAZONE (phenylbutazone) should be used with commensurately greater care in these patients.

Gastrointestinal system:

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs phenylbutazone should be discontinued, an appropriate treatment instituted and patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of APO-PHENYLBUTAZONE therapy when and if these adverse reactions appear.

Renal function:

As with other nonsteroidal anti-inflammatory drugs, long-term administration of phenylbutazone to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Phenylbutazone and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. In these cases lower doses of APO-PHENYLBUTAZONE should be anticipated and patients carefully monitored.

During long-term therapy kidney function should be monitored periodically.

Hepatic function:

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance:

Fluid retention and edema have been observed in patients treated with phenylbutazone. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. APO-PHENYLBUTAZONE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention. A low-salt diet may help to guard against the possibility of fluid retention.

Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk.

Hematology:

As serious and sometimes fatal blood dyscrasias including aplastic anemia have occurred, hematologic evaluation should be performed at weekly intervals during the initial treatment and then at regular intervals while on maintenance therapy. Additional laboratory examinations should be performed as indicated. If there is any significant change in total leukocyte count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit or platelet count, treatment with this drug should be discontinued immediately and a complete hematologic investigation should be made. Hematologic toxicity may occur shortly after initiation of therapy or after prolonged treatment; it may develop abruptly or gradually and may become apparent days or weeks after cessation of therapy. It is manifested by the appearance of anemia, leukopenia, thrombocytopenia, or clinically significant hemorrhagic diathesis.

Infection:

In common with other anti-inflammatory drugs, phenylbutazone may mask the usual signs of infection.

Ophthalmology:

Blurred and/or diminished vision has been reported with the use of phenylbutazone and other nonsteroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Central nervous system:

Since convulsions have been observed in rare cases of overdosage with phenylbutazone, APO-PHENYLBUTAZONE should be employed with caution in epileptics.

Hypersensitivity reactions:

In patients under treatment with phenylbutazone, isolated occurrences of an "acute pulmonary syndrome" marked by dyspnoea, fever, shadows in radiographs of the lungs, and sometimes also by eosinophilia, have been reported. Although a causal connection with phenylbutazone has not been proven, the drug should be withdrawn if signs of this syndrome appear, for the treatment of which corticosteroids and measures to support the cardiovascular system may be necessary.

In patients with lupus erythematosus disseminatus, phenylbutazone may aggravate or acutely exacerbate the disease, therefore caution should be employed in such cases.

Use in children:

Phenylbutazone is not recommended for use in children. Keep out of reach of children.

Information for patients:

While on the drug, patients should be cautioned about participation in activity necessitating alertness and coordination, as driving a car, etc. Concomitant ingestion of alcohol may further impair psychomotor skills.

Drug interactions:

General:

Phenylbutazone competitively displaces other drugs, e.g., other anti-inflammatory agents, oral anticoagulants, oral antidiabetics, sulfonamides, sodium valproate and phenytoin, from serum binding sites. The activity, duration of effect and toxicity of the displaced drugs may thus be increased.

Anticoagulants:

Phenylbutazone accentuates the prothrombin depression produced by coumarin-type anticoagulants. When administered alone, phenylbutazone does not affect prothrombin activity. APO-PHENYLBUTAZONE may induce the hepatic microsomal metabolism of dicoumarol.

Methotrexate:

Since phenylbutazone may potentiate the effect of methotrexate, caution is indicated in cases where these drugs are given concomitantly.

Lithium:

Phenylbutazone increases the serum concentration of lithium by increasing tubular reabsorption.

Miscellaneous interactions:

Phenylbutazone may induce the hepatic microsomal metabolism of aminopyrine, digitoxin, hexobarbital and cortisone. Conversely, it may inhibit the metabolism of phenytoin.

Concomitant administration of phenylbutazone and phenytoin may result in increased serum levels of phenytoin which could lead to increased phenytoin toxicity.

Inducers of hepatic microsomal enzymes, e.g., barbiturates, promethazine, chlorpheniramine, rifampin and corticosteroids (prednisone), may decrease the half life of phenylbutazone. The effects of insulin, antidiabetic and sulfonamide drugs may be potentiated by phenylbutazone along with a reduction of the renal clearance of sulfonylureas (the plasma half-life of certain antibiotics and sulfonamides may be prolonged by phenylbutazone).

Methylphenidate is reported to prolong the half-life of phenylbutazone and to increase the serum level of oxyphenbutazone. Cholestyramine reduces the enteral absorption of phenylbutazone.

Clinical laboratory tests:

Phenylbutazone reduces iodine uptake by the thyroid and may interfere with laboratory tests of thyroid function. (Thyroid hyperplasia, goiters, and hypothyroidism have also been reported; see ADVERSE REACTIONS.)

ADVERSE REACTIONS

The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particularly in the elderly.

The adverse reactions for phenylbutazone listed in the following table have been arranged into two groups: (1) incidence greater than 1% and (2) incidence less than 1%. The probability of a causal relationship exists between phenylbutazone and these adverse reactions, some of which have been reported only rarely.

Incidence greater than 1%	Incidence less than 1%
GASTROINTESTINAL: Abdominal discomfort and distress* nausea; dyspepsia; including indigestion and heartburn.	Vomiting; abdominal distention with flatulence; constipation; diarrhea; esophagitis; salivary gland enlargement; stomatitis, sometimes with ulceration; ulceration and perforation of the intestinal tract including acute and reactivated peptic ulcer; exacerbation of Crohn's disease; anemia due to occult gastrointestinal bleeding.
ALLERGIC:	Urticaria; anaphylactic shock; arthralgia; fever; vasculitis; Lyell's syndrome; serum sickness; Stevens-Johnson syndrome; activation of systemic lupus erythematosus; aggravation of temporal arteritis.

CENTRAL NERVOUS SYSTEM:	Headache; drowsiness; agitation; confusional states and lethargy; tremors; numbness; weakness.
DERMATOLOGIC: Rash.	Pruritus; erythema nodosum; erythema multiforme; nonthrombocytopenic purpura.
CARDIOVASCULAR:	Congestive heart failure; hypertension; pericarditis; interstitial myocarditis.
SPECIAL SENSES:	Hearing loss; tinnitus.
HEMATOLOGIC:	Aplastic anemia; agranulocytosis; bone marrow depression; thrombocytopenia; pancytopenia; leukopenia; anemia; hemolytic anemia.
RENAL:	Hematuria; proteinuria; ureteral obstruction with uric acid crystals; anuria; glomerulonephritis; acute tubular necrosis; cortical necrosis; renal stones; nephrotic syndrome; impaired renal function and renal failure; interstitial nephritis.
HEPATIC:	Hepatitis.
FLUID and ELECTROLYTE: Edema, water retention*.	Sodium and chloride retention; fluid retention and plasma dilution; metabolic acidosis; respiratory alkalosis.
ENDOCRINE-METABOLIC:	Hyperglycemia.

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* Reactions occurring in 3% to 9% of patients treated with phenylbutazone. (Those reactions occurring in less than 3% of the patients are unmarked.)

Causal relationship unknown:

Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians:

Incidence less than 1%:

Hematologic: Leukemia

Special Senses: Blurred vision; optic neuritis; toxic amblyopia; scotomata; retinal detachment; retinal hemorrhage; oculomotor palsy.

Endocrine-Metabolic: Thyroid hyperplasia; goiters associated with hyperthyroidism and hypothyroidism; pancreatitis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The first signs and symptoms, referable chiefly to the stomach and the nervous system, appear 1 to 2 hours after ingestion of the overdose in children and somewhat later in adults.

The signs and symptoms of phenylbutazone poisoning can be summarized as follows:

Mild poisoning

Nausea, abdominal pain, drowsiness.

Severe poisoning

Early onset

Upper abdominal pain, nausea, vomiting, hematemesis, diarrhea, restlessness, dizziness, agitation, hallucinations, psychosis, coma, convulsions (more prevalent in children), hyperpyrexia, electrolyte disturbances, hyperventilation, alkalosis or acidosis, respiratory arrest, hypotension, hypertension, cyanosis.

Late onset (2-7 days)

Acute renal failure, edema, hematuria, oliguria, abnormal laboratory test results, jaundice, electrocardiographic abnormalities, cardiac arrest, blood dyscrasias (anemia, thrombocytopenia, leukopenia, leukocytosis, hypoprothrombinemia).

Abnormalities evident on laboratory tests after overdosage may include respiratory or metabolic acidosis, impaired hepatic or renal function, and abnormalities of formed blood elements.

Treatment: There is no specific antidote.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before lavage; emesis should not be induced. Adequate respiratory exchange should be maintained; respiratory stimulants should not be used. Shock should be treated with appropriate supportive measures. Seizures should be controlled with intravenous diazepam or short-acting barbiturates. Hemoperfusion has been used as an adjunct to supportive therapy in cases with poor prognosis.

DOSAGE AND ADMINISTRATION

In selecting the appropriate dosage in any specific case, consideration should be given to the patient's age, weight, general health, and any other factors that may influence his response to the drug.

Phenylbutazone is contraindicated in children 14 years of age or less and in senile patients. The efficacy and the safety of phenylbutazone are unpredictable. Therefore, the goal of therapy should be **short-term** relief of **severe** symptoms to a tolerable level using the **smallest** possible drug dosage. When a longer treatment is unavoidable special precautions should be taken (see PRECAUTIONS).

To minimize gastric upset, phenylbutazone should always be taken with meals or with a full glass of milk. (The tablets should be swallowed whole.)

Ankylosing Spondylitis:

Initial Dosage:

The initial dosage in adults ranges from 300 mg to 600 mg daily, divided into 3 or 4 equal doses. In most instances, it is unnecessary to exceed 400 mg daily to ensure maximum therapeutic response. A trial period of one week of therapy is considered adequate to determine the therapeutic effect of the drug. In the absence of a favorable response, therapy should be discontinued.

Maintenance Dosage:

When improvement is obtained, the dosage should be promptly decreased to the minimum effective level to maintain relief. This maintenance dosage should not exceed 400 mg/day because of possible cumulative toxic effects. Satisfactory effect is often achieved with as little as 100 to 200 mg daily. Treatment should be discontinued as soon as possible.

Elderly Patients (sixty years and over):

Every effort must be made to discontinue therapy on, or as soon as possible after the seventh day, because of the exceedingly high risk of severe, fatal toxic reactions in this age group.

Acute Gouty Arthritis:

Initial dose of 400 mg, followed by 100 mg every 4 hours until articular inflammation subsides, usually within 2 to 3 days. Treatment should not exceed 7 days.

AVAILABILITY

APO-PHENYLBUTAZONE (phenylbutazone) 100 mg tablets are red, round, biconvex in shape and film coated. They are supplied in bottles of 100, and 1000.

INFORMATION TO THE PATIENT

APO-PHENYLBUTAZONE

Brand of Phenylbutazone Tablets

Phenylbutazone (fen-ill-BYOO-ta-zone), which has been prescribed to you by your doctor, is one of a large group of nonsteroidal anti-inflammatory drugs (NSAID's) and is used to treat the symptoms of certain types of arthritis, gout, and ankylosing spondylitis. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and helping to control inflammation and other body reactions.

IMPORTANT

You should take APO-PHENYLBUTAZONE only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered.

Be sure to take APO-PHENYLBUTAZONE regularly as prescribed. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis or drink alcoholic beverages while taking APO-PHENYLBUTAZONE unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medication is not causing unwanted effects.

Along with its beneficial effects, APO-PHENYLBUTAZONE like other NSAID's, may cause some undesirable reactions. Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with your doctor immediately if any of the following are noted:

- fever, sore throat or lesions in the mouth;
- unusual bleeding or bruising;
- bloody or black tarry stools;
- shortness of breath, wheezing, any trouble in breathing or tightness in the chest;
- skin rash, swelling, hives or itching;
- indigestion, nausea, vomiting, stomach pain or diarrhea;
- yellow discolouration of the skin or eyes, with or without fatigue;
- any changes in the amount or colour of your urine (such as dark; red or brown);
- swelling of the face, hands, feet or lower legs;

- weight gain (rapid);
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness; hearing problems. If you experience any of these effects do not operate machinery or motor vehicle and do not take any sedating medications such as tranquilizers, sleeping pills and certain antihistamines unless approved by your doctor.

Symptoms of phenylbutazone overdose:

- Bluish colour of fingernails, lips or skin;
- headache (severe and continuing).

ALWAYS REMEMBER

- Before taking this medication tell your doctor and pharmacist if you:
- are allergic to phenylbutazone or other related medicines of the NSAID group such as acetylsalicylic acid, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin;
- have a history of stomach upset, ulcers, or liver or kidney diseases;
- are pregnant or intend to become pregnant while taking this medication;
- are breast feeding;
- are taking any other medication (either prescription or non-prescription);
- have any other medical problem(s)

- <u>While taking this medication</u>:
- tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication;
- be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or light-headed after taking this medication;
- check with your doctor if you are not getting any relief or if any problems develop.
- report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- Your regular medical checkups are essential.
- If you require more information on this drug, consult your doctor or pharmacist.
- Keep out of children's reach.

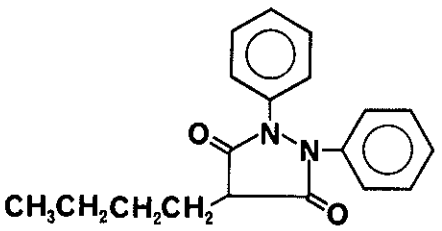
PHARMACEUTICAL INFORMATION

Drug Substance

Name: Phenylbutazone

Chemical Name: 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione

Structural Formula:



Molecular Weight: 308.38

Description: Phenylbutazone is a white to off-white, odourless crystalline powder. It is very slightly soluble in water; freely soluble in acetone and in ether; soluble in alcohol. The melting point is 104.5-106.5°C.

TOXICOLOGY

The acute and chronic toxicity of phenylbutazone has been studied in several species of animals.

Acute Toxicity

The LD_{50} for mice by the intravenous route was found to be 123 mg/kg. By the intraperitoneal route in rats the LD_{50} was 215 mg/kg. Toxic symptoms prior to death consisted of tetanic convulsions.

Chronic Toxicity

Chronic toxicity was studied in rats for a period of 90 days. The animals refused to eat a 1% phenylbutazone diet and, therefore, the study at this level was stopped. At the 0.5% level, the rate of growth was significantly reduced compared with the control animals. At levels of 0.1% and 0.05%, there was no significant effect on growth, although food consumption was somewhat reduced. Hematologic values in all groups remained within normal range. None of the animals died as a result of the experiment. However, at autopsy, enlarged thyroids, enlarged kidneys, and bloody urine were found in the animals at the 0.5% level.

Chronic oral administration of phenylbutazone to dogs at levels of 10 and 100 mg/kg/day for a total of 90 days produced no gross evidence of drug toxicity. At a level of 200 mg/kg/day for approximately 11 weeks, there was anorexia with a gradual loss of weight, and consistently low red blood cell counts and hemoglobin values. Histopathologic study of the liver, spleen, kidneys and bone marrow of these dogs revealed no changes associated with the drug.

REPRODUCTION STUDIES

Reproduction studies in rats and rabbits given phenylbutazone in oral doses up to 16 times the maximum daily human dose have revealed no evidence of teratogenicity due to phenylbutazone. However, slightly reduced litter sizes were observed after oral or subcutaneous administration of phenylbutazone to pregnant rats or rabbits; an increase in stillbirths and a reduced survival of offspring were observed after oral administration of 3.5 times the maximum daily human dose of phenylbutazone to rats during late pregnancy and lactation.

CARCINOGENICITY AND MUTAGENICITY

Long-term carcinogenicity studies in animals have not been performed with phenylbutazone.

An increased incidence of chromosome anomalies has been reported in cultured leukocyte cells from patients receiving therapeutic doses of phenylbutazone. In other similar studies in humans and horses, results were inconclusive or negative. In Chinese-hamster fibroblast cells in vitro, chromosome aberrations were induced at a concentration of phenylbutazone exceeding 20 times the human plasma level of 43 mg/L. In mice, Chinese hamsters, and rats given up to 33 times the maximum daily human dose of phenylbutazone, no evidence of mutagenic activity or adverse effects on fertility was found. Phenylbutazone was not mutagenic in bacteria or fungi.

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