Ethacrynic Acid Tablets USP

Ethacrynic acid is a potent diuretic which, if given in excessive amounts, may lead to profound diuresis with the attendant depletion of electrolytes and fluid volume. Therefore, careful medical supervision is required, and dose and dose schedule must be adjusted to the individual patient’s needs (see DOSAGE AND ADMINISTRATION).

DESCRIPTION

Ethacrynic acid is an unsubstituted benzene derivative of an acyclic acid. It is designated chemically as (2,3-dihydro-2-oxo-1-naphthalene-1-acetic acid) and has a molecular weight of 318.34. Ethacrynic acid is a white or practically white, crystalline powder, very slightly soluble in water, but soluble in most organic solvents such as alcohol, chlor仿, and benzene. Its empirical formula is C13H12Cl2O4 and its structural formula is:

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\text{H}_2\text{C} = \text{CH} - \text{COCH}_2 - \text{COCl} \]

Ethacrynic Acid Tablets USP are supplied as 25 mg tablets for oral use. The tablets contain the following inactive ingredients: calcium carbonate, cellulose, colloidal silicon dioxide, dextrose monohydrate, pre-gelatinized starch, and talc.

USP Dissolution Test is pending.

PHARMACOLOGY

Pathophysiology and Metabolism

Ethacrynic acid acts on the ascending limb of the loop of Henle and on the proximal and distal tubules. Electrolyte excretion may be increased several times over that observed with thiazide diuretics, since ethacrynic acid inhibits reabsorption of a much greater proportion of filtered sodium than most other diuretics. Therefore, ethacrynic acid is effective in many patients who have significant degrees of renal insufficiency (see WARNINGS concerning deafness). Ethacrynic acid has little or no effect on glomerular filtration or on renal blood flow, except following pronounced reductions in plasma volume when associated with rapid diuresis.

The electrolyte excretion pattern of ethacrynic acid varies from that of the thiazides and mercurial diuretics. Initial sodium and chloride excretion is usually substantial and chloride loss exceeds that of sodium. With prolonged administration, chlor仿 excretion decreases, and potassium and hydrogen ion excretion may increase. Ethacrynic acid is effective whether or not there is clinical acidosis or alkalosis.

Although ethacrynic acid, in carefully controlled studies in animals and experimental subjects, produces a more favorable sodium/potassium excretion ratio than the thiazides, in patients with increased diuresis increased amounts of potassium may be excreted. Onset of action is rapid, and diuresis begins after an oral dose of ethacrynic acid tablets. After oral use, diuresis peaks in about 2 hours and lasts about 6 to 8 hours.

The sulfhydryl binding property of ethacrynic acid differs somewhat from that of the organomercurials. Its mode of action is not by a carbamino or aseptobase inhibition. Ethacrynic acid does not cross the blood-brain barrier.

INDICATIONS AND USAGE

Ethacrynic Acid Tablets USP are indicated for treatment of edema when an agent with greater diuretic potency than those commonly employed is required. Treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

Short-term management of ascites due to malignancy, idiopathic edema, and nephrosis.

Short-term management of hospitalized pediatric patients, other than infants, with congestive heart disease or the nephrotic syndrome.

Looph diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. The safety and efficacy of ethacrynic acid in hypertension have not been established. However, the dosage of coadministered antihypertensive agents may require adjustment.

Oral ethacrynic acid may occur following vigorous or excessive diuresis. A transient increase in serum ura nitrogen may occur. Usually, this is readily reversible when the drug is discontinued.

As with other diuretics used in the treatment of renal edema, hypokalemia may reduce responsiveness to ethacrynic acid and the use of salt poor aliments should be considered.

A number of drugs, including ethacrynic acid, have been shown to displace warfarin from plasma protein; a reduction in the usual anticoagulant dosage may be required in patients receiving both drugs.

Ethacrynic acid may increase the risk of gastric hemorrhage associated with concomitant therapy.

Laboratory Tests

Frequent serum electrolytes. Glucometer determinations should be performed early in therapy and periodically thereafter during active diuresis. Any electrolyte abnormalities should be corrected or the drug temporarily withdrawn.

Increases in blood glucose and alterations in glucose tolerance tests have been observed in patients receiving ethacrynic acid.

Drug Interactions

Lithium generally should not be given with diuretics because they reduce its renal clearance and increase a risk of lithium toxicity.

Read circulars for lithium preparations before use of such concomitant therapy.

Ethacrynic acid may increase the ototoxic potential of other drugs such as aminoglycosides and some cephalosporin antibiotics. Their concurrent use should be avoided.

A number of drugs, including ethacrynic acid, have been shown to displace warfarin from plasma protein; a reduction in the usual anticoagulant dosage may be required in patients receiving both drugs.

In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, ethacrynic acid and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a tumorigenic effect in a 2-year oral chronic toxicity study in rats at doses up to 45 times the human dose. Ethacrynic acid had no effect on fertility in a two-litter study in rats or in a two-generation study in mice at 10 times the human dose.

Pregnancy

Pregnancy Category B

Reproduction studies in the mouse and rabbit at doses up to 50 times the human dose showed no evidence of external abnormalities of the fetus due to ethacrynic acid.

In a two-litter study in the dog and rat, oral doses of 5 or 10 mg/kg/day (5% to 10 times the human dose), respectively, did not interfere with pregnancy or growth and development of the pups. Although there was reduction in the mean body weights of the fetuses in a teratogenic study in the rat at a dose level of 100 mg/kg (50 times the human dose), there was no effect on mortality or postnatal development. Functional and morphologic abnormalities were not observed.

There are, however, no adequate and well-controlled studies in pregnant women. Since animal reproductive studies are not always predictive of human response, ethacrynic acid should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ethacrynic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use

There are no well-controlled clinical trials in pediatric patients. The information on oral dosing in pediatric patients, other than infants, is supported by evidence from empiric use in this age group.

For information on oral use in pediatric patients, other than infants, see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

Safety and effectiveness of oral in infants have not been established (see CONTRAINDICATIONS).

Geriatric Use

Of the total number of subjects in clinical studies of ethacrynic acid/ethacrynic acid sodium, approximately 224 patients (25%) were 65 to 74 years of age, while approximately 100 patients (9%) were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. (See WARNINGS.)

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS.)

Gastrointestinal Reactions

Aureomycin, malaise, abdominal discomfort or pain, dyspepsia, nausea, vomiting, and diarrhea have occurred. These are most frequent with large doses or after one to three months of continuous therapy. In a few patients have had sudden onset of pruritis, watery diarrhea. Discontinue Ethacrynic Acid Tablets USP if diarrhea is severe and do not give it again. Gastrointestinal bleeding has occurred in some patients. Rarely, acute pancreatitis has been reported.

Metabolic

Hemolytic anemia has been rarely reported. Acute symmetric polyneuropathy with concomittance occurred in 2 urtic patients who received doses above those recommended. Polyneuropathy has been reported. Rarely, jaundice and abnormal liver function tests have been reported in seriously ill patients receiving multiple drug therapy, including Ethacrynic Acid Tablets USP.

Special Sensitivity

Agranulocytosis or severe neutropenia has been reported in a few critically ill patients also receiving agents known to produce this effect. Thrombocytopenia has been reported rarely. Henoch-Schönlein purpura has been reported rarely in patients with rheumatic heart disease receiving multiple drug therapy, including Ethacrynic Acid Tablets USP.

Ethacrynic Acid Tablets USP

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MISCELLANEOUS

Skin rash, hoarseness, hematuria.

OVERDOSAGE

Overdosage may lead to excessive diuresis with electrolyte depletion and dehydration.

In the event of overdosage, symptomatic and supportive measures should be employed. Enemas should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma, and hypotension by established procedure; if required, give oxygen or artificial respiration for respiratory impairment.

In the mouse, the oral LD50 of ethacrynic acid is 627 mg/kg and the intravenous LD50 of ethacrynate sodium is 173 mg/kg.

DOSAGE AND ADMINISTRATION

Dosage must be regulated carefully to prevent a more rapid or substantial loss of fluid or electrolyte than is indicated or necessary. The magnitude of diuresis and natriuresis is largely dependent on the degree of fluid accumulation present in the patient. Similarly, the extent of potassium excretion is determined in large measure by the presence and magnitude of aldosteronism.

Oral Use

Ethacrynic Acid Tablets USP are available for oral use as 25 mg tablets.

Dosage

To Initiate Diuresis

Dosage

In Adults

The smallest dose required to produce gradual weight loss (about 1 to 2 pounds per day) is recommended. Onset of diuresis usually occurs at 50 to 100 mg for adults. After diuresis has been achieved, the minimally effective dose (usually from 50 to 200 mg daily) may be given on a continuous or intermittent dosage schedule. Dosage adjustments are usually in 25 to 50 mg increments to avoid derangement of water and electrolyte excretion.

The patient should be weighed under standard conditions before and during the institution of diuretic therapy with this compound. Small alterations in dose should effectively prevent a massive diuretic response. The following schedule may be helpful in determining the smallest effective dose.

Day 1 — 50 mg once daily after a meal
Day 2 — 50 mg twice daily after meals, if necessary
Day 3 — 100 mg in the morning and 50 to 100 mg following the afternoon or evening meal, depending upon response to the morning dose.

A few patients may require initial and maintenance doses as high as 200 mg twice daily. These higher doses, which should be achieved gradually, are most often required in patients with severe, refractory edema.

In Pediatric Patients (excluding infants. see CONTRAINDICATIONS). The initial dose should be 25 mg. Careful stepwise increments in dosage of 25 mg should be made to achieve effective maintenance.

Maintenance Therapy

It is usually possible to reduce the dosage and frequency of administration once dry weight has been achieved.

Ethacrynic Acid Tablets USP may be given intermittently after an effective diuresis is obtained with the regimen outlined above.

Dosage may be on an alternate daily schedule or more prolonged periods of diuretic therapy may be interspersed with rest periods. Such an intermittent dosage schedule allows time for correction of any electrolyte imbalance and may provide a more efficient diuretic response.

The diuretic effect of this agent may give rise to retention of bicarbonate and a metabolic alkalosis. This may be corrected by giving chloride (ammonium chloride or arginine chloride). Ammonium chloride should not be given to cirrhotic patients.

Ethacrynic acid has additive effects when used with other diuretics. For example, a patient who is on maintenance dosage of an oral diuretic may require additional intermittent diuretic therapy, such as an organomercurial, for the maintenance of basal weight. The intermittent use of ethacrynic acid orally may eliminate the need for injections of organomercurials. Small doses of ethacrynic acid may be added to existing diuretic regimens to maintain basal weight. This drug may potentiate the action of carbonic anhydrase inhibitors, with augmentation of natriuresis and kaliuresis. Therefore, when adding ethacrynic acid, the initial dose and changes of dose should be in 25 mg increments, to avoid electrolyte depletions. Rarely, patients who failed to respond to ethacrynic acid have responded to older established agents.

While many patients do not require supplemental potassium, the use of potassium chloride or potassium-sparing agents, or both, during treatment with ethacrynic acid is advisable, especially in cirrhotic or nephritic patients and in patients receiving digitalis.

Salt liberalization usually prevents the development of hyponatremia and hypochloremia. During treatment with ethacrynic acid, salt may be liberalized in a greater extent than with other diuretics. Cirrhotic patients, however, usually require at least moderate salt restriction concomitant with diuretic therapy.

Intravenous Use

Ethacrynate sodium is for intravenous use when oral intake is impractical or in urgent conditions, such as acute pulmonary edema.

HOW SUPPLIED

Ethacrynic Acid Tablets USP, 25 mg, are white, capsule shaped, scored tablets, debossed with “4” on left side of the score and “05” on the right side of the score on one side and plain on the other side. They are supplied as follows:

NDC 42799-405-01 in bottles of 100.

Storage

Store in a tightly closed container at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

Manufactured for:

Edenbridge Pharmaceuticals, LLC

Parsippany, NJ 07054

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