Ethacrynic Acid Tablets USP

Ethacrynic acid is a potent diuretic which, if given in excessive amounts, may lead to profound diuresis with water and electrolyte depletion. 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 unsaturated ketone derivative of an anhydric acid. It is designated chemically as (3,3-dichloro-2-hydroxy-1-propyl)acetic acid, and has a molecular weight of 303.4. Ethacrynic acid is a white, or practically white, crystalline powder, very slightly soluble in water, but soluble in most organic solvents such as alcohols, chloroform, and benzene. Its empirical formula is C_{13}H_{12}Cl_{2}O_{4} and its structural formula is:

\[
\text{CH}_3 \text{CH}_2 \text{COOH} \quad \text{Cl} \quad \text{Cl} \quad \text{CH}_3 \text{CH}_2 \text{COOH}
\]

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

USP Dissolution Test is pending.

CLINICAL PHARMACOLOGY

Pharmacodynamics and Metabolism

Ethacrynic acid acts on the ascending limb of the loop of Henle and on the proximal and distal tubules. Urinary output is usually dose dependent and related to the magnitude of fluid accumulation. Water and 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 diuretic agents. 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, chloride excretion declines, 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 excess amounts of potassium and hydrogen ions are excreted. Shift of potassium is rapid, usually in 30-60 minutes after an oral dose of ethacrynic acid tablets. After oral use, diuresis peaks in about 2 hours and lasts about 6 hours.

The sulffhydryl binding propensity of ethacrynic acid differs somewhat from that of the organomercurials. Its empirical formula is C_{13}H_{12}Cl_{2}O_{4} and its structural formula is:

\[
\text{CH}_3 \text{CH}_2 \text{COOH} \quad \text{Cl} \quad \text{Cl} \quad \text{CH}_3 \text{CH}_2 \text{COOH}
\]

The sulfhydryl binding propensity of ethacrynic acid differs somewhat from that of the organomercurials. Its empirical formula is C_{13}H_{12}Cl_{2}O_{4} and its structural formula is:

\[
\text{CH}_3 \text{CH}_2 \text{COOH} \quad \text{Cl} \quad \text{Cl} \quad \text{CH}_3 \text{CH}_2 \text{COOH}
\]

CONTRAINDICATIONS

- All diuretics, including ethacrynic acid, are contraindicated in anuria. If increasing electrolyte imbalance, azotemia, and/or oliguria occur during treatment of severe, progressive renal disease, the diuretic should be discontinued.
- In a few patients this diuretic has produced severe, watery diarrhea. If this occurs, it should be discontinued and not used again. Until further experience in infants is accumulated, therapy with oral ethacrynic acid is contraindicated. Hypersensitivity to any component of this product.

WARNINGS

The effects of ethacrynic acid on electrolytes are related to its renal pharmacologic activity and are dose dependent. The possibility of profound electrolyte and water loss may be avoided by weighing the patient throughout the treatment period, by careful adjustment of dosage, by initiating treatment with small doses, and by using the drug on an intermittent schedule when possible. When excessive diuresis occurs, the drug should be withdrawn rapidly. When excessive electrolyte loss occurs, the dosage should be reduced or the drug temporarily withdrawn.

Initiation of diuretic therapy with ethacrynic acid in the cirrhotic patient with ascites is best carried out in the hospital. When maintenance therapy has been established, the individual can be satisfactorily followed in an outpatient setting. Ethacrynic acid should be given with caution to patients with advanced cirrhosis of the liver, particularly those with a history of previous episodes of electrolyte imbalance or hepatic encephalopathy. Like other diuretics it may precipitate hepatic coma and death.

Since ethacrynic acid, as evidenced by rapid and excessive weight loss, may induce an acute hypertensive episode. In elderly cardiac patients, rapid contraction of plasma volume and the resultant hemoconcentration should be avoided to prevent the development of thromboembolic episodes, such as cerebral or peripheral thromboses and pulmonary emboli which may be fatal. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving anticoagulants.

A number of possible drug-related deaths have occurred in critically ill patients refractory to other diuretics. These generally have fallen into two categories: (1) patients with severe myocardial disease who have been receiving diuretics and possibly developed acute hypokalemia with fatal arrhythmia; (2) patients with severe azotemia, with diabetic coma or acidosis, with hyperkalemia, who were in electrolyte imbalance and died because of intoxication of the electrolyte defect.

Diabetes, tumors, and variety with a sense of fullness in the ears have occurred, most frequently in patients with severe renal failure. These symptoms have been associated most often with intravenous administration and with doses in excess of those recommended. The deafness has usually been reversible and of short duration (one to 24 hours). However, in some patients the hearing loss has been permanent. A number of these patients were also receiving drugs known to be ototoxins. Ethacrynic acid may increase the ototoxic potential of other drugs (see PRECAUTIONS, Drug Interactions).

When a metabolic alkalosis may be anticipated, e.g., in cirrhosis with ascites, the use of potassium chloride or a potassium-sparing agent before and during therapy with ethacrynic acid may mitigate or prevent the hypokalemia.

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

Oral contraceptive may occur in patients receiving other antihypertensive agents when given ethacrynic acid.

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. A transient increase in serum urea nitrogen may occur. Usually, this is readily reversible when the drug is discontinued.

As with other diuretics used in the treatment of renal edema, hypotension may reduce responsiveness to ethacrynic acid and the use of salt-poor albumin 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.

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, ethacrynic acid and non-steroidal anti-inflammatories 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-week oral chronic toxicity study in rats at doses up to 45 times the human dose. Ethacrynic acid and the isomeric sodium salt had an effect on fertility in a two-generation study in mice at 10 times the human dose.

Pregnancy

Reproduction studies in the mouse and rabbit at doses up to 50 times the human dose, respectively, did not interfere with pregnancy or with 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 fetal mortality or postnatal development. Functional and morphologic abnormalities were not observed.

There, however, are no adequate and well-controlled studies in pregnant women. Since animal reproduction 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.

Pediatric 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 use in this age group.

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

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

Geriatric Use

The total number of subjects in clinical studies of ethacrynic acid/sodium/ethacrynic acid, approximately 224 patients (21%) 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 patients, 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.)

ADVERSE REACTIONS

Gastrointestinal

Anorexia, malaise, abdominal discomfort or pain, epigastritis, nausea, vomiting, and diarrhea have occurred. These are more frequent with large doses or after one or two months of continuous therapy. A few patients have had sudden onset of proptosis, 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

Reversible hyperuricemia and acute gout have been reported. Acute symptomatic hyperuricemia with concomitant occurrence in two uremic patients who received doses above those recommended. Hyperuricemia has been reported. Rarely, jaundice and abnormal liver function tests have been reported in elderly infants receiving multiple drug therapy, including Ethacrynic Acid Tablets USP.

Hematologic

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.

Special Senses (see WARNINGS)

Deafness, tinnitus and vertigo with a sense of fullness in the ears, and blurred vision have occurred.

Central Nervous System

Headache, fatigue, apprehension, confusion.

Ethacrynic Acid Tablets USP
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.

**Skin rash, fever, chills, 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. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma, and hypotension by established procedures. 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 175 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

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.

In Adults

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

(including 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 chlorothiazide 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 depletion. 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 nephrotic patients and in patients receiving digitalis.

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

**Intravenous Use**

Ethacrynic acid 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 “44” 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
877-381-3336
552201

Rev. 05/2021