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CLASSES

Antidotes, Systemic
Chelating Agents

DEA CLASS

Rx

DESCRIPTION

Oral copper chelating agent for the treatment of Wilson's disease.

COMMON BRAND NAMES

Syprine

HOW SUPPLIED

Syprine Oral Cap: 250mg

DOSAGE & INDICATIONS

For the treatment of Wilson's disease (hepatolenticular degeneration).

In patients intolerant to penicillamine.

NOTE: Determination of free copper in the serum is the most reliable index for monitoring treatment. The difference between quantitatively determined total copper and ceruloplasmin-copper is the serum free copper concentration. Adequately treated patients usually have less than 10 mcg of free copper per dl of serum.

NOTE: Every 6—12 months, monitor response with a 24-hour urinary copper analysis. Collect urine in copper-free glassware. If 0.5—1 mg of copper is present in a 24-hour urine collection, the patient on a low copper diet should be in the desired negative copper balance state.

NOTE: According to the guidelines for Wilson's disease developed by the American Association for the Study of Liver Diseases, monitor serum copper concentrations, ceruloplasmin concentrations, liver biochemistries, and international normalized ratio, and conduct a physical examination on a routine basis. Measure 24-hour urinary excretion of copper while on medication at least on a yearly basis. More frequent determination may be needed when compliance is questioned and when medication dosage is adjusted. Obtain a complete blood count with differential and urinalysis on a regular basis.

Oral dosage

Adults and Adolescents

Initially, 750—1250 mg PO per day, divided into 2—4 doses. Increase dosage only if clinical response is inadequate or if free serum copper concentration is persistently above 20 mcg/dl. Determine the optimal long-term maintenance dosage at 6—12 month intervals. Maximum daily dose is 2000 mg.

Children

Initially, 500—750 mg PO per day in 2—4 divided doses. Increase dosage only if clinical response is inadequate or if free serum copper concentration is persistently above 20 mcg/dl. Determine the optimal long-term maintenance dosage at 6—12 month intervals. Maximum daily dose is 1500 mg.

In previously untreated patients with liver failure†.

Oral dosage

Adults

1000 mg PO daily plus zinc 150 mg PO daily for at least 4 months, then zinc monotherapy, led to survival and improved liver function in all 8 patients with an initial Child-Turcotte-Pugh score indicative of liver transplantation candidacy. One patient had a Nazer score > 6, which is predictive of nonsurvival with penicillamine. Marked reduction in liver fibrosis was noted in the 3 patients with baseline and follow-up (53 months to 10 years) biopsy data.

In patients with a neurologic presentation†.

NOTE: Seven of the 23 patients had not been treated for more than 4 weeks with penicillamine, and 1 patient had received 7 days of trientine.

Oral dosage

Adults

500 mg PO twice daily plus zinc 50 mg PO twice daily for 8 weeks, then zinc 50 mg PO three times daily as monotherapy, led to an absence of neurologic deterioration in 17 of 23 patients. Three of the 6 patients with neurologic deterioration died, and 2 patients had severe, permanent neurologic impairment.

In combination with penicillamine†.

NOTE: Trientine and penicillamine administration were separated by 1 hour.

Oral dosage

Adults

2500 mg PO daily plus penicillamine 100 mg PO daily and zinc led to an increased urinary copper excretion in a patient with liver dysfunction who developed leukopenia while on a higher penicillamine dose. The average daily urinary copper excretion was 2.04 mg on penicillamine 1000—1400 mg/day, 0.192 mg on trientine 2500 mg/day, and 0.428 mg on penicillamine 100 mg/day and trientine 2500 mg/day.

MAXIMUM DOSAGE

Adults

2000 mg/day PO.

Elderly

2000 mg/day PO.

Adolescents

2000 mg/day PO.

Children

1500 mg/day PO.

DOSING CONSIDERATIONS

Hepatic Impairment

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Renal Impairment

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

ADMINISTRATION

NOTE: Take the patient's temperature every night for the first month of treatment. Fever or skin eruption may warrant trientine discontinuation (see Adverse Reactions).

Oral Administration

Oral Solid Formulations

Trientine capsules are to be swallowed intact with water either 1 hour before food or 2 hours after food and at least 1 hour apart from milk or other drug ingestion.
Do not crush, chew, or break the capsules. Promptly wash with water any exposure site to capsule contents.

STORAGE

Syprine:
- Store between 36 to 46 degrees F

CONTRAINDICATIONS / PRECAUTIONS

General Information

Trientine should not be used in patients with a prior history of trientine hydrochloride hypersensitivity (see Adverse Reactions).

Pregnancy

Trientine is a FDA pregnancy risk category C drug. No adequate and well-controlled studies in pregnant women have been conducted, but teratogenicity in animals has been noted. Trientine hydrochloride was teratogenic in rats at doses similar to the human dose. The frequencies of both resorptions and fetal abnormalities, including hemorrhage and edema, increased while fetal copper concentrations decreased when trientine hydrochloride was given in the maternal diets of rats. Outcome data are available for 19 pregnancies of women who used trientine. A woman with presymptomatic Wilson's disease was treated with trientine 1000 mg daily during her pregnancy. She delivered a healthy, full-term baby, and her liver function was unchanged during and after the pregnancy. Further, 7 healthy infants were born to 5 other women. Of 11 other pregnancies in 7 women, 8 healthy babies, 1 miscarriage at 14 weeks, 1 therapeutic abortion, and 1 premature child with a chromosome defect (isochromosome X) occurred. The manufacturer recommends trientine use in a pregnant woman only if the potential benefit justifies the potential risk to the fetus. However, treatment continuation during pregnancy with trientine dosage reduction to the minimum amount necessary is recommended in the guidelines for Wilson's disease developed by the American Association for the Study of Liver Diseases. Therapy interruption has resulted in fulminant hepatic failure.

Breast-feeding

Excretion of trientine into breast milk is not known. Administer trientine with caution to women who are breast-feeding their infants. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-

feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Children

The safety and efficacy of trientine in children have not been established. However, trientine has been used in children as young as 6 years of age (see Dosage).

Gelatin hypersensitivity

Trientine may be inappropriate for patients with gelatin hypersensitivity, as the capsules contain gelatin.

Anemia, hemochromatosis, iron-deficiency anemia, sideroblastic anemia

Use trientine cautiously in patients with hemochromatosis or anemia. Trientine may impair iron metabolism and transport and may cause sideroblastic anemia (see Adverse Reactions). Iron depletion for hemochromatosis or iron repletion for iron-deficiency anemia may be needed. Dose reduction may help sideroblastic anemia.

Geriatric

Clinical studies of trientine did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Cautious use of trientine in geriatric patients may be warranted.

Biliary cirrhosis

Trientine is not indicated for the treatment of biliary cirrhosis. Of 4 patients with primary biliary cirrhosis who took trientine 1200 mg daily for 6 months, 2 developed gastrointestinal (GI) side effects, 1 developed GI side effects and a skin rash, and 1 developed acute rhabdomyolysis within 48 hours of receiving the first trientine dose. Due to the side effects, trientine was discontinued in all 4 patients. Although the data are only from 4 patients, all 4 had adverse reactions. The rate of adverse events appears to be higher than the rate observed in patients who received trientine for Wilson's disease (see Adverse Reactions).

ADVERSE REACTIONS

Severe

sideroblastic anemia / Delayed / Incidence not known
lupus-like symptoms / Delayed / Incidence not known

Moderate

anemia / Delayed / Incidence not known
hemosiderosis / Delayed / Incidence not known
zinc deficiency / Delayed / Incidence not known
thrombocytopenia / Delayed / Incidence not known
contact dermatitis / Delayed / Incidence not known
colitis / Delayed / Incidence not known

Mild

rash (unspecified) / Early / Incidence not known
arthralgia / Delayed / Incidence not known
pyrosis (heartburn) / Early / Incidence not known
abdominal pain / Early / Incidence not known
diarrhea / Early / Incidence not known

DRUG INTERACTIONS

Food: Take trientine either 1 hour before food or 2 hours after food and at least 1 hour apart from milk in order to minimize the likelihood of trientine inactivation by metal binding in the gastrointestinal tract.
Minerals: If possible, avoid mineral supplement administration to a patient taking trientine. Mineral supplements (minerals, multimineral formulas, multivitamin and multimineral with fluoride and iron formulas, multivitamin and multimineral with iron formulas, multivitamin with fluoride and iron formulas, multivitamin with iron formulas, multivitamin with fluoride formulas, and vitamin and mineral formulas) may block trientine absorption. If iron administration is necessary, give iron salts or polysaccharide-iron complex and trientine at least 2 hours apart from one another. Take trientine at least 1 hour apart from any other drug ingestion in order to minimize the likelihood of trientine inactivation by metal binding in the gastrointestinal tract.

PREGNANCY AND LACTATION

Pregnancy

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MECHANISM OF ACTION

Mechanism of Action: Trientine hydrochloride is an oral chelator that is structurally unique from other known chelating agents. Trientine chelates heavy metals including copper, iron, and zinc and forms stable complexes that can be excreted by the kidneys. Urinary copper, iron, and zinc concentrations all increased in parallel with trientine excretion. Copper is chelated by forming a stable complex with the 4 constituent nitrogens in a planar ring. Cupriuresis is dose-dependent. Both trientine and a metabolite acetyltrien chelate copper, although the chelating ability of acetyltrien is lower. In addition to increased urinary copper excretion, trientine decreases intestinal copper absorption.

PHARMACOKINETICS

Trientine is administered orally.

Both trientine and two metabolites, 1-N-acetyltriethylenetetramine (or acetyltrien) and 1-N-10-N-diacetyltriethylenetetramine, are excreted in the urine. The amount of trientine excreted in the urine is about 1% of the administered dose, and the amount of the acetyltrien metabolite excreted in the urine is about 8% of the dose. Most of the parent drug occurs in the urine over the first 6 hours after drug receipt whereas acetyltrien excretion occurs over at least 26 hours.

Among patients who got penicillamine for at least 1 year and had a basal copper excretion rate of 17—19 mcg over 6 hours, the mean 6-hour excretion rate of copper was 234 mcg after a single 1200 mg trientine dose. In contrast, the mean 6-hour excretion rate of copper was 320 mcg after a single 500 mg penicillamine dose. Among patients who had not previously received a chelating agent, the mean basal excretion rate of copper over 6 hours was 68—71 mcg, and the rate after a single trientine dose was 1326 mcg and after a single penicillamine dose was 1074 mcg.

After a single trientine 1200 mg dose to 8 patients who were basically untreated, the plasma copper concentration rose slightly for the first few hours after a dose before falling by 6 hours after drug administration. After trientine 1200—2400 mg/day for 43 months, the baseline plasma copper concentration was much lower, and the concentration after a single 1200 mg dose fell slightly over 6 hours. Trientine still increased copper clearance after 43 months of use.

Oral Route

The bioavailability of trientine is approximately 6—18%; it is taken on an empty stomach in order to minimize the likelihood of inactivation by metal binding in the gastrointestinal tract. Food, milk, drugs, and mineral supplements could form a complex with trientine in the GI tract, which may prevent trientine absorption (see Drug Interactions).