PRODUCT MONOGRAPH

THEOLAIR

(theophylline anhydrous)

Theolair Liquid 80 mg/15 mL

Bronchodilator

Manufactured by:
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Date of Revision:
February 13th, 2013

Address Updated:
September 4, 2014

Control No.: 162338

NAME OF DRUG

THEOLAIR (theophylline anhydrous)

Theolair Liquid (80 mg/15 mL)

THERAPEUTIC CLASSIFICATION

Bronchodilator

DESCRIPTION

Each 15 mL of citrus-berry flavoured, non-alcoholic liquid contains 80 mg of theophylline.

ACTION

Theophylline is a xanthine structurally related to theobromine and caffeine. Theophylline relaxes certain smooth muscles, including those of the bronchi, promotes dilation of blood vessels, other than cerebral vessels, increases cardiac output and acts as a mild diuretic. Theophylline stimulates central nervous system, cardiac muscles, skeletal muscles and causes an increase in gastric secretion.

INDICATION AND CLINICAL USES

Theolair is indicated for the symptomatic treatment of reversible bronchoconstriction associated with bronchial asthma, chronic obstructive pulmonary emphysema, chronic bronchitis and related bronchospastic disorders.

CONTRAINDICATIONS

Hypersensitivity to other theophylline derivatives of xanthines; peptic ulcer, in coronary artery disease when in the physician’s judgement myocardial stimulation might prove harmful.

WARNINGS

Theophylline has a relatively narrow margin of safety and patients should be carefully observed for signs of toxicity.

Use with caution in the presence of severe hypertension and other cardiovascular diseases.

Theolair Liquid is not recommended for children under 5 years of age. Children are very sensitive to theophylline and the margin of safety is small. Care should be taken to see that children receiving oral theophylline are not also being administered drug by the rectal route.

PRECAUTIONS

There is a marked variation in blood levels achieved in different patients given the same dose of theophylline. This may lead to serious side effects in some patients. This variability in blood levels is probably due to differences in the rate of metabolism. Therefore, it is advisable to individualize the dose regimens. The possibility of overdose should be considered in all patients receiving doses considered to be conventional. Overdose of theophylline may cause peripheral vascular collapse and fatalities have been reported.

The equivalent content of anhydrous theophylline is the active ingredient that determines blood concentration and clinical response. If a change in theophylline product is made and it involves a change in anhydrous theophylline equivalence, the physician should adjust the patient's dose accordingly in order to avoid overdosage or underdosage.

The incident of toxicity increases at serum theophylline levels greater than 15 mcg/mL and levels about 20 mcg/mL are usually quite toxic in most patients (adults).

Caution is necessary in patients with severe pulmonary or cardiovascular disease and in patients with hepatic dysfunction as metabolism of theophylline may be impaired in these patients leading to the possibility of toxic blood levels when on a fixed dosage regimen.

Theophylline should also be used with caution in elderly patients, and patients with severe hypoxemia, uncompensated cardiac failure, cor pulmonale, or hyperthyroidism.

Theophylline may also worsen pre-existing arrhythmias.

Caution should be exercised when theophylline is used concurrently with sympathomimetic amines, since the incidence and severity of adverse reactions may be increased. The concurrent administration of other theophylline derivatives along with Theolair is not recommended. Other xanthines should not be administered within 6 hours of Theolair. Theophylline may cause an increase in urine catecholamines and plasma free fatty acids.

Xanthines have been shown to be nephrotoxic with prolonged use at high dosage. Coincident toxicity should therefore be borne in mind, when other potentially nephrotoxic drugs are administered concurrently.

USE IN PREGNANCY

Theophylline crosses the placental barrier and also passes freely into breast milk, where concentrations are similar to plasma levels. Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. Therefore, use of theophylline in pregnant women should be balanced against the risks of uncontrolled asthma.

DRUG INTERACTIONS

Theophylline pharmacokinetics are altered by the concurrent use of various drugs as listed below:

Terbinafine

Single dose terbinafine did not significantly alter the pharmacokinetics of theophylline in a randomized, open-label, single-dose, three-period crossover study, in healthy male and female adult subjects (n = 18) treated orally with 250 mg terbinafine, 375 mg theophylline, and 250 mg terbinafine plus 375 mg theophylline.

Multiple dose terbinafine increased the AUC and half-life of theophylline by 16% and 24%, respectfully, and decreased the oral clearance of theophylline by 14%, in a randomized, open-label, two-period crossover study in healthy male and female adult subjects (n = 12) treated orally with a single dose of 5 mg/kg theophylline alone (mean 345 mg, range 307 to 397 mg) and 2 hours after the last of 4 daily doses of 250 mg terbinafine.

Concurrent use of theophylline influences the actions of certain drugs:

Terbinafine

Theophylline increased the C_{max} and AUC of terbinafine by 25% each, and decreased the oral clearance of terbinafine by 24% in a randomized, open-label, single-dose, three-period crossover study, in healthy male and female adult subjects (n = 18) treated orally with 250 mg terbinafine, 375 mg theophylline, and 250 mg terbinafine plus 375 mg theophylline.

Theophylline potentiates the diuretic action of diuretics, and the cardiac effect of digitalis glycosides. Cimetidine, influenza vaccine and propranolol may increase the effect of theophylline by decreasing theophylline clearance.

Smoking may decrease theophylline effect by increasing clearance.

Theophylline has been shown to increase the ratio of clearance of lithium/creatinine and thus may decrease serum lithium to ineffective levels.

Erythromycin preparations may cause an increase in serum theophylline to toxic levels. Serum theophylline levels should be carefully monitored in all patients who are on high doses of theophylline and who use erythromycin concurrently.

Acidifying agents, by increasing urinary excretion of weak bases like the xanthines, inhibit theophylline action.

Alkalinizing agents, by decreasing urinary excretion of weak bases like the xanthines, potentiate theophylline action.

The methylxanthines increase blood levels of prothrombin and fibrinogen, shorten the prothrombin time and thus antagonize the effects of coumarin anticoagulants.

Combined use of several xanthines may cause excessive CNS stimulation. Xanthines may antagonize the antihyperuricemic action of allopurinol.

Xanthines antagonize the uricosuric action of probenecid and sulfinpyrazone and uricosuric activity of pyrazalon derivatives.

Combined use of xanthines with sympathomimetics may cause excessive CNS stimulation.

ADVERSE REACTIONS

The most common adverse reactions are nausea, vomiting, epigastric pain, headache and tremor. These are usually early signs of toxicity; however, with high doses, ventricular arrhythmias or seizures may be the first signs to appear.

Adverse reactions reported with theophylline preparations include:

1. **Gastroinestinal**

   Theophylline frequently causes gastric irritation, nausea, vomiting and epigastric pain, particularly when given on an empty stomach. In addition, the patient may experience upper abdominal discomfort, anorexia, diarrhea, reactivation of peptic ulcer and intestinal bleeding. These gastrointestinal effects may be minimized by administration of Theolair Liquid with milk or meals. The use of antacids concurrent with theophylline does not interfere with drug absorption.

2. **Central Nervous System**

   Central nervous system stimulation, headache, excitement, restlessness, light headedness, irritability, insomnia, reflex hyperexcitability, tremors, muscle twitching and clonic and tonic convulsions.

3. **Cardiovascular System**

   Palpitation, hypotension, circulatory failure, tachycardia, flushing, extrasystoles, life threatening ventricular arrhythmias.

4. **Respiratory**

   Tachypnea.

5. **Renal**

   Albuminuria, diuresis and hematuria.

6. **Others**

   Urticaria, generalized pruritis, angioneurotic edema, contact dermatitis, hyperglycemia and inappropriate ADH syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptomatology

1. Early symptoms include wakefulness, restlessness, mild excitement or irritability alternating with drowsiness, tinnitus, flashes of light, rapid pulse and extrasystoles.
2. Anorexia, nausea, emesis usually begin early.
3. Fever, increased vomiting, diuresis, dehydration, extreme thirst occurs as toxicity increases.
4. Eventually bloody, syrup-like or "coffee ground" vomitus, tremors, delirium, tonic extensor spasm interrupted by clonic convulsions, apathy, stupor and coma occur.
5. Cardiovascular and respiratory collapse, leading to shock, cyanosis and death can result from theophylline overdosage.

Treatment

A. If potential oral overdose is established and seizures have not occurred:

1. Induce vomiting.
2. Administer a cathartic (this is particularly important if sustained-release preparations have been taken).
3. Administer activated charcoal.

B. If patient is having a seizure:

1. Establish an airway.
2. Administer O_2.
3. Treat the seizure with intravenous diazepam, 0.1 to 0.3 mg/kg up to 10 mg.
4. Monitor vital signs, maintain blood pressure and provide adequate hydration.

C. Post-Seizure Coma:

1. Maintain airway and oxygenation.

2. If a result of oral medication, follow above recommendations to prevent absorption of drug, but intubation and lavage will have to be performed instead of inducing emesis, and the cathartic and charcoal will need to be introduced via a large bore gastric lavage tube.

3. Continue to provide full supportive care and adequate hydration while waiting for drug to be metabolized. In general, the drug is metabolized sufficiently rapidly so as not to warrant consideration of dialysis.

DOSAGE AND ADMINISTRATION

Individual requirements may vary considerably and the physician should be prepared to adjust the patient's dose accordingly.

Because of the large inter-subject variability, monitoring of plasma theophylline concentrations is extremely important, especially in the initial stages of therapy. The optimum serum theophylline concentration is in the range of 8 – 20 mcg/mL depending on the severity of the condition. The incidence of adverse effects increases at levels in excess of 15 mcg/mL. In cases where it is not possible to monitor serum theophylline, patients should be closely observed for signs of toxicity (see PRECAUTIONS).

Adults: Initial dose of 4 – 5 tablespoonfuls (60 – 75 mL or 320 – 400 mg theophylline). Subsequent doses should be titrated and given every 6 hours or as required based on the patient's clinical response and or serum theophylline level which should be in the 10 – 20 mcg/mL range. Usually the dose should not exceed about 1000 mg theophylline per 24 hours.

Children Over 5 Years of Age: Initial dose of 4 – 5 mg/kg with subsequent doses being titrated and given every 6 hours or as required by the patient's clinical response and for serum theophylline levels which should be in the 10 – 20 mcg/mL range. Generally, the total dose in 24 hours should not exceed 15 mg theophylline/kg.

Maintenance Therapy:

Adults: Initially 30 – 45 mL (160 – 240 mg theophylline) may be given followed by 30 – 45 mL every 6 – 8 hours. Total daily dose should be individually titrated based on the patient's clinical response and for serum theophylline concentration which should be in the range of 8 – 20 mcg/mL. The total daily dose will usually be 480 – 960 mg theophylline (or 90 -180 mL) per 24 hours.

Children Over 5 Years of Age: The initial dose is usually 3 mg/kg with subsequent doses of 3 – 4 mg/kg administered every 6 – 8 hours. The total daily dose should be titrated based on the patient's clinical response for serum theophylline levels which should be in the range of 8 – 20 mcg/mL. Usually the dose will be between 9 and 12 mg/kg theophylline per 24 hours.

It is recommended that Theolair Liquid be taken prior to meals or with milk.

DOSAGE FORM AND AVAILABILITY

Theolair is available as a citrus-berry flavoured non-alcoholic liquid (50% sucrose w/v) containing 80 mg theophylline per 15 mL (one tablespoonful), in 500 mL bottles.

Store at controlled room temperature. 15 – 30°C (59 – 86°F).