

Choledyl® SA 

Erf Canada Inc.

Oxtriphylline

Bronchodilator

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Pharmacology: Oxtriphylline is the theophylline salt of choline and contains 64% theophylline with the properties attributed to it. Choledyl SA is a sustained release tablet which produces peak blood levels of theophylline (44 to 67 $\mu\text{mol/L}$ [8 to 12 mg/mL]) between 2 and 4 hours. Once the steady-state level has been reached, the therapeutic blood levels persist for 12 hours.

Indications: For maintenance therapy in adult patients for the symptomatic relief of reversible bronchoconstriction associated with bronchial asthma, pulmonary emphysema, chronic bronchitis and related bronchospastic disorders.

Contraindications: In those patients who have shown hypersensitivity to it or to other theophylline derivatives; in coronary artery disease when in the physician's judgment myocardial stimulation might prove harmful. It should not be used in patients with peptic ulcer, or in patients with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

Warnings: Children are very sensitive to xanthines: the margin of safety above the therapeutic dose is small. The use of Choledyl SA tablets in children is not recommended at present as dose schedules for this age group have not been established. Use with caution in the presence of severe hypertension and other cardiovascular diseases.

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. Ideally all individuals should have serum theophylline levels measured and a theophylline half-life calculated which would enable doses and dosing regimens to be tailored to each patient to maintain a therapeutic level, to ensure optimal clinical response and to avoid toxicity. Concurrent tea, coffee or cocoa administration may affect assay results. The possibility of overdose must be considered in all patients and especially when large doses are used, because fatalities have been reported with theophylline-containing products. Overdoses of oxtriphylline may cause peripheral vascular collapse.

Caution should be exercised when theophylline is used concurrently with sympathomimetic amines or other xanthines, as such use may increase the incidence and severity of adverse reactions. Choledyl SA should not be given within 12 hours of the ingestion of other xanthines. Special 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 on fixed dosage regimen.

Theophylline may cause an elevation of serum uric acid, urine catecholamines and plasma free fatty acids.

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, the use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma.

Lactation: There are insufficient adequate and well-controlled studies in lactating women. Therefore, oxtriphylline should be used in nursing mothers only if clearly needed.

Theophylline is found in breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, 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.

Laboratory Tests: Serum levels should be monitored periodically to determine the theophylline level associated with observed clinical response and as the method for predicting toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, 1 to 2 hours after administration for nonsustained release products. It is important that the patient will not have missed or taken additional doses during the previous 48 hours and that dosing intervals will have been reasonably equally spaced.

Dosage adjustment based on serum theophylline measurements when these instructions have not been followed may result in dosage modifications that present risk of toxicity to the patient.

Drug Interactions: Synergism with ephedrine has been documented and may occur with other sympathomimetic amines. Theophylline may cause increased excretion of lithium carbonate. Theophylline antagonizes the effect of propranolol. Theophylline potentiates the effects of diuretics and the cardiac effect of digitalis glycosides. The concomitant use of morphine, curare may antagonize the effect of theophylline since these drugs stimulate histamine release and thereby induce bronchoconstriction.

Cigarette smoking and phenobarbital shorten, while alcohol consumption increases the half-life of theophylline.

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.

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.

Combined use of several xanthines may cause excessive CNS stimulation.

Toxic reactions as a result of significant elevations of serum theophylline levels have been observed in patients after initiation of treatment with erythromycin preparations. Particular attention should therefore be directed toward monitoring the serum theophylline levels in such patients.

The methylxanthines increase blood levels of prothrombin and fibrinogen, shorten the

prothrombin time and thus antagonize the effects of coumarin anticoagulants.

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

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

Cimetidine, erythromycin, influenza vaccine and propranolol may increase the effect of theophylline by decreasing theophylline clearance.

Allopurinol, antibiotics (fluoroquinolones, clarithromycin, lincomycin) mexiletine, oral contraceptives, thiabendazole ticlopidine and verapamil are associated with increased serum theophylline levels.

Isoproterenol, phenytoin, rifampin and sulfinpyrazone have been associated with decreased serum theophylline levels. The following drug interactions with theophylline have also been reported: Adenosine: decreased adenosine effect; furosemide: increased furosemide diuresis; hexamethonium: decreased hexamethonium-induced chronotropic effect; reserpine: reserpine-induced tachycardia; chlordiazepoxide: chlordiazepoxide-induced fatty acid mobilization. Drug-laboratory Test Interactions : Currently available analytical methods, including high pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Theophylline and other methylxanthines are known to produce a false elevation in the automated uric acid levels when measured by the Bittner adapted method.

Adverse Effects: The most common adverse reactions are gastric irritation, nausea, vomiting, epigastric pain, 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:

Gastrointestinal: nausea, vomiting, epigastric pain, anorexia, reactivation of peptic ulcers, abdominal cramps, diarrhea, intestinal bleeding and hematemesis.

CNS: headache, nervousness, insomnia, dizziness, lightheadedness, irritability, restlessness, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular System: palpitation, hypotension, circulatory failure, tachycardia, extrasystole, life-threatening ventricular arrhythmias, flushing.

Urinary Tract: albuminuria, diuresis, hematuria.

Skin: urticaria, generalized pruritus, angioneurotic edema, contact dermatitis, rash and alopecia.

Blood: bone marrow suppression, leukopenia, thrombocytopenia and hemorrhagic diathesis.

Others: tachypnea, hyperglycemia and inappropriate ADH syndrome.

Overdose: Symptoms: The most consistent reactions observed with toxic overdoses of xanthine derivatives are: Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

CNS: In addition to those cited above, the patient may exhibit hyperreflexia, fasciculations and clonic and tonic convulsions. These are especially prone to occur in cases of overdosage in infants and small children.

Cardiovascular: In addition to those outlined above, marked hypotension and circulatory failure may be manifest.

Respiratory: Tachypnea and respiratory arrest may occur.

Renal: Albuminuria and microhematuria may occur. Increased excretion of renal tubular cells

has been observed.

General systemic effects: syncope, collapse, fever and dehydration.

Management: It is suggested that the management principles (consistent with the clinical status of the patient when first seen) outlined below be instituted.

Treatment: When potential oral overdose is established and seizure has not occurred:

a) If patient is alert and seen within the early hours after ingestion, induction of emesis may be of value. Gastric lavage may be of greatest value when performed within 1 hour of ingestion. b) Administer a cathartic. Sorbitol solution is reported to be of value. c) Administer repeated doses of activated charcoal and monitor theophylline serum levels. d) Prophylactic administration of phenobarbital has been shown to increase the seizure threshold in laboratory animals and administration of this drug can be considered.

If patient presents with a seizure: a) Establish an airway. b) Administer oxygen. c) Treat the seizure with i.v. diazepam, according to established procedure. If seizures cannot be controlled, the use of general anesthesia should be considered. d) Monitor vital signs, maintain blood pressure and provide adequate hydration.

If postseizure coma is present: a) Maintain airway and oxygenation. b) If coma is a result of oral medication, follow above recommendations to prevent absorption of the 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. c) Continue to provide full supportive care and adequate hydration until the drug is metabolized. In general, drug metabolism is sufficiently rapid so as not to warrant dialysis. If repeated oral activated charcoal is ineffective (as noted by stable or rising serum levels) charcoal hemoperfusion may be indicated.

Note: It is particularly important to administer a cathartic when the sustained release preparation (Cholelyl SA), has been taken.

Dosage: Adults: The average recommended initial adult dose is one 400 or 600 mg tablet every 12 hours. If desired response is not achieved, and there are no adverse reactions, the dose may be increased by 3 to 4 mg/kg oxtriphylline daily at 3-day intervals. The maximum daily dose should not exceed 1 600 mg oxtriphylline. Tablets should not be chewed or crushed, but may be halved. Because of large differences in individual requirements, the physician should be prepared to adjust the dose according to the patient's clinical response and/or serum theophylline level which should be in the range of 55 to 110 $\mu\text{mol/L}$ (10 to 20 mg/L). Children: Not recommended for children.

The following equivalents facilitate changing from one xanthine preparation to another:
theophylline anhydrous 100 mg=aminophylline 118 mg=oxtriphylline 156 mg=theophylline sodium glycinate 200 mg.

Supplied: 400 mg: Each scored, glossy, pink-colored biconvex, ellipsoid, coated, sustained-release tablet contains: oxtriphylline 400 mg. Nonmedicinal ingredients: carnauba wax, hydrogenated soybean oil, magnesium stearate and sugar; coating: candelilla wax, hydroxypropyl cellulose, opaseal, opaspray pink and talc. Energy: 1.3 kJ (0.3 kcal).

600 mg: Each scored, glossy, tan-colored, biconvex, ellipsoid, coated, sustained-release tablet contains: oxtriphylline 600 mg. Nonmedicinal ingredients: carnauba wax, hydrogenated soybean oil, magnesium stearate and sugar; coating: candelilla wax, hydroxypropyl cellulose,

opaseal, opaspray tan and talc. Energy: 2.5 kJ (0.6 kcal).

Both are gluten-, lactose-, paraben-, sodium-, sulfite- and tartrazine-free. Bottles of 100. Store between 15 to 30°C.

(Shown in Product Identification Section)

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