PRESCRIBING INFORMATION
PRODUCT MONOGRAPH

CHOLEDYL* SA TABLETS

(Oxtriphylline MANUFACTURER STANDARD)

SUSTAINED ACTION SCORED TABLETS

600 mg tablets equivalent to 386.4 mg anhydrous theophylline
400 mg tablets equivalent to 257.6 mg anhydrous theophylline

BRONCHODILATOR

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PRESCRIBING INFORMATION

CHOLEDYL* SA TABLETS

Oxtriphylline

Sustained Action Scored Tablets 600 and 400 mg

(Equivalent to 386.4 and 257.6 mg anhydrous theophylline respectively)

THERAPEUTIC CLASSIFICATION

Bronchodilator

ACTION AND CLINICAL PHARMACOLOGY

Choledyl (oxtriphylline) is the theophylline salt of choline and contains 64% theophylline with the properties attributed to it. The therapeutic effects of CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) are a function of theophylline blood levels.

Theophylline is a xanthine structurally related to theobromine and caffeine. As with other xanthine derivatives, the precise mechanism of action of oxtriphylline has not been determined. Oxtriphylline stimulates the central nervous system and skeletal muscles, stimulates cardiac muscle, relaxes certain smooth muscles including those of the bronchi, produces diuresis, and causes an increase in gastric secretion.

CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) are sustained release tablets which produces peak blood levels of theophylline (47 to 67 μmol/L [8 to 12 mg/L]) between 2 and 4 hours. Once the steady-state level has been reached, the therapeutic blood levels persist for 12 hours.

Oxtriphylline's pharmacologic action is essentially the same as that of theophylline. Its pharmacologic effects include stimulation of respiration, augmentation of cardiac inotrophy and chronotrophy, relaxation of smooth muscle, including that in the bronchi and blood vessels other than cerebral vessels, and diuresis.

Following oral administration, theophylline is usually readily absorbed. Compared to aminophylline, oxtriphylline is reported to be more soluble, more stable, better absorbed from the GI tract and less irritating to the gastric mucosa. The drug is 55 to 65% bound to plasma proteins in the therapeutic plasma concentration range of 8 to 20 mg/L; it is not likely to be subject to pronounced displacement effects. Theophylline has a mean plasma half-life of 4.5 hours in adults (range 3.0 to 9.5 hours) and a slightly shorter mean half-life of 3.6 hours in children (range 1.5 to 9.5 hours), with great variability between individual patients.

In view of the relatively short half-life of theophylline, steady state plasma concentrations are achieved within 1 to 2 days in most patients. Following absorption, theophylline is in the extracellular fluids and uniformly to all tissues. However, there seems to be a wide variation in metabolism which appears to be largely responsible for the great variation in serum concentrations of different individuals. It is metabolized by the liver to -1- methyl-uric-acid and 1,3-dimethyluric acid, chiefly; about 10% of a dose is excreted unchanged in the urine.

Biliary excretion, with subsequent reabsorption, may occur but has not been demonstrated in man. The enzymes responsible for theophylline metabolism are unknown but do not include xanthine oxidase. Serum uric acid concentrations do not increase; therefore, the drug is not contraindicated in the presence of either gout or allopurinol administration.

Theophylline directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels, thus acting mainly as a bronchodilator and smooth muscle relaxant. It has also been demonstrated that aminophylline has a potent effect on diaphragmatic contractility in normal persons and may then be capable of reducing fatigability and thereby improve contractility in patients with chronic obstructive airway disease. The exact mode of action remains unclear. Although theophylline does cause inhibition of phosphodiesterase with a resultant increase in intracellular cyclic AMP, other agents similarly inhibit the enzyme producing a rise of cyclic AMP but are not associated with any demonstrable bronchodilation. Other mechanisms proposed include an effect of translocation of intracellular calcium, prostaglandin antagonism, stimulation of catecholamines endogenously, inhibition of cyclic guanosine monophosphate metabolism and adenosine receptor antagonism. None of these mechanisms has been proven, however.

In vitro, theophylline has been shown to act synergistically with beta agonists; there is data which demonstrates an additive effect in vivo with combined use.

Pharmacokinetics

The half-life of theophylline is influenced by a number of known variables. It may be prolonged in patients with chronic alcoholism, particularly those with liver disease (cirrhosis or alcoholic liver disease), in patients with congestive heart failure, and in those patients taking certain other drugs. (See PRECAUTIONS, Drug Interactions.) Newborns and neonates have extremely slow clearance rates compared to older pediatric patients, i.e., those over one year. Older pediatric patients have rapid clearance rates while most non-smoking adults have clearance rates between these two extremes. In premature neonates, the decreased clearance is related to oxidative pathways that have yet to be established.

In pediatric patients, theophylline has a mean half-life of 3.7 hours with a range of 1-9 hours. In adults, the mean half-life is 7.7 hours with a range of 3-15 hours. In cigarette smokers (1-2 packs/day) the mean half-life is 4-5 hours, much shorter than in non-smokers. The increase in clearance associated with smoking is presumably due to stimulation of the hepatic metabolic pathway by components of cigarette smoke. The duration of this effect after cessation of smoking is unknown but may require three months to two years before the rate approaches that of the non-smoker.

Bioavailability

Four bioavailability studies have been performed on Choledyl-SA tablets.

In the first study, performed on 12 healthy volunteers, twice daily administration of the 600 mg tablets (equivalent to 384 mg theophylline) was compared to both a single dose of Choledyl Elixir and to Choledyl Elixir (15 mL, equivalent to 192 mg theophylline) given four times daily for 4 days.

Theophylline plasma determinations were made by high pressure liquid chromatography (HPLC). Analyses of variance performed on areas under the plasma concentration time curves failed to show a significant difference in the bioavailability of the tablets and elixir. Table I indicates plasma theophylline concentrations obtained on the 4th day of taking Choledyl-SA 600 mg tablets every 12 hours. The Table shows maximum and minimum values observed among the 12 subjects, also mean values and their standard deviation.

TABLE I

MEAN STEADY STATE OF PLASMA THEOPHYLLINE CONCENTRATION AFTER RECEIVING CHOLEDYL, 600 mg SA TABLETS B.I.D.

Time in hours following Choledyl Administration

Theophylline in mcg/mL	Day 4 8:00	9:00	A.M. 10:00	11:00	12:00	P.M. 1:00	6:00	Day 5 8:00 A.M.
Maximum	12.4	14.6	14.3	14.3	13.0	12.0	10.0	9.8
Minimum	4.4	4.8	7.2	6.5	5.8	4.9	4.0	3.5
Mean	7.8	10.0	10.3	9.6	8.6	7.7	6.8	7.1
Standard Deviation	2.4	2.7	2.4	2.5	2.3	2.3	2.0	2.1

Calculations of interdose peak-trough swings indicated that Choledyl-SA tablets, when administered every 12 hours in an appropriate dose will maintain theophylline levels in the therapeutic range, therefore, the product qualifies as a sustained release dose form.

The second study on Choledyl-SA 600 mg scored tablets, compared the bioavailability of the product in 12 healthy volunteers when it was taken whole and when taken as 2 halves. Table II indicates measurement of peak plasma theophylline concentrations, areas under the concentration curves (AUC), times of peak concentrations (T max.) and elimination half lives ($t_{1/2}$).

TABLE II

PHARMACOKINETIC MEASUREMENTS ON CHOLEDYL-SA 600 mg SCORED TABLETS FOLLOWING ORAL ADMINISTRATION OF A WHOLE TABLET AND TWO HALVES

	WHOLE TABLET	TWO HALVES
AUC ± SD	81.3 ± 28.4	84.5 ± 25.6
Peak Plasma Theophylline mcg/mL ± SD	6.0 ± 1.6	6.3 ± 1.6
T max hours ± SD	3.8 ± 1.3	3.6 ± 1.3
t½ hours ± SD	7.54 ± 4.07	7.68 ± 3.43

The above data indicate that Choledyl-SA 600 mg scored tablets, when taken whole or in two halves are bioequivalent.

The third study in 12 healthy adult volunteers was performed in a crossover fashion. Choledyl SA 400 mg, (1 tablet, 400 mg or 1 1/2 tablets 600 mg) was administered as a single dose and compared against equivalent doses of Choledyl Elixir (400 mg or 600 mg).

Analysis of variance performed on areas under the plasma concentration/time profile (Table III) failed to show a significant difference in the bioavailability of the new Choledyl SA 400 mg tablet and the Elixir.

TABLE III

BIOAVAILABILITY PARAMETERS AS CALCULATED FOR CHOLEDYL SA 400 mg TABLETS - SINGLE DOSE (1 = 400 mg, 1 1/2 = 600 mg) and 400 mg Elixir or 600 mg Elixir.

Dosage Form	AUC (mcg.Hr./mL)		Cmax mcg/mL		Tmax (hr.)		T 1/2 (hr.)	(± SD)
1 tablet	65.6	(24.1)	3.8	(1.0)	4.8	(1.0)	6.9	(2.4)
400 mg Elixir	71.9	(29.5)	7.9	(2.5)	1.1	(0.6)	5.2	(1.6)
1 1/2 tablet	102.3	(39.9)	6.5	(2.0)	4.3	(0.8	7.1	(3.5)
600 mg Elixir	122.4	(44.3)	11.6	(2.0)	1.5	(0.6)	5.5	(1.8)

In the fourth study, performed on 18 healthy, volunteers, twice daily administration of 800 mg Choledyl SA (two whole 400 mg tablets) was compared to twice daily administration of 600 mg Choledyl SA (1 1/2 tablets of Choledyl 400 mg) in a cross over fashion. The doses were administered every 12 hours for 6 days. Plasma determinations of theophylline was made at various intervals using HPLC methodology. Table IV shows the plasma theophylline concentrations on Day 5.

TABLE IV

MINIMUM AND MAXIMUM PLASMA THEOPHYLLINE CONCENTRATIONS FOLLOWING THE ADMINISTRATION OF 600 MG AND 800 MG CHOLEDYL SA (i.e. 1 1/2 or 2 tablets B.I.D.).

DAY 5

Plasma Theophylline	Theophylline Plasma Concentration µg/mL			
Maximum at:	0700*	0900	1900	2100
600 mg BID	13.3	16.5	9.7	15.2
800 mg BID	14.9	24.3	14.1	18.2
Minimum at:				
600 mg BID	1.5	3.1	0.9	3.3
800 mg BID	2.1	5.2	2.0	5.3
Mean ± SD at:				
600 mg BID	5.7 ± 3.3	8.7 ± 4.5	5.2 ± 2.8	7.5 ± 3.5
800 mg BID	7.7 ± 4.3	12.6 ± 5.6	7.6 ± 3.5	10.6 ± 4.1

*pre-dose sampling

Estimations of the between dose peak/through variations demonstrate that the Choledyl SA 400 mg tablet (2 whole or 1 1/2), when administered every 12 hours will satisfactorily maintain the plasma concentration of theophylline qualifying the dosage form as sustained release.

INDICATIONS AND USAGE

CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets, MANUFACTURER STANDARD) are indicated 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

CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets, MANUFACTURER STANDARD) are contraindicated 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 (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) 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.

While not completely predictive of toxicity, serum theophylline level measurement remains the best method of predicting toxicity. Serum levels of theophylline above 20 mcg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced for any reason, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been

documented in the following readily identifiable groups: 1) patients with impaired liver function, 2) patients over 55 years of age, particularly males and those with chronic lung disease, 3) those with cardiac failure from any cause, 4) patients with sustained high fever, 5) neonates and infants under 1 year of age, and 6) those patients taking certain drugs. (See PRECAUTIONS, Drug Interactions). In addition reduced theophylline clearance resulting in theophylline toxicity has been associated with viral upper respiratory tract infections. Frequently, patients with the conditions or under the circumstances described above have markedly prolonged theophylline serum levels following discontinuation of the drug. Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e. nausea and restlessness) may occur frequently when initiating therapy, but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/mL. Serious toxicity is not reliably preceded by less severe side effects. This serum concentration measurement is the only reliable method of predicting potentially life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process so that the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen pre-existing arrhythmias and any significant change in rate and or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

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 CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) 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 Tablets (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) 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.

General

On average, theophylline half-life is shorter in cigarette and marijuana smokers than in non-smokers, but any individual smoker can have a plasma theophylline half-life as long as non-smokers. CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) should not be administered concurrently with other xanthines. Use with caution in patients with hypoxemia, hypertension, or those with history of peptic ulcer. Theophylline may occasionally act as a local irritant to the gastrointestinal tract although gastrointestinal symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 mcg/mL.

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, which occurs at 4 to 6 hours after administration of the sustained 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.

Pregnancy:
CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets, MANUFACTURER STANDARD) 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.
Animal reproduction studies have not been conducted with choline theophylline. It is not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. There are insufficient adequate and well-controlled studies in pregnant women. Therefore, choline theophyllinate should be used in pregnancy only if clearly needed.

Lactation:
There are insufficient adequate and well-controlled studies in lactating women. Therefore, CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets, MANUFACTURER STANDARD) 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.

Usage in Pediatric Patients:
Sufficient numbers of infants under the age of one year have not been studied in clinical trials to support use in this age group. There is evidence recorded that the use (in pediatric patients under one year of age) of dosage recommendations for older pediatric patients (16 mg/kg/24 hours of anhydrous theophylline) may result in the development of toxic serum levels. Such findings very probably reflect differences in the metabolic handling of the drug related to absent or underdeveloped enzyme systems. Consequently, the use of the drug in this age group should carefully consider the associated benefits and risks. If used, a dosage form which allows small incremental doses is desirable for initiating therapy. A liquid preparation should be considered for children to permit both greater ease of and more accurate dosage adjustment.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies have not been performed with theophylline. Chromosone-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentration in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intra-peritoneally in doses up to 30 times the maximum daily oral dose.

Studies to determine the effect of theophylline on fertility have not been performed.

Drug Interactions **:**

Toxic synergism with ephedrine has been documented and may occur with other sympathomimetic amines. In addition, the following drug interactions have been demonstrated:

Drug	Interaction
Allopurinol (high doses)	Increased serum theophylline levels
Antibiotics (fluoroquinolones, pipemidic acid, clarithromycin, erythromycin, lincomycin, troleandomycin)	" "
Cimetidine	Increased serum theophylline levels
Mexiletine	" "
Oral Contraceptives	" "
Propranolol	Increased serum theophylline levels and antagonism of propranolol effect
Tacrine	Increased serum theophylline levels
Thiabendazole	" "
Ticlopidine	" "
Verapamil	" "
Isoproterenol	Decreased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Rifampin	Decreased theophylline levels
Sulfinpyrazone	" "
Adenosine	Decreased adenosine effect
Lithium carbonate	Increased renal excretion of lithium
Furosemide	Increased furosemide diuresis

Drug	Interaction
Hexamethonium	Decreased hexamethonium-induced chronotropic effect
Reserpine	Reserpine-induced tachycardia
Chlordiazepoxide	Chlordiazepoxide-induced fatty acid mobilization

CHOLEDYL SA (Oxtriphylline Extended-release Tablets, MANUFACTURER STANDARD) antagonizes the effect of propranolol.

Theophylline potentiates the effects of diuretics and the cardiac effect of digitalis glycosides. The concomitant use of morphine, stilbamidine, curare may antagonize the effect of theophylline since these drugs stimulate histamine release and thereby induce bronchoconstriction. Cigarette smoking and phenobarbital shorten, and 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 fibrogen, shorten the prothrombin time and thus antagonize the effects of coumarin anticoagulants.

Xanthines antagonize the uricosuric action of prebenecid and of sulfinpyranzone 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. Theophylline has been shown to increase the ratio of clearance of lithium/creatinine and may thus decrease serum lithium to ineffective concentrations.

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 immnuno-assay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytical methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs 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 occurring with CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) 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.

The following adverse reactions have been observed with choline theophyllinate, but there has not been enough systemic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.
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, excitement, irritability, restlessness, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular System: Palpitation, hypotension, circulatory failure, tachycardia, extrasystoles, ventricular arrhythmias, flushing.

Respiratory: Tachypnea and respiratory arrest may occur

Urinary Tract: Albuminuria, diuresis.

Renal: Potentiation of diuresis.

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

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

Others: Tachypnea, hyperglycemia and inappropriate ADH syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

Insomnia, restlessness, mild excitement or irritability, and rapid pulse are the early symptoms of overdosage with CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) which may progress to mild delirium. Sensory disturbances such as tinnitus or flashes of light are common. Anorexia, nausea and vomiting are frequently early manifestations of theophylline overdosage. Fever, diuresis, dehydration and extreme thirst are also seen. Severe poisoning results in bloody, syrup like "coffee ground" vomitus, tremors, tonic extensor spasm interrupted by clonic convulsions, exrasystoles, quickened respiration, stupor and finally coma. Cardiovascular disorders and respiratory collapse, leading to shock, cyanosis and death follow gross overdosages.

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:

1. 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 had been shown to increase the seizure threshold in laboratory animals and administration of this drug can be considered.

2. If patient presents with a seizure:

a) Establish an airway.

b) Administer oxygen.

c) Treat 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.

3. If post-seizure 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.

d) 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.

Treatment should be supportive and symptomatic; symptoms can often be controlled by CNS depressants such as short-acting barbiturates. Convulsions may be controlled by anesthetics or with i.v. diazepam. Also parenteral fluids, electrolyte solutions, oxygen and/or therapy for shock may be indicated**.**

Note: It is particularly important to administer a cathartic when the sustained release preparation CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets, MANUFACTURER STANDARD), has been taken.

DOSAGE AND ADMINISTRATION

Note: Each 100 mg of CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) is equivalent to 64 mg of anhydrous theophylline.

Dosage Recommendations:

The average recommended initial adult dose is one CHOLEDYL SA (Oxtriphylline Extended-release Tablets –MANUFACTURER STANDARD), 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 oxtriphylline per kg body weight per day at 3-day intervals. The maximum daily dose should not exceed 1600 mg oxtriphylline. CHOLEDYL SA 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 μmol/L (10 to 20 mg/L). Choledyl SA 600 mg and 400 mg tablets are not recommended for children. To be used only on the advice of a physician.

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.

Composition

400 mg: Each scored, glossy, pink-colored biconvex, ellipsoid, coated, CHOLEDYL SA Tablet (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) contains: oxtriphylline 400 mg. Non-medicinal 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, CHOLEDYL SA Tablet (Oxtriphylline Extended-release Tablets MANUFACTURER STANDARD) contains: oxtriphylline 600 mg. Non-medicinal 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.

Stability and Storage Recommendations

Store CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets, MANUFACTURER STANDARD) at controlled room temperature 15 to 30°C.

AVAILABILITY OF DOSAGE FORMS

CHOLEDYL SA preparations are formulated as sustained action, scored tablets containing 600 or 400 mg of oxtriphylline (equivalent to 386.4 and 257.6 mg anhydrous theophphylline, respectively). When broken, into halves, each half will provide 300 or 200 mg oxtriphylline (equivalent to 193.2 and 128.8 mg anhydrous theophylline, respectively).

CHOLEDYL SA Tablets (Oxtriphylline Extended-release Tablets, MANUFACTURER STANDARD) 400 mg and 600 mg are available in bottles of 100.

PHARMACEUTICAL INFORMATION

Drug Substance

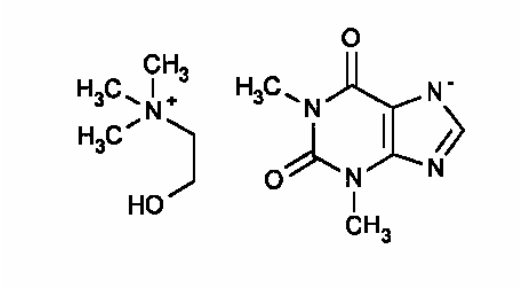
Proper Name: Oxtriphylline

Chemical Name: 1H-Purine-2,6-dione 3,7-dihydro-1,3-dimethyl (Theophylline anhydrous)

Empirical Formula: $C_{12}H_{21}N_5O_3$

Molecular Weight: 283.33

Structural Formula:



TOXICOLOGY

Acute:

The acute toxicity of oxtriphylline (LD_{50}) is reported to be as follows:

Animal	Route	LD_{50} mg/kg
Mouse	i.v.	112
	i.m.	360
	Oral	770
Rat	i.p.	185
	i.m.	240
	Oral	600
Guinea Pig	i.v.	118
	i.m.	185
	Oral	210

The human oral lethal dose of theophylline is estimated to range from 50 to 500 mg/kg. Tolerance to many oil theophylline's toxic effects is widely recognized. Rectal dosages of theophylline, as the ethylenediamine salt (aminophylline), have produced toxic symptoms in children at 9 mg/kg. Children appear to be more susceptible to theophylline's lethal effects than older patients. The incidence of adverse effects increase at plasma concentrations over 15 I.g/mL. Therapeutic plasma concentration range is 8-20 µg/mL. Serum concentrations exceeding 20 µg/mL are usually quite toxic to most adult patients.

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