

**PRESCRIBING INFORMATION**

**CHOLEDYL\* EXPECTORANT ELIXIR**

**(Oxtriphylline - Guaifenesin MANUFACTURER STANDARD)**

**100 mg Oxtriphylline and 50 mg Guaifenesin / 5 mL**

**BRONCHODILATOR - EXPECTORANT**



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Montréal, QC  
Canada, H4P 2P5

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### **THERAPEUTIC CLASSIFICATION**

Bronchodilator-Expectorant

### **ACTION AND CLINICAL PHARMACOLOGY**

CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) contains 64% theophylline and has the properties attributed to theophylline.

As with other xanthine derivatives, the precise mechanism of action of CHOLEDYL ELIXIR (Oxtriphylline Oral Solution U.S.P.) 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.

Oxtriphylline's pharmacologic action is essentially the same as that of theophylline. Its pharmacologic effects include stimulation of respiration, augmentation of cardiac inotropy and chronotropy, 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 mcg/ml; 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 distributed in the extra-cellular 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 re-absorption, 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 non-smoking 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.

### **INDICATIONS AND CLINICAL USE**

CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) is indicated for the symptomatic relief of reversible bronchoconstriction associated with bronchial asthma, chronic obstructive pulmonary emphysema, chronic bronchitis and related bronchospastic disorders, and where expectoration is required.

### **CONTRAINDICATIONS**

CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) is 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, in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication). It should not be used in patients with peptic ulcer.

### **WARNINGS**

Children are very sensitive to xanthines; the margin of safety above the therapeutic dose is small. CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) is not recommended for children under 10 years of age. 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. Thus 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 preexisting 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**

Patients starting CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) therapy should be carefully observed to determine if this fixed dose combination is suitable for them. The use of single drug preparations to allow for more accurate dose adjustment for each component may be preferable in some patients. The dose of oxtriphylline required to achieve therapeutic blood concentrations varies considerably among patients.

CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) should not be administered more often than every 4 hours or within 12 hours following oral, parenteral or rectal use of other xanthine containing preparations. Simultaneous use of additional xanthines by any route should be avoided in all patients, especially children.

### **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. Theophylline 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, 1 to 2 hours after administration for non-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.**

**Parents should be cautioned against overdosage to children. Children are very sensitive to xanthines; the margin of safety above therapeutic doses is small.**

Ensure that children receiving CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) are not also receiving xanthines by the rectal route.

The possibility of overdose must be considered in all patients and especially when large doses are used, because fatalities have been reported. Overdosage of oxtriphylline may cause peripheral vascular collapse.

There is a marked variation in blood levels achieved in different patients given the same dose of CHOLEDYL EXPECTORANT ELIXIR. 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 concentrations 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.

Concurrent use of other xanthine-containing preparations can affect assay results (Schack and Waxler method), and may lead to adverse reactions, particularly CNS stimulation in children. Theophylline may cause an elevation of serum uric acid, urine catecholamines and plasma free fatty acids.

In patients with severe pulmonary or cardiovascular disease and in patients with hepatic dysfunction oxtriphylline metabolism may be impaired and thus toxic concentrations may be reached with standard dose regimens.

Exercise caution when oxtriphylline is used concurrently with sympathomimetic amines or other xanthines. In general, oxtriphylline should not be given more frequently than every 6 hours or within 12 hours of the ingestion of other xanthines.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:**

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

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

**Pregnancy:**

CHOLEDYL EXPECTORANT ELIXIR 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 theophyllinate. 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 EXPECTORANT ELIXIR 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, the maintenance dose must be conservative and in accord with the guidelines presented in Dosage and Administration.

### **Drug Interactions:**

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

<b>Drug</b>	<b>Interaction</b>
Allopurinol (high doses)	Increased serum theophylline levels
Antibiotics (fluoroquinolones, piperimidic 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
Hexamethonium	Decreased hexamethonium-induced chronotropic effect
Reserpine	Reserpine-induced tachycardia

Drug	Interaction
Chlordiazepoxide	Chlordiazepoxide-induced fatty acid mobilization

CHOLEDYL EXPECTORANT ELIXIR antagonizes the effect of propranolol. The concomitant use of morphine or 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.

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 probenecid 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.

CHOLEDYL EXPECTORANT ELIXIR and xanthines derivatives, potentiate the diuretic action of thiazide diuretics and the cardiac effect of digitalis glycosides.

Oxtriphylline increases 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.

Drug-laboratory Test Interactions: Currently available analytical methods, including high pressure liquid chromatography and immuno-assay techniques, for measuring serum theophylline levels that 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.

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.

### **ADVERSE REACTIONS**

The following adverse reactions have been observed with choline theophyllinate, but there has not been enough systematic 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 Tract

Nausea, vomiting, upper abdominal discomfort, epigastric pain, anorexia, reactivation of peptic ulcers, abdominal cramps, diarrhea, intestinal bleeding, hematemesis.

#### Central Nervous System

Headache, nervousness, insomnia, dizziness, lightheadedness, excitement, irritability, restlessness, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

#### Cardiovascular System

Palpitation, sinus tachycardia, increased pulse rate, peripheral vascular constriction and/or collapse, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

#### Urinary Tract

Albuminuria, diuresis.

Renal

Potential of diuresis.

Skin

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

Blood

Very rarely bone marrow suppression, leukopenia, thrombocytopenia and hemorrhagic diathesis. have also been reported but their association with theophylline therapy is questionable.

Others

Tachypnea, hyperglycemia, and inappropriate ADH syndrome.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

**Symptoms:**

The most consistent reactions observed with toxic overdoses of of CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) and its derivatives are:

*Gastrointestinal:* Anorexia, 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.

Insomnia, restlessness, mild excitement or irritability, and rapid pulse are the early symptoms of overdosage, which may progress to mild delirium. *Sensory disturbances* such as tinnitus or flashes of light are common. 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, extrasystoles, quickened respiration, stupor and finally coma. *Cardiovascular:* In addition to those outlined above, marked hypotension and circulatory failure may be manifest.

Cardiovascular disorders and respiratory collapse, leading to shock, cyanosis and death follow gross overdoses. *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.

N.B.: Guaifenesin is a phenol (carbolic acid) derivative.

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 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.

## **DOSAGE AND ADMINISTRATION**

Usual maintenance doses of CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin): Patients over 14 years: 10 mL 4 times daily; 10 to 14 years: 5 mL 4 times daily.

The following mg 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**

Each 5 mL of red, cherry-flavored CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) liquid contains: oxtriphylline 100 mg equivalent to 64.4 mg anhydrous theophylline and guaifenesin 50 mg. Nonmedicinal ingredients: alcohol, anethole, citric acid, FD&C Red No. 2, FD&C Yellow No. 6, flavouring agents, glycerin, sodium citrate, sodium cyclamate and sugar. Alcohol: 20%. Energy: 74.1 kJ (17.7 kcal)/5 mL. Sodium: <1 mmol (10.4 mg)/5 mL. Gluten-, lactose-, paraben-, sulfite- and tartrazine-free.

### **Stability and Storage Recommendations**

Store CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) at controlled room temperature 15 to 25°C.

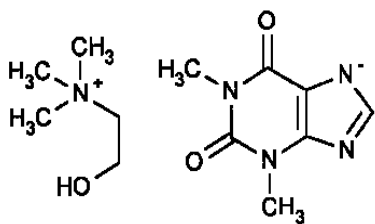
## **AVAILABILITY OF DOSAGE FORMS**

CHOLEDYL EXPECTORANT ELIXIR (oxtriphylline-guaifenesin) is available in bottles of 250 mL and 500 mL.

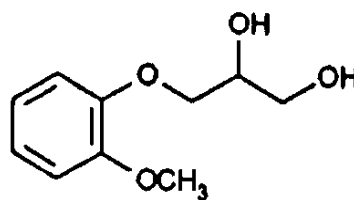
## PHARMACEUTICAL INFORMATION

### Drug Substance

Proper Name:	Oxtriphylline-Guaifenesin
Chemical Name:	
Oxtriphylline (Choline theophyllinate)	1H-Purine-2,6-dione 3,7-dihydro-1,3-dimethyl (theophylline anhydrous)
Guaifenesin	1,2-Propanediol, 3-(2-methoxyphenoxy)-, (±)-. (±)-3-(o-methoxyphenoxy)-1, 2,-propanediol.
Empirical Formula:	
Oxtriphylline	$C_{12}H_{21}N_5O_3$
Guaifenesin	$C_{10}H_{14}O_4$
Molecular Weight:	
Oxtriphylline	283.33
Guaifenesin	198.22
Structural Formula:	



Oxtriphylline



Guaifenesin

**REFERENCES**

1. Birkett DJ, Miners JO, Attwood J. Evidence for a dual action of sulphinyprazone on drug metabolism in man: theophylline-sulphinpyrazone interaction. *Br J Clin Pharmacol* 1983; 15:567-569.
2. Colli A, Buccino G, Cocciolo M et al. Ticlopidine-theophylline interaction. *Clin Pharmacol Ther* 1987; 41:358-362.
3. DiMarco JP, Sellers TD, Lerman BB et al. Diagnostic and therapeutic use of adenosine in patients with supraventricular arrhythmias. *J Am Coll Cardiol* 1985; 6:417-425.
4. Duncan, PE et al.: Bronchodilator Drug Efficacy Via Cyclic AMP. *Thorax* 30: 192-196, 1975.
5. Fox RW, Saber SS, Lockey RF et al. Study of oxtriphylline SA in 50 asthmatics. *J Asthma* 1963; 20(3):177-181.
6. Kamada AK, Hill MR, Brenner AM et al. Effect of low-dose troleandomycin on theophylline clearance: implications for therapeutic drug monitoring. *Pharmacotherapy* 1992; 12:98-102.
7. Lew G, Murray WE, Lane JR et al. Theophylline-thiabendazole drug interaction. *Clin Pharm* 1989; 8:225-227.
8. Niki Y, Soejima R, Kawane H et al. New synthetic quinolone antibacterial agents and serum concentration of theophylline. *Chest* 1987; 92:663-669.
9. Orange, RP et al.: Immunological Release of Histamine and Slow-Reacting Substance of Anaphylaxis from Human Lung. *J. Exp. Med.* 134:136-148, 1971.
10. O'Rourke PP, Crone RK. Effect of isoproterenol on measured theophylline levels. *Crit Care Med* 1984; 12:373-375.
11. Paulus HE, Coutts A, Calabro JJ et al. Clinical significance in hyperuricemia in routinely screened hospitalized men. *JAMA* 1970; 211:277-281.
12. Ritchie, JM : The Xanthines, in Goodman, L.S. and Gilman, A. (Eds.), *The Pharmacological Basis of Therapeutics*, ed. 5, New York MacMillan Publishing Co., 1975, p. 374.
13. Schachter, R.J. et al.: Pharmacology of Choline Theophylline. *Internat. Rec. of Medicine and G.P. Clinics*, 248-250, May 1954.



14. Schneider D, Gannion R, Sweeney K et al. Theophylline and antiparasitic drug interactions: a case report and study of the influence of thiabendazole and mebendazole on theophylline pharmacokinetics in adults. *Chest* 1990; 97:84-87.
15. Smits P, Lenders JWM, Thien T. Caffeine and theophylline attenuate adenosine-induced vasodilation in humans. *Clin Pharmacol Ther* 1990; 48:410-418.
16. Stringer KA, Mallet J, Clarke M, Lindenfeld JA. The effect of three different oral doses on the disposition of theophylline. *Eur J Clin Pharmacol* 1992; 43(1):35-38.
17. Ueno K, Miyai K, Kato M et al. Mechanism of interaction between theophylline and mexiletine. *DICP* 1991; 25:727-730.
18. Upton RA. Pharmacokinetic interactions between theophylline and other medication (Part 1). *Clin Pharmacokinet* 1991; 20:66-88.
19. Upton RA. Pharmacokinetic interactions between theophylline and other medication (Part II). *Clin Pharmacokinet* 1991; 20:135-150.
20. Wijnands WJ, Vree TB. Interaction between the fluoroquinolones and the bronchodilator theophylline. *J Antimicrob Chemother* 1988; 22(Suppl C):109-114.
21. Wijnands WJA, Vree TB, van Herwaarden CLA. The influence of quinolone derivatives on theophylline clearance. *Br J Clin Pharmacol* 1986a; 22:677-683.