PRODUCT MONOGRAPH

PrTEVA-THEOPHYLLINE SR

(Theophylline Anhydrous)

100, 200 and 300 mg Tablets (Sustained Release)

Teva Standard

Bronchodilator

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THERAPEUTIC CLASSIFICATION

Bronchodilator

AGTION AND CLINICAL PHARMACOLOGY

TEVA-THEOPHYLLINE SR (theophylline) relieves bronchospasm and increases flow rates and vital capacity through the relaxation of the smooth muscle of the bronchial airways and pulmonary blood vessels. It also produces other actions typical of the xanthine derivatives: coronary vasodilation, diuresis, increase in gastric secretion, and cardiac, cerebral and skeletal muscle stimulation. The actions of theophylline may be mediated through inhibition of phosphodiesterase and the consequent increase in intracellular cyclic adenosine monophosphate, but the exact mechanism(s) has not been determined.

Theophylline is usually readily absorbed and distributed into all body compartments. Protein binding is approximately 55 to 65 %. The primary site of metabolism is the liver. The therapeutic serum concentration range commonly accepted is 10 to 20 μg/mL (55 to 110 μg/mL; levels above 20 μg/mL are associated with toxic reactions. A number of variables influence the pharmacokinetics of theophylline. These include age, disease state, smoking and concomitant medications. Therefore, the optimum therapeutic maintenance dose should be determined by individual titration.

TEVA-THEOPHYLLINE SR (theophylline) are sustained release tablets which produce blood levels between 5 to 8 hours after dosing in adults and between 4 to 6 hours after dosing in children 6 years of age and older. Once the steady state level has been reached (3 days), the therapeutic blood levels persist for 12 hours in most adult patients. The mean elimination half-life of theophylline in nonsmoking adults is about 8 hours and in

children, about 4 hours. The degree of fluctuation between peak and trough theophylline levels can be defined as follows:

% Theophylline Fluctuation		
	Children	**Nonsmoking Adults**
Theophylline SR (200, 300, 450 mg)	38%	16%
Theophylline SR (100 mg)	87%	34%

INDICATIONS AND CLINICAL USE

TEVA-THEOPHYLLINE SR (theophylline) is indicated for the symptomatic treatment of reversible bronchospasm associated with asthma, chronic bronchitis, emphysema and related bronchospastic disorders.

CONTRADICATIONS

TEVA-THEOPHYLLINE SR (theophylline) is contraindicated in patients with:

- hypersensitivity to theophylline or xanthine derivatives;
- peptic ulcer;
- coronary artery disease (when, in the physician's judgement, myocardial stimulation might prove harmful).

WARNINGS

TEVA-THEOPHYLLINE SR (theophylline) is not suitable in clinical situations where intermediate bronchodilation is required, such as status asthmaticus.

Theophylline has a narrow therapeutic index, and the margin of safety above therapeutic doses is small.

Therapy with TEVA-THEOPHYLLINE SR should be reassessed in patients showing intolerance to theophylline.

Various disease states, age of patient, concomitant use of other medications and lifestyle habits can change theophylline clearance (see PRECAUTIONS).

In children under the age of six years, the use of TEVA-THEOPHYLLINE SR is not recommended as a dose schedule in this age group has not been established.

PRECAUTIONS

TEVA-THEOPHYLLINE SR TABLETS SHOULD NOT BE CHEWED OR CRUSHED, BUT MAY BE HALYED.

Marked differences in serum levels may be seen in patients receiving the same theophylline dose. This may be explained by differences between patients in the rate of metabolism. Smokers and children are usually high metabolizers. Dosage regimens should therefore be individualized.

Theophylline half-life is shorter in smokers than in nonsmokers. Smokers may require larger or more frequent doses of theophylline.

Serum theophylline levels should, ideally, be monitored in all patients and a theophylline half-life calculated, enabling doses and dosing regimens to be tailored to each patient to maintain a therapeutic level to ensure optimal clinical response and to avoid toxicity.

At serum theophylline levels greater than 15 μg/mL (82.5 μM/L), the incidence of toxicity increases and levels above 20 μg/mL (110 μM/L) are usually quite toxic in most adult patients.

High serum levels may be seen in some patients receiving doses considered to be conventional, therefore, the possibility of overdose should not be considered with large doses only. Theophylline overdosage may cause peripheral vascular collapse.

Reduced theophylline clearance has been documented in the following groups:

(1) Patients with impaired renal or hepatic function.
(2) Patients older than 55 years of age, particularly males and those with chronic lung disease.
(3) Those with cardiac failure from any cause.
(4) Patients taking certain drugs (i.e., macrolide antibiotics and cimetidine). Decreased clearance may be associated with either influenza immunization or active infection with influenza.

Laboratory monitoring of serum theophylline is especially appropriate in the above individuals to maintain an appropriate theophylline dosage.

Serious side effects such as tachycardia, arrhythmia, seizures, vascular collapse and even death may occur without warning and may not be preceded by less severe symptoms such as nausea and restlessness.

Use with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, in the elderly (especially males).

Patients with congestive heart failure frequently have markedly prolonged serum levels, with theophylline persisting in serum for long periods following discontinuation of the drug.

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 μg/mL (110 μM/L).

Theophylline increases gastric secretion, and caution should be exercised in patients with a history of peptic ulcer.

Although TEVA-THEOPHYLLINE SR has pharmacokinetic properties similar to other sustained release theophylline products, it is not possible to ensure interchangeability between different products. Careful clinical monitoring is required when changing from one drug product to another.

The concurrent administration of other theophylline derivatives along with TEVA-THEOPHYLLINE SR is not recommended.

Laboratory Test Interactions

In the interpretation of biochemistry tests, it should be remembered that theophylline may cause an elevation of urine catecholamines and plasma free fatty acids.

In vitro, serum theophylline concentrations as measured by spectrophotometric methods may be falsely elevated by coffee, tea, cola beverages, chocolate and acetaminophen.

When high pressure liquid chromatography (HPLC) method is used, serum theophylline concentrations may be falsely increased by caffeine, some cephalosporin and sulfa medications.

Food Interaction

When diet includes a low carbohydrate, high protein intake, or a high carbohydrate, low protein intake and there is a chronic ingestion of charcoal broiled meats, theophylline clearance is increased. However, the administration of TEVA-THEOPHYLLINE SR with meals appears not to significantly affect the release of theophylline from TEVA-THEOPHYLLINE SR tablets (see BIOAVAILABILITY).

Usage in Pregnancy and Lactation

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. Therefore, use of theophylline for uncontrolled asthma in pregnant women and nursing mothers should be balanced against the risk of potential effects on the fetus or on the nursing newborn.

Drug Interactions

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

	DRUG		**THEOPHYLLINE**
(a)	Cimetidine, propranolol, allopurinol, macrolide antibiotics (erythromycin), oral contraceptives	$\uparrow T_{1/2}$	↓ clearance
(b)	Alkalinizing agents	$\uparrow T_{1/2}$	↓ clearance
(c)	Influenza vaccine	$\uparrow T_{1/2}$	clearance reported to be decreased or no change.
(d)	Phenytoin, barbiturates, carbamazepine, isoproterenol, rifampin	$\downarrow T_{1/2}$	↑ clearance
(e)	Smoking (tobacco)	$\downarrow T_{1/2}$	↑ clearance
(f)	Acidifying agents	$\downarrow T_{1/2}$	↑ clearance

B. Concurrent use of theophylline influences effects of certain drugs:

(a)	Digitalis glycosides	↑ cardiac effect
(b)	Thiazides	↑ diuresis
(c)	Nephrotoxic drugs	↑ nephrotoxicity
(d)	Lithium	↑ ratio of lithium/creatinine clearance, thus decrease serum lithium
(e)	Sympathomimetic amines	↓ toxicity, CNS stimulation
(f)	Coumarin anticoagulants	↓ anticoagulant activity, increase prothrombin and fibrinogen blood concentrations, shorten prothrombin time
(g)	Allopurinol	↓ antihyperuricemic action
(h)	Probenecid and pyrazolon derivatives	↓ uricosuric action
(i)	Ketamine	↓ threshold value for inducing convulsions

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 cardiac arrhythmias or seizures may be the first signs to appear. Adverse reactions reported with theophylline preparations include:

Gastrointestinal:
nausea, vomiting, epigastric pain, hematemesis, diarrhea, anorexia, reactivation of peptic ulcer, intestinal bleeding.

Central Nervous System: headaches, irritability, restlessness, insomnia, hyperactivity, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

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

Respiratory: tachypnea.

Renal: albuminuria, diuresis and hematuria.

Others: hyperglycemia and inappropriate ADH syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

Insomina, restlessness, mild excitement or irritability, and rapid pulse are early symptoms which may progress to mild delirium. Sensory disturbances such as tinnitus or flashes of light are common. Anorexia, nausea and vomiting are frequently early observations of theophylline overdosage.

Fever, diuresis, dehydration and extreme thirst may be seen. Severe poisoning results in blood, syrup-like "coffee-ground" vomitus, tremors, tonic extensor spasm interrupted by clonic convulsions, extrasystoles, quickened respiration, stupor and finally coma.

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

Treatment:

A. Monitoring serum theophylline levels:
   Following intake of TEVA-THEOPHYLLINE SR, the blood theophylline peak levels may not show until 5 to 8 hours post-ingestion in adults and 4 to 6 hours in children. Patients ingesting overdoses of sustained release theophylline formulations may have, after the initial rise in blood theophylline, also a secondary increase in theophylline levels. One report on fatal self-poisoning has attributed this to compacted tablet masses in the gastrointestinal tract. Careful clinical and laboratory monitoring of stabilized patients is advisable.

B. If potential oral overdose is established and seizure has not occurred:
   1) Induce vomiting;
   2) Administer a cathartic (this is particularly important when a sustained release preparation has been taken);
   3) Administer activated charcoal.

C. If patient is having a seizure:
   1) Establish an airway;
   2) Administer oxygen;
   3) Treat the seizure with intravenous diazepam, 0.1 to 0.3 mg/kg up to a total dose of 10 mg;
   4) Monitor vital signs, maintain blood pressure and provide adequate hydration.

D. 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 vomiting, 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. However, if serum levels exceed 50 μg/mL (257 μM/L), charcoal hemoperfusion may be indicated.

DOSAGE AND ADMINISTRATION

Therapeutic serum levels are generally considered to be between 10 and 20 µg/mL (55 μM/L and 110 μM/L). There is patient-to-patient variation in dosage needed to achieve a therapeutic serum level. This is due to variable rates of elimination. Because of the variation from patient-to-patient, the variation within the same patient, and the relatively

narrow therapeutic range, dosage should be individualized. Monitoring of serum theophylline concentrations is also extremely important, especially in the initial stages of therapy (see PRECAUTIONS).

It is preferable to monitor peak concentrations rather than trough concentrations. Blood samples should, therefore, be drawn 4 to 8 hours after TEVA-THEOPHYLLINE SR dosing. It should be ascertained that all doses have been taken for 60 hours prior to blood sampling (steady state is usually achieved within 3 days). Depending on the sensitivity of the assay method used, dietary xanthines may interfere with assay results. If a dosage increase is not tolerated, dosage should be reduced to the previously tolerated level. Do not attempt to maintain dosage which is not tolerated or which produces serum concentrations above the therapeutic range.

TEVA-THEOPHYLLINE SR TABLETS SHOULD NOT BE CHEWED OR CRUSHED, BUT MAY BE HALVED.

Adult Dose:

The usual initial adult dose is 200 to 300 mg every 12 hours. This dose may be increased by 50 to 100 mg every 12 hours at 3-day intervals until a satisfactory response is obtained or toxic effects appear.

Dosage adjustments should be based upon serum theophylline concentration and/or upon the patient's clinical response. However, doses of 450 mg every 12 hours or higher (900 mg/day) should not be given unless serum theophylline concentration can be monitored. It should not be necessary to exceed a daily dose of 16 mg/kg in adult patients. Even with serum level monitoring, this dose may lead to side effects because of day-to-day variations in blood levels within individual patients.

Children's Dose:

The usual initial dose for children (ages 6 to 12 years) is 6 mg/kg given every 12 hours (12 mg/kg/day).

If the desired response is not obtained after 3 days, and there are no adverse effects, dosage may be increased to 8 mg/kg every 12 hours (16 mg/kg/day). This dose should be considered the maximum unless serum theophylline concentrations can be monitored to guide further dose increases.

If serum concentrations are monitored, and there are no adverse effects, the dosage may be increased by 2 to 3 mg/kg/day at intervals of not less than 3 days, until the desired response is obtained, or until side effects appear. It should not be necessary to exceed a daily dose of 21 mg/kg to obtain an adequate response in children. Even with serum theophylline concentration monitoring, this dose (21 mg/kg/day) may lead to side effects because of day-to-day variations of blood levels within individual patients.

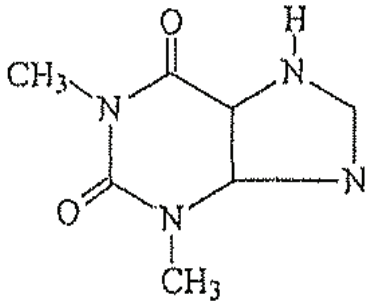
Dividing the daily dosage into 3 doses administered at 8-hour intervals may be indicated if symptoms repeatedly occur at the end of the 12-hour dosing intervals.

PHARMACEUTICAL INFORMATION

Trade Name: TEVA-THEOPHYLLINE SR

Proper Name: Theophylline Anhydrous

Structural Formula:



Molecular Formula: $C_7H_8N_4O_2$ Molecular Weight: 180.2

Chemical Name: 1,3-dimethyl-xanthine

Description: Theophylline is a white, odourless, crystalline powder which has a bitter taste. Theophylline is slightly soluble in water, alcohol and chloroform; sparingly soluble in ether; and soluble in strongly basic solutions.

AVAILABILITY

TEVA-THEOPHYLLINE SR is available in three strengths: 100 mg, 200 mg and 300 mg.

TEVA-THEOPHYLLINE SR 100 mg: white, round film-coated tablets, engraved modified **N|N** on one side and **100** on the reverse.

TEVA-THEOPHYLLINE SR 200 mg: white, oval-shaped film-coated tablets, engraved **novo** and **200** on one side and bisect on the reverse.

TEVA-THEOPHYLLINE SR 300 mg: white, capsule shaped film-coated tablets, engraved modified **N|N** on one side and **300** on the reverse.

TEVA-THEOPHYLLINE SR 100 mg, 200 mg and 300 mg are supplied in bottles of 100, 500 and 1000 tablets, and in unit dose boxes of 100 tablets.

Store bottles between 15° and 30°C. Unit dose boxes should be stored between 15° and 25°C and protected from high humidity.

PATIENT INFORMATION LEAFLET

PrTEVA-THEOPHYLLINE SR

Brand of Theophylline Anhydrous

100, 200 and 300 mg Sustained Release Tablets

Theophylline anhydrous (sustained release) which has been prescribed to you by your doctor is used to treat breathing conditions such as asthma, bronchitis, and emphysema. Theophylline works to open up air passages in the lungs and helps prevent wheezing and shortness of breath.

TEVA-THEOPHYLLINE SR is a "sustained release" form of theophylline. This means its effects last longer than some other forms of this drug. Other brands of "sustained release" theophylline are available. In general, these work in a similar way to TEVA-THEOPHYLLINE SR and have the same side effects.

This leaflet should not take the place of information given by your doctor or pharmacist. Because of YOUR specific health condition, these professionals may have given you different or additional information. If so, be sure to follow their advice. If you have any questions or concerns after reading this leaflet, or if any of the information seems different, talk to your doctor or pharmacist as soon as you can. Do not stop taking your TEVA-THEOPHYLLINE SR without the advice of your doctor.

BEFORE TAKING TEVA-THEOPHYLLINE SR:

Be sure to tell your doctor:

- about all other health problems you have now, or have had in the past;
- about all other medicines you take, including ones you can buy without a prescription;
- about any allergies or bad reactions you have or have had in the past, to foods or drugs;
- if you are pregnant or plan to become pregnant;
- if you are breast-feeding;

- if you are on any kind of diet;
- if you smoke, or have smoked regularly within the past two years.

HOW TO TAKE TEVA-THEOPHYLLINE SR:

- Take TEVA-THEOPHYLLINE SR exactly as prescribed by your doctor. Do not miss doses and do not take extra tablets without your doctor's advice. If you are not clear about the directions, ask your doctor or pharmacist.
- It is important to take all doses of TEVA-THEOPHYLLINE SR, even when you feel well. This keeps a constant amount of theophylline in your body so it can help prevent breathing problems.
- Take TEVA-THEOPHYLLINE SR at evenly spaced times through the day. For example, if you are to take 2 tablets a day, take each one about 12 hours apart. You should also get into the habit of taking each dose around the same time(s) every day.
- It is a good idea to ask your doctor or pharmacist ahead of time what to do about missed doses. In general, if you remember a missed dose within several hours, take it as soon as possible; then go back to your regular schedule. However, if it is almost time for your next dose do not take the missed dose. Just take your next dose on schedule. Never take a double dose of TEVA-THEOPHYLLINE SR to make up for missed tablets.
- TEVA-THEOPHYLLINE SR tablets MUST not be crushed, chewed or broken into small pieces. If you are having trouble swallowing TEVA-THEOPHYLLINE SR, your pharmacist can show you how to break them in half.
- TEVA-THEOPHYLLINE SR should not be used to relieve sudden breathing attacks because it would take too long to start working.

SPECIAL PRECAUTIONS:

- TEVA-THEOPHYLLINE SR has been prescribed for YOUR CURRENT CONDITION ONLY. Do not use it for any other problem unless your doctor tells you. Do NOT give it to other people to use.

- Do not change brands or dosage forms of TEVA-THEOPHYLLINE SR without your doctor's advice. Check the bottle label for the name TEVA-THEOPHYLLINE SR and if a refill of your medicine looks different, check with your pharmacist.
- Do not take any other medicine(s) without the advice of a doctor or pharmacist. Some medicines MAY affect the way TEVA-THEOPHYLLINE SR works for you. This includes vaccines (e.g., for flu), and medicines you can buy without a prescription.

Your dose of TEVA-THEOPHYLLINE SR may need to be changed under certain conditions. Check with your doctor at once if:

- you develop diarrhea, chest infection, fever or flu (influenza);
- you plan to become pregnant;
- you start or stop smoking;
- you eat large amounts of charcoal broiled foods;
- you wish to go on a high protein, low carbohydrate diet or low protein, high carbohydrate diet.
- Keep TEVA-THEOPHYLLINE SR out of the reach of children. As heat and moisture may cause the medicine to break down, do not keep your bottle in the bathroom medicine cabinet or other such places.

POSSIBLE SIDE EFFECTS:
TEVA-THEOPHYLLINE SR is very effective for breathing problems. But like all medicines, it may cause side effects in some people. These can occur with any theophylline medicine.

Theophylline affects different people in different ways. Just because other people have reported these effects, does not mean you will get them.

The following may be early warning signs of too much theophylline for your body. Tell your doctor right away if you notice any of these symptoms. TEVA-THEOPHYLLINE

SR may NOT have caused these problems in your case, but only a doctor can assess this.

- unexplained digestive or stomach problems, such as: nausea, vomiting, heartburn, loss of appetite, stomach pains, diarrhea, black stools (bowel movements) or blood in your stools.

- unexplained changes in general well-being, such as: mood change (restlessness, nervousness, irritability, difficulty sleeping), confusion, memory problems, dizziness, unusual tiredness or weakness, trembling or muscle twitching, convulsions (seizures).

- any of the following unless easily explained by something else: hearing changes (e.g., ringing or buzzing in the ears), vision changes (e.g., seeing flashes of light), unusually fast breathing, unusually fast, pounding or irregular heartbeat, headache, fever, flushing, extreme flushing, extreme thirst, or an unusual increase or decrease in urination ("passing water").

Other side effects which cannot be predicted may occur in some people. If you notice ANY bothersome or unusual effects while taking TEVA-THEOPHYLLINE SR, check with a doctor (or pharmacist) right away.

GENERAL INFORMATION

- More detailed information about TEVA-THEOPHYLLINE SR has been written for health professionals. If you require more information on this drug, consult your doctor or pharmacist.

Teva Canada Limited

PHARMACOLOGY

Theophylline stimulates respiration, augments cardiac inotropy and chronotropy, relaxes smooth muscles, including those in the bronchi and blood vessels (other than cerebral vessels) and increases diuresis. The main use of theophylline has been in the treatment of reversible airway obstruction.

Theophylline is usually readily absorbed following oral administration. The drug is 55 to 65% bound to plasma proteins at the therapeutic plasma concentration range of 10 to 20 μg/mL (55 to 110 μM/L). It is not likely to be subject to pronounced displacement effect. In most patients, steady-state plasma concentrations are achieved within 3 days.

Theophylline is distributed into all body compartments. It crosses the placental barrier thus producing high fetal concentrations. It is also excreted in human breast milk.

The apparent volume of distribution (Vd) ranges from 0.3 to 0.7 L/kg (30 to 70% ideal body weight) and averages about 0.45 L/kg in children and adults. Since protein binding is reduced in premature neonates, adults with hepatic cirrhosis or uncorrected acidemia, and the elderly, the mean Vd is slightly larger since protein binding is reduced in these patients.

Theophylline is metabolized by the liver to 3-methylxanthine, 1-methyluric acid and 1,3-dimethyluric acid. Theophylline and its metabolites are excreted mainly by the kidneys; about 10% excreted unchanged in the urine. Small amounts of theophylline are excreted unchanged in the feces.

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.

The half-life of theophylline is influenced by a number of variables. It is prolonged in patients suffering from chronic alcoholism, impaired hepatic or renal function, congestive heart failure, and in patients receiving macrolide antibiotics and cimetidine. Older adults (over the age of 55) and patients with chronic obstructive pulmonary disease, with or without cor pulmonale, may also have much slower clearance rates. The theophylline half-life may exceed 24 hours in such patients.

Newborns and neonates have extremely slow clearance rates compared to older infants (over 6 months) and children, and may also have theophylline half-life of over 24 hours. The rate of theophylline elimination may also be reduced by high fever for prolonged periods.

Administration of influenza vaccine and infection with influenza have been associated with an impaired rate of theophylline elimination and consequent increases in serum theophylline levels, sometimes with toxic symptoms.

The half-life of theophylline in smokers, smoking one to two packs/day, averages 4 to 5 hours, being much shorter than the half-life in non-smokers which averages 7 to 9 hours. The increase in theophylline clearance caused by smoking is probably the result of induction of drug-metabolizing enzymes that do not readily normalize after cessation of smoking. The effect of smoking on theophylline pharmacokinetics appears to require between three months and two years for normalization.

BIOAVAILABILIIY:

Effect of Food on Theophylline Bioavailability:

The potential for food interacting with theophylline resulting in altered bioavailability has been studied by several authors.

In one study, the effects of four different diets on the metabolism of sustained release theophylline were evaluated in 10 subjects in a four-way crossover study as follows:

i) one 300 mg tablet taken with 250 mL of water after a 12 hour fast;
ii) a liquid diet with low fat, low carbohydrate and moderate protein followed by one 300 mg tablet;
iii) a low fat, moderate protein, high carbohydrate diet followed by one 300 mg tablet;
iv) a high fat, moderate protein and carbohydrate diet followed by one 300 mg tablet.

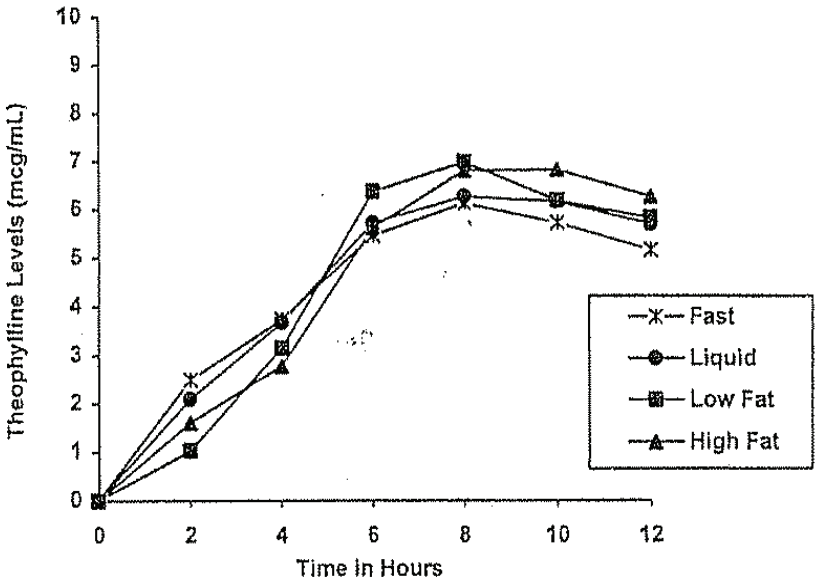
All tablets were taken with 250 mL of water. No additional food or drink was permitted for four hours following medication administration. Serum theophylline levels were measured up to 24 hours post dose.

The mean serum theophylline (pg/mL) data is summarized as follows:

Diet	**Peak Theophylline Values**	**Range of Peak Values**	**Tmax**
Fasting	6.35	4.7 – 8.4	8.4
Liquid	6.75	3.1 – 9.6	8.6
Low Fat	7.16	4.4 – 10.4	7.6
High Fat	7.48	5.0 – 10.3	9.0

Results indicate no major change in the sustained-release characteristics of theophylline tablets associated with the diets tested. Mean theophylline levels have been presented in the following Figure 1.

Figure 1:



Mean theophylline level on the four testing days.
from Tinkelman, et al.

TOXICOLOGY

Theophylline has a narrow therapeutic range which, in connection with an inter-and intra-individual pharmacokinetic variation, makes it difficult to estimate a toxic dose. Usually, a dose of 600 mg theophylline given to an adult will not cause any toxic effects. The risk of toxic effects is related to the plasma level of theophylline. Plasma concentrations above 20 μg/mL (110 μM/L) may produce toxic effects.

The risk of severe toxic effects is markedly increased with plasma concentrations in excess of 25 μg/mL (140 μM/L). In one study, toxicity, primarily consisting of nausea, vomiting and anorexia, occurred in patients with concentrations greater than 13 mg/L and was especially common in patients with concentrations greater than 20 mg/L.

Tolerance to many of the toxic effects of theophylline is widely recognized. The tolerance of an oral overdose of theophylline is individual, and doses of 50 mg/kg and higher have been reported as lethal. In eight patients with theophylline concentrations ranging from 25 to 70 mg/L, seizures and four deaths occurred. Rectal administration of 9 mg/kg theophylline as aminophylline (ethylenediamine salt of theophylline) has produced adverse drug experiences in children.

Concentration-independent effects of theophylline have been reported. One study identified nervousness, nausea and CNS stimulation at the start of theophylline therapy which resolved with continuous therapy.

Theophylline has the potential to cause behaviour changes. In a study involving six children, changes in attention, concentration and memory during theophylline treatment were noted. Improvement was observed when theophylline therapy was discontinued.

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