

Revised: June 2009 (12th version)

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| Standard Commodity Classification No. of Japan |
| 872251 |

- Sustained-release theophylline preparation -

Theolong[®] Tablets 50mg**Theolong[®]** Tablets 100mg**Theolong[®]** Tablets 200mg**Theolong[®]** Granules 50%

| |
|---|
| Powerful drug: Theolong Tablets 200mg and Granules 50% Prescription drug |
|---|

| | Tablets 50 mg | Tablets 100 mg | Tablets 200 mg | Granules 50 % |
|--|------------------|------------------|------------------|------------------|
| Approval No. | 16100AMZ04455000 | 16100AMZ04456000 | 16100AMZ04457000 | 16100AMZ04458000 |
| Date of listing in the NHI reimbursement price | Oct 1987 | Oct 1987 | Oct 1987 | Oct 1987 |
| Date of initial marketing in Japan | Oct 1987 | Oct 1987 | Oct 1987 | Oct 1987 |
| Date of latest approval of indications | Jan 1989 | | | |

| Storage |
|---|
| THEOLONG should be stored at room temperature. THEOLONG bottled tablets should be protected from moisture after opening package. (Hardness of tablets may be decreased by moisture.) THEOLONG granules should be protected from moisture after opening package. (Granules may absorb moisture.) |

| Expiration date |
|---|
| THEOLONG should be used before the expiration date indicated on the package or label. |

Caution: Use only as directed by a physician.**CONTRAINDICATIONS (THEOLONG is contraindicated in the following patients.)**

Patients with a history of serious adverse reactions to THEOLONG or other xanthine derivatives

DESCRIPTION**1. Composition****Tablets 50 mg:**

Each white, speckled sustained-release tablet contains 50 mg of theophylline.

It also contains ethylcellulose, croscarmellose sodium, light anhydrous silicic acid, microcrystalline cellulose, hydrogenated oil, calcium stearate, talc, corn starch, lactose hydrate, hydroxypropylcellulose and hydrated silicon dioxide as inactive ingredients.

Tablets 100 mg:

Each white, speckled sustained-release tablet contains 100 mg of theophylline.

It also contains ethylcellulose, croscarmellose sodium, light anhydrous silicic acid, microcrystalline cellulose, hydrogenated oil, calcium stearate, talc, corn starch, lactose hydrate, hydroxypropylcellulose and hydrated silicon dioxide as inactive ingredients.

Tablets 200 mg:

Each white, speckled sustained-release tablet contains 200 mg of theophylline.

It also contains ethylcellulose, croscarmellose sodium, light anhydrous silicic acid, microcrystalline cellulose,

hydrogenated oil, calcium stearate, talc, corn starch, lactose hydrate, hydroxypropylcellulose and hydrated silicon dioxide as inactive ingredients.

Granules 50%:

Each 1 g of white, sustained-release granules contains 500 mg of theophylline.

It also contains light anhydrous silicic acid, hydrogenated oil, talc, povidone and hydrated silicon dioxide as inactive ingredients.

2. Product description

| Brand name | Dosage form and identification code | Appearance | | | Description |
|------------------------|-------------------------------------|-----------------------|--------------------|-----------------------|---|
| | | Face | Reverse | Lateral | |
| THEOLONG Tablets 50mg | Sustained-release tablets | | | | White, speckled pattern due to sustained-release granules |
| | E TE50 | Diameter (mm) 7.1 | Weight (mg) 135 | Thickness (mm) 3.3 | |
| THEOLONG Tablets 100mg | Sustained-release tablets | | | | White, speckled pattern due to sustained-release granules |
| | E TE100 | Diameter (mm) 8.1 | Weight (mg) 235 | Thickness (mm) 4.2 | |
| THEOLONG Tablets 200mg | Sustained-release tablets | | | | White, speckled pattern due to sustained-release granules |
| | E TE200 | Diameter (mm) 10.1 | Weight (mg) 470 | Thickness (mm) 5.5 | |
| THEOLONG Granules 50% | Granules | | | | White, sustained-release |

INDICATIONS

Bronchial asthma, asthmatic (asthmatoïd) bronchitis, chronic bronchitis and pulmonary emphysema

<Precautions>

THEOLONG Tablets 50mg, Tablets 100mg and Granules 50%

(Tablets 200mg are not approved for use in children.)

Asthmatic (asthmatoïd) bronchitis:

It should be considered to prioritize other drug therapy since this indication is often accompanied by fever. [Many cases of convulsions during the administration of theophylline is much infants with fever.]

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 200 mg of theophylline twice daily, in the morning and at bed time. The usual children's dosage for oral use is 100 - 200 mg of theophylline twice daily, in the morning and at bed time.

The dosage may be adjusted depending on patient's age and symptoms.

Tablets 50 mg:

The usual adult dosage for oral use is 4 tablets twice daily in the morning and at bed time. The usual children's dosage for oral use is 2 to 4 tablets twice daily, in the morning and at bed time.

The dosage may be adjusted depending on patient's age and symptoms.

Tablets 100 mg:

The usual adult dosage for oral use is 2 tablets twice daily, in the morning and at bed time. The usual children's dosage for oral use is 1 to 2 tablets twice daily, in the morning and at bed time.

The dosage may be adjusted depending on patient's age and symptoms.

Tablets 200 mg:

The usual adult dosage for oral use is 1 tablet twice daily, in the morning and at bed time.

The dosage may be adjusted depending on patient's age and symptoms.

Granules 50%:

The usual adult dosage for oral use is 0.4 g of theophylline twice daily, in the morning and at bed time.

The usual children's dosage for oral use is 0.2 - 0.4 g of theophylline twice daily, in the morning and at bed time.

The dosage may be adjusted depending on patient's age and symptoms.

<Precautions>

THEOLONG Tablets 50mg, Tablets 100mg and Granules 50%

(Tablets 200mg are not approved for use in children.)

This drug should be administered with caution carefully observing clinical symptoms and monitoring while its blood level.

Please refer to the Guideline* and other relevant updates for recommended dosage and regimen for pediatric use of this drug in bronchial asthma.

*Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005

1. Recommended dose of theophylline (usually administered 2 times daily)

| Age | Recommended dose |
|-----------------------------|-------------------------------------|
| Under 6 months | Not to be administered in principle |
| 6 months - under 1 year old | 3 mg/kg |
| 1 year - under 2 years old | 4-5 mg/kg |
| 2 years - 15 years old | 4-5 mg/kg |

2. Cases requiring special attention for administration:

Excepting the case of patients of 2 years of age and older with chronic severe symptoms, when other drugs have lacked effectiveness, THEOLONG should be administered after full consideration of indication it is being used for based on careful observation of the patient's condition (symptoms such as pyrexia, convulsions, etc...). In principle, it is not recommended for patients under 2 years of age with convulsive disorders such as febrile convulsions and epilepsy.

PRECAUTIONS

1. Careful Administration (THEOLONG should be administered with care in the following patients.)

- (1) Patients with epilepsy

[Seizures may be caused by central nervous system (CNS) stimulation.]
- (2) Patients with hyperthyroidism

[Hypermetabolism accompanying hyperthyroidism and the action of catecholamines may be potentiated.]
- (3) Patients with acute nephritis

[Since THEOLONG enhances kidney load, urinary protein may increase.]
- (4) Patients with congestive heart failure

[Since the theophylline clearance may diminish causing an increase in the blood theophylline concentration, the dosage should be reduced on the basis of the determined blood theophylline concentration, etc.]
- (5) Patients with hepatic function disorders

[Since the theophylline clearance may diminish causing an increase in the blood theophylline concentration, the dosage should be reduced on the basis of the determined blood theophylline concentration, etc.]
- (6) Elderly patients

[See "Use in the Elderly" section.]
- (7) Pregnant women, women suspected of being pregnant, parturient women or nursing mothers

[See "Use during Pregnancy, Delivery or Lactation" section.]
- (8) Children
 - 1) Since convulsions are likely to occur in children (especially nursing infants) more frequently than in adults, and also, because theophylline clearance may be variable, THEOLONG should be administered with care to them, monitoring the blood theophylline concentration. Particular care is required with the following.

- a) Children with a history of epilepsy or convulsions
[Convulsions may occur.]
- b) Children with fever
[The blood theophylline concentration may increase and convulsions or other symptoms may occur.]
- c) Nursing infants (<6 months)
[The theophylline clearance is unsteady in nursing infants. There may be an decrease in the theophylline clearance and an increase in the blood theophylline concentration in nursing infants (<6 months).]
- 2) The safety in low birth weight infants and neonates has not been established (no clinical experience).

2. Important Precautions

- (1) The occurrence of adverse reactions due to theophylline may cause an increase in the blood theophylline concentration. It is advisable to regularly monitor the blood theophylline concentration and based on this, set up an individual dosage plan for each patient.
- (2) If adverse reactions occur, THEOLONG should be reduced in dosage or discontinued, and it is advisable to determine the blood theophylline concentration.
- (3) When the drug is administered to children, especially infants, it is advisable that the parents be instructed in advance to take actions such as temporarily decreasing the dosage or discontinuing the drug in the case that pyrexia is observed.
- (4) When the drug is used for children, due to their general inability to complain of subjective symptoms, parents should be advised to observe their condition carefully, and if any abnormality is observed, report this immediately to the physician, or take other appropriate measures.

3. Drug Interactions

THEOLONG is metabolized mainly by CYP1A2. [See “PHARMACOKINETICS” section.]

Precautions for coadministration (THEOLONG should be administered with care when coadministered with the following drugs.)

| Drugs | Signs, Symptoms, and Treatment | Mechanism and Risk Factors |
|---|---|---|
| Other xanthine derivatives Aminophylline Choline theophylline Diprophylline Caffeine, etc. CNS stimulants Ephedrine hydrochloride Ephedra herb, etc. | THEOLONG may cause excessive CNS stimulation. [See “Overdosage” section.] Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken. | When concomitantly administered with these drugs, CNS stimulation may be potentiated. |

| | | |
|---|--|--|
| Sympathetic nervous system stimulants (β-stimulants) Isoprenaline hydrochloride Clenbuterol hydrochloride Tulobuterol hydrochloride Terbutaline sulphate Procaterol hydrochloride, etc. | Adverse reactions due to β-stimulants such as hypokalemia or cardiovascular symptoms (tachycardia, arrhythmia, etc.) may be potentiated. Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken. | It is considered that the action of β-stimulants may be potentiated due to their cardiostimulatory action. The mechanism of hypokalemia enhancement is unknown. |
| Halothane | Adverse reactions such as arrhythmia, etc. may be potentiated. Also, continuous coadministration with halothane may cause an increase in the blood theophylline concentration. Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken. | It is considered that theophylline and halothane have synergistic and additive effects with respect to the heart. |
| Ketamine hydrochloride | Convulsions may occur. Caution should be exercised with respect to convulsions. In the event of abnormal findings, appropriate measures such as the administration of an anticonvulsant, should be taken. | Considered to be due to lowering of the convulsant threshold. |
| Cimetidine Mexiletine hydrochloride Propafenone hydrochloride Amiodarone hydrochloride Enoxacin Pipemidic acid trihydrate Ciprofloxacin hydrochloride Norfloxacin Tosufloxacin tosilate Pazufloxacin mesilate Prulifloxacin Erythromycin Clarithromycin Roxithromycin Tiabendazole Ticlopidine hydrochloride Verapamil hydrochloride Diltiazem hydrochloride Fluvoxamine maleate Fluconazole Disulfiram | Symptoms of theophylline toxicity may occur. [See “Overdosage” section.] Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken. | It is considered that the blood theophylline concentration increases due to decreasing theophylline clearance by the inhibition of hepatic drug metabolizing enzymes. |
| Aciclovir Valaciclovir hydrochloride Interferon Ipriflavone Ciclosporin Allopurinol | | Considered to be due to increase in the blood theophylline concentration. |
| Zafirlukast | Symptoms of theophylline toxicity may occur. [See “Overdosage” section.] Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken. Also THEOLONG may decrease the blood concentration of zafirlukast. | It is considered that the blood theophylline concentration increases due to decreasing theophylline clearance caused by the inhibition of hepatic drug metabolizing enzymes. The mechanism by which THEOLONG decreases the blood concentration of zafirlukast is unknown. |

| | | |
|---|---|--|
| Rifampicin Phenobarbital Lansoprazole Ritonavir | Effect of theophylline may be diminished. As the blood theophylline concentration may decrease, appropriate measures should be taken. | It is considered that the blood theophylline concentration decreases due to increasing theophylline clearance through the induction of hepatic drug metabolizing enzymes. |
| Phenytoin Carbamazepine | The effects of theophylline and the coadministered drug may be diminished. As the blood theophylline concentration may decrease, appropriate measures should be taken. Also, caution should be exercised with respect to decreasing effect and blood concentration of coadministered drug. | It is considered that the blood theophylline concentration decreases due to increasing theophylline clearance through the induction of hepatic drug metabolizing enzymes. |
| Dipyridamole | THEOLONG may diminish the effect of dipyridamole. | Due to adenosine antagonism. |
| Ramatroban | THEOLONG may elevate the blood concentration of ramatroban. | The mechanism of elevation of the blood concentration of ramatroban is unknown. |
| Riluzole | THEOLONG may increase the action of riluzole (induction of adverse reactions). | An <i>in vitro</i> study has suggested that THEOLONG inhibits the metabolism of riluzole. |
| Cigarette smoking | Symptoms of theophylline toxicity may occur when someone stops smoking (including during use of nicotine preparations as a supporting agent to stop smoking). [See "Overdosage" section.] Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken. | It is considered that the blood theophylline concentration decreases due to the increasing theophylline clearance, through the induction of hepatic drug metabolizing enzymes by smoking. Also, it is considered that blood theophylline concentration is increased by stopping smoking. |
| <i>Hypericum perforatum</i> (foods including St. John's Wort) | Foods including <i>Hypericum perforatum</i> may potentiate the metabolism of THEOLONG and decrease the blood theophylline concentration. These foods should be avoided when taking THEOLONG. | It is considered that hepatic drug metabolizing enzymes induced by <i>Hypericum perforatum</i> potentiate the metabolism of THEOLONG and increase theophylline clearance. |

4. Adverse Reactions

Adverse reactions were reported in 139 of 842 patients (16.51%). (At the approval)

(1) Clinically significant adverse reactions (incidence unknown)

1) Convulsions and disturbed consciousness

Convulsions or disturbed consciousness such as delirium or coma, may occur. Appropriate measures, such as the administration of an anticonvulsant, should be taken.

2) Acute encephalopathy

Acute encephalopathy may occur in continuation to convulsions and disturbed consciousness. In the event of such symptoms, treatment should be discontinued

and appropriate measures, such as administration of anticonvulsants, taken.

3) Rhabdomyolysis

Since rhabdomyolysis may occur, caution should be exercised with respect to weakness, myalgia or elevation of CK (CPK), etc. In the event of such symptoms, treatment should be discontinued and appropriate measures taken. Caution should be exercised with respect to acute renal failure due to rhabdomyolysis.

4) Gastrointestinal hemorrhage

Gastrointestinal hemorrhage (hematemesis of melena) caused by ulcers may occur. In the event of such symptoms, appropriate measures, such as discontinuation of the medication, should be taken.

5) Pure red cell aplasia

Pure red cell aplasia may occur. In the event of anemia, appropriate measures, such as discontinuation of the medication, should be taken.

6) Anaphylactic shock

Anaphylactic shock (urticaria, pallor, diaphoresis, decrease in blood pressure or dyspnea, etc.) may occur. In the event of such symptoms, treatment should be discontinued and appropriate measures taken.

7) Hepatic function disorders and jaundice

Hepatic function disorders (elevation of AST (GOT) or ALT (GPT), etc.) and jaundice may occur. Patients should be carefully observed. In the event of abnormal findings, treatment should be discontinued and appropriate measures taken.

8) Tachypnea and hyperglycemia

Tachypnea or hyperglycemia may occur.

(2) Other adverse reactions

| | ≥5% | 5% > ≥0.1% | Incidence unknown |
|------------------|-------------------------------|--|--|
| Hypersensitivity | | Rash and pruritus | Urticaria, erythema (erythema exsudativum multiforme, etc.) and fixed eruption |
| Psychoneurologic | | Headache, insomnia, dizziness, tinnitus, tremor and numbness | Nervousness (excitement, moroseness and irritated feeling), anxiety, involuntary movement and hyper-tonia |
| Cardiovascular | | Palpitations and facial pallor | Hot facial flushes, tachycardia and arrhythmia (ventricular extrasystole, etc.) |
| Gastrointestinal | Nausea, vomiting and anorexia | Diarrhea, abdominal pain, feeling of enlarged abdomen and dyspepsia (heart burn, etc.) | Hiccups |
| Urinary | | | Albuminuria and polyuria |
| Metabolic | | | Elevation of blood uric acid and CK (CPK), etc. |
| Hepatic | | | Elevation of AST (GOT), ALT (GPT), Al-P, LDH and γ-GTP, etc. |
| Hematologic | | | Anemia and eosinophilia |
| Others | | malaise | Edema, arthralgia, melosalgia, sweating, chest pain, hypokalaemia, epistaxis and numbness (mouth and periglottic area) |

5. Use in the Elderly

THEOLONG should be administered with care to elderly patients watching for the occurrence of adverse reactions.

[When elderly subjects were compared with young subjects, it was reported that the peak blood theophylline concentration and AUC were higher in the elderly than in the young.]

6. Use during Pregnancy, Delivery or Lactation

(1) THEOLONG should only be used for pregnant women or women suspected of being pregnant, if the expected therapeutic benefits are evaluated to outweigh the possible risk of treatment.

[THEOLONG has been reported to have reproductive toxicity, such as teratogenic effects on the fetus, etc. in animals (mice, rats and rabbits). Also, THEOLONG may be transported across the placenta to the fetus and cause vomiting and nervousness, etc. in neonates.]

(2) Nursing mothers should discontinue breast feeding during treatment.

[THEOLONG is excreted into human milk, giving rise to nervousness in nursing infants.]

7. Pediatric Use

THEOLONG should be administered with care to children [See "Careful Administration" section.]

8. Overdosage

(1) Symptoms

When the blood theophylline concentration is high, toxic symptoms, such as gastrointestinal symptoms (notably nausea or vomiting), psychoneurologic symptoms (headache, insomnia, anxiety, excitement, convulsions, delirium, disturbed consciousness or coma, etc.), cardiovascular symptoms (tachycardia, ventricular tachycardia, atrial fibrillation or decrease in blood pressure, etc.), hypokalemia or other electrolyte abnormalities, stimulated respiration or rhabdomyolysis, etc. are likely to occur. Serious symptoms may appear immediately, without developing gradually from mild symptoms.

(2) Treatments

In the case of overdosage, theophylline should be withdrawn and symptomatic therapy for toxic symptoms conducted. Procedures for the removal of residual theophylline in the gastrointestinal tract are emesis, gastric lavage, administration of purgatives and oral administration of activated charcoal, etc. Procedures for removal of theophylline in the blood are accelerated elimination using an infusion solution, oral administration of activated charcoal, hemoperfusion or hemodialysis using charcoal as adsorbent, etc. Although the blood theophylline concentration may have decreased, it may rise again due to the transfer of theophylline from the tissues.

1) If the patient has no convulsions or arrhythmias

a) If the patient is seen within a few hours of overdosage, induction of emesis may be of value. This is particularly effective if it is within 1 hr.

b) Administer purgatives. But, caution should be exercised with respect to body fluid and electrolyte abnormalities.

c) Administer repeated doses of activated charcoal and monitor the blood theophylline concentration.

d) If convulsions are anticipated, the administration of phenobarbital, etc., should be considered. Since phenobarbital may cause respiratory depression, caution should be exercised in administration.

2) If the patient has convulsions

a) Establish an airway.

b) Supply oxygen.

c) Treat the convulsions with intravenous diazepam, etc. If they cannot be controlled, the use of a general anesthetic should be considered.

d) Monitor vital signs, maintain blood pressure and provide adequate hydration.

3) If the patient is in a post-convulsion coma

a) Maintain an airway and supply oxygen.

b) Purgatives and activated charcoal will need to be administered via a large bore gastric lavage tube.

c) Keep the patient in the ICU with adequate hydration until the blood theophylline concentration falls. If the repeated oral administration of activated charcoal does not decrease the blood concentration, hemoperfusion or hemodialysis using activated charcoal should be considered.

4) If the patient has arrhythmia

a) Take adequate measures such as pacing, direct current defibrillation or the use of antiarrhythmic drugs, etc.

b) Monitor vital signs, maintain blood pressure and provide adequate hydration. Also, if electrolyte abnormalities are present, they should be corrected.

9. Precautions concerning Use

(1) Preparation

When THEOLONG granules are dispensed, it is desirable that combination with other drugs be avoided since temporary adjustment of the THEOLONG dosage or its discontinuation will be required in the case that pyrexia is observed.

(2) Caution in handing over drug

1) THEOLONG should be taken without chewing since it is a sustained release preparation.

2) THEOLONG should be taken orally with water.

3) For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in serious complications such as mediastinitis.]

(3) White granules derived from THEOLONG may rarely be present in feces.

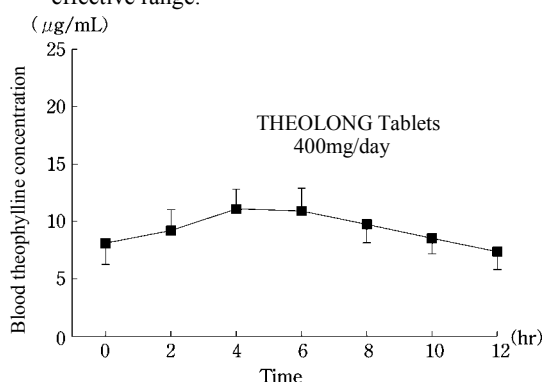
PHARMACOKINETICS

1. Blood concentration

(1) Change in the blood concentration

THEOLONG Tablets were administered to seven patients with asthma at a dose of 200 mg of theophylline twice daily for three days to achieve a steady state in the theophylline blood concentration.

The blood theophylline concentration was determined 12 hr after the final administration. The mean blood concentration (C_{ave}) was 10.16 $\mu\text{g}/\text{mL}$. The area under plasma concentration-time curve (AUC), the mean residence time (MRT), the peak plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) are shown in the table below. It was demonstrated that both C_{max} and the trough plasma concentration (C_{min}) were inside the effective range. ¹⁾



Time course of blood concentration in steady state until 12 hr after administration in morning for THEOLONG Tablets 200mg twice daily at consecutive dosage

(Mean \pm S.E.M., n=7)

Pharmacokinetic parameters for steady state of theophylline blood concentration after administration of THEOLONG 200 mg twice daily at consecutive dosage

| AUC ₀₋₁₂ ($\mu\text{g} \cdot \text{hr}/\text{mL}$) | MRT ₀₋₁₂ (hr) | t_{max} (hr) | C_{max} ($\mu\text{g}/\text{mL}$) | C_{min} ($\mu\text{g}/\text{mL}$) | ΔC ($\mu\text{g}/\text{mL}$) | C_{ave} ($\mu\text{g}/\text{mL}$) |
|--|-----------------------------|-------------------|--|--|---|--|
| 132.7 ± 27.4 | 5.9 ± 0.2 | 4.9 ± 1.5 | 12.58 ± 2.42 | 7.48 ± 2.23 | 5.09 ± 0.88 | 10.16 ± 2.07 |

(Mean \pm S.E.M., n=7)

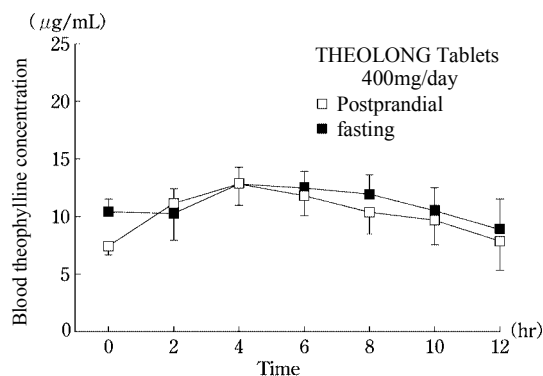
(2) Therapeutic Drug Monitoring (TDM)

Range of effective blood concentration: 8-20 $\mu\text{g}/\text{mL}$ in adults

Main cytochrome P450 subfamily involved in metabolism: CYP1A2

2. Effect of meal

THEOLONG Tablets were administered to three patients with asthma at 200 mg of theophylline twice daily for consecutive dosage. The blood theophylline concentration at the steady state was compared for the fasting and postprandial states. The change in the blood theophylline concentration and pharmacokinetic parameters are shown in following table. ¹⁾



Time course in blood concentration in steady state until 12 hr after administration at morning of THEOLONG Tablets 200mg twice daily at consecutive dosage

(Mean \pm S.E.M., n=3)

Effect of meals on pharmacokinetic parameters in steady state after administration of THEOLONG 200 mg twice daily for consecutive dosage

| Diet | AUC ₀₋₁₂ ($\mu\text{g} \cdot \text{hr}/\text{mL}$) | MRT ₀₋₁₂ (hr) | t_{max} (hr) | C_{max} ($\mu\text{g}/\text{mL}$) | C_{min} ($\mu\text{g}/\text{mL}$) | ΔC ($\mu\text{g}/\text{mL}$) | C_{ave} ($\mu\text{g}/\text{mL}$) |
|---------------|--|-----------------------------|-------------------|--|--|---|--|
| post-prandial | 134.9 ± 23.9 | 6.0 ± 0.2 | 4.7 ± 1.2 | 13.18 ± 1.75 | 8.42 ± 2.71 | 4.77 ± 0.98 | 10.96 ± 2.31 |
| Fasting | 126.0 ± 20.7 | 5.8 ± 0.3 | 4.7 ± 1.2 | 12.85 ± 1.07 | 7.11 ± 2.06 | 5.74 ± 1.03 | 10.08 ± 2.43 |

(Mean \pm S.E.M., n=3)

3. Absorption, metabolism and excretion

According to the results of studies done outside Japan, orally administered theophylline is little affected by the first-pass effect but is metabolized in the liver and is almost completely excreted in the urine (theophylline 12.5%, 1-methyl uric acid 20.2%, 3-methylxanthine 13.1%, 1-methylxanthine 1.0% and 1,3-dimethyl uric acid 53.2%). ^{2, 3)}

CLINICAL STUDIES

1. Open labeled clinical trials for dose-finding ⁴⁻⁸⁾

| Subjects (Number of patients) | Utility rating (%) | |
|----------------------------------|---------------------------------|-----------------------------|
| | Moderately to remarkably useful | Fairly to remarkably useful |
| Bronchial asthma | Children (284 patients) | 73.6 % 91.2 % |
| | Adults (242 patients) | 59.9 % 83.9 % |
| Chronic Bronchitis (22 patients) | 45.5 % | 86.4 % |
| Pulmonary emphysema (5 patients) | 40.0 % | 60.0 % |

2. Double-blind clinical trial

The clinical usefulness of THEOLONG has been demonstrated in a multicenter double-blind clinical trial on adult patients with bronchial asthma. ⁹⁾

PHARMACOLOGY

1. Bronchodilative action

In experiments with isolated bronchial muscle of guinea pigs and humans, theophylline dilated the muscle. Also, clinically, it has been demonstrated that theophylline reduced the respiration resistance of patients with bronchial asthma. ¹⁰⁻¹³⁾

2. Mechanism of action

Several hypotheses have been proposed to elucidate the mechanism of action of theophylline: they include increasing the cellular concentration of c-AMP through inhibition of

phosphodiesterase activity; antagonism to adenosine receptors; regulation of intracellular Ca²⁺ distribution, etc.^{2, 13)}

PHYSICOCHEMISTRY

Nonproprietary name: Theophylline (JAN)

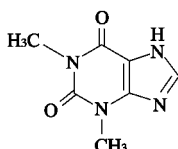
Chemical name:

3,7-Dihydro-1,3-dimethyl-1*H*-purine-2,6-dione

Molecular formula: C₇H₈N₄O₂

Molecular weight: 180.16

Structural formula:



Description:

Theophylline occurs as white crystals or crystalline powder. It is odorless.

It is soluble in *N, N*-dimethylformamide, slightly soluble in water, in ethanol(95) and in chloroform, and practically insoluble in diethylether. It dissolves in potassium hydroxide TS and in ammonia TS.

Melting point: 271-275°C

PACKAGING

THEOLONG Tablets 50 mg:

Boxes of 100 and 500 in press-through packages

THEOLONG Tablets 100 mg:

Boxes of 100, 140 (14 Tabs.×10), 500 and 1,400 (14 Tabs.×100) in press-through packages, and bottles of 500

THEOLONG Tablets 200 mg:

Boxes of 100, 140 (14 Tabs.×10) and 1,000 in press-through packages, and bottles of 500

THEOLONG Granules 50%:

Cans of 100 g

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