Leaftet Theograd

Size: 332 x 207mm

Date: Revised on 18-6-2015

Theophylline

Pharmacological Properties

Pharmacodynamic Properties

Pharmacotherapeutic group: Anti-Asthmatic medicines. Xanthines

Theophylline is a methylxanthine (purine-derivative). Its wide pharmacological spectrum of action includes:

- Relaxation of the smooth muscle tissue of the bronch and pulmonary vessels
- Improvement of capillary clearance
- Inhibition of mediator release from mast cells and other inflammatory cells
- Reduction in the severity of bronchoconstriction
- Reduction in the severity of acute and late asthma reactions
- Increased diaphragmatic contractility

Theophylline's mechanisms of action are not yet fully understood. Inhibition of phosphodiesterase and elevation of intracellular c-AMP may only be of significance at concentrations in the upper therapeutic range. Other mechanisms that have been postulated include adenosine receptor antagonism, prostaglandin antagonism and translocation of intracellular calcium. However, these effects also often occur with high doses of theophylline.

Pharmacokinetic properties

Theophylline is fully absorbed after oral dosing. Food intake may affect the absorption rate (delay or acceleration, dose dumping) and the relative bioavailability of sustained release dosage forms.

Multiple dose studies (twice daily administration, 12 hour dose interval) with theophylline SR 375 mg (theophylline) in fasted subjects and after ingestion of a high fat meal disclosed no evidence of food-drug interactions.

Relative bioavailability is 102 % compared with administration to fasted subjects. Fasting doses and postprandial doses are bioequivalent.

Peak theophylline SR forte concentrations at steady state (Omax) were 9.16 mg/mL (geometric mean) in fasted subjects and 9.42 mg/mL (geometric mean) in fasted subjects.

Theophylline's bronchodilatory action correlates with the plasma concentration. Optimum therapeutic effects in the presence of a calculable effective range (approximately 40% in neonates and adults with cirrhosis of the liver).

About 60% of plasma theophylline is protein-bound. Theophylline is eliminated by hepatic biotransformation and renal excretion. Adults excrete about 7 to 15% of a dose intact in the urine. Theophylline is mainly excreted by the kidneys in the pediatric population. Neonates excrete about 50% unchanged drug and substantial portions in the form of caffeine.

Effective plasma concentrations: 5-12 mcg/mL (do not exceed 20 mcg/mL).

Production of bronchodilation may cease if concentrations fall below this range. Plasma concentrations should be monitored and the dose adjusted accordingly. Theophylline therapy is best monitored by measuring plasma levels. Monitoring should be performed:

- Immediately before and six to eight hours after administration
- In certain circumstances, more frequently
- When the patient changes to a different preparation or dosage form
- If plasma theophylline levels are very high, hemoperfusion or hemodialysis may achieve rapid and complete detoxication.

Because of the high morbidity and mortality associated with theophylline-induced seizures, treatment should be rapid and aggressive.

Oral activated charcoal (0.5 g/m² up to 20 g and repeat at least once two hours after the first dose) is extremely effective in blocking the absorption of theophylline throughout the gastrointestinal tract, even when administered several hours after ingestion. A single dose of sorbitol may be used to promote stooling to facilitate removal of theophylline bound to charcoal from the gastrointestinal tract. Although emetics induce vomiting, they do not reduce the absorption of theophylline unless administered within five minutes of ingestion and even then is less effective than oral activated charcoal.

Electrocardiographic monitoring should be initiated on presentation and continued until the serum theophylline level has returned to a non-toxic level. Serum electrolytes and glucose should be measured on presentation and at appropriate intervals as assessed by clinical circumstance. Monitoring and treatment should be continued until the serum concentration decreases below 20 mcg/mL.

Specific recommendations

Serum Concentration > 20 - 30 mcg/mL

1. Administer a single dose of oral activated charcoal.
2. Monitor the patient and obtain a serum theophylline concentration in two to four hours to ensure that the concentration is not increasing.

Serum Concentration > 30 - 100 mcg/mL

1. Administer multiple-dose oral activated charcoal and measures to control emesis.
2. Monitor the patient and obtain serial theophylline concentrations every two to four hours to gauge the effectiveness of therapy and to guide further treatment decisions.
3. Institute extracorporeal removal if emesis, seizures, or cardiac arrhythmias cannot be adequately controlled.

Serum Concentration > 100 mcg/mL

1. Consider prophylactic anticonvulsant therapy.
2. Administer multiple-dose oral activated charcoal and measures to control emesis.
3. Consider extracorporeal removal, even if the patient has not experienced a seizure.
4. Monitor the patient and obtain serial theophylline concentrations every two to four hours to gauge the effectiveness of therapy and to guide further treatment decisions.

Extracorporeal removal

Increasing the rate of theophylline clearance by extracorporeal methods may rapidly decrease serum concentrations. Charcoal hemoperfusion is the most effective method of extracorporeal removal, increasing theophylline clearance up to six fold, but serious complications, including hypotension, hypocalcemia, platelet consumption, and bleeding diatheses may occur. Hemodialysis is about as efficient as multiple-dose oral activated charcoal. Hemoperfusion is usually about as efficient as multiple-dose oral activated charcoal but is more expensive and uncomfortable. In very severe cases of overdose that fail to respond to treatment further treatment decisions.

Two to four hours to gauge the effectiveness of therapy and to guide further treatment decisions.

How supplied

Theograd 350 mg gradumet Tablets are supplied in blister strips of 10x10s in carton. (No. 8498)

Manufactured by: Abbott Laboratories (Pakistan) Ltd. Landhi, Karachi.

SOLID 1003058897 17 JULY 2014

THEOGRAD (Theophylline)

Theophylline Gradumet tablets contain theophylline in a Gradumet sustained-release formulation for oral administration. Theophylline is a bronchodilator, structurally classified as a xanthine. It occurs as a white, crystalline, partially water-soluble taste.

The Gradumet is an inert, porous, plastic matrix, which is impregnated with micronized theophylline. The drug is released slowly from the Gradumet as it passes through the gastrointestinal tract. The expanded matrix is not absorbed and is excreted in the stool.

Clinical Therapeutic indications

Prevention and treatment of bronchospasm due to asthma and chronic obstructive airways diseases. Sustained release theophylline preparations are not intended for the acute treatment of status asthmaticus or acute bronchospasm. Theophylline should not be used as first drug of choice in the treatment of asthma in children.

Pharmacological form

Theophylline Gradumet tablets contain theophylline in a Gradumet sustained-release formulation for oral administration. Theophylline is a bronchodilator, structurally classified as a xanthine. It occurs as a white, crystalline, partially water-soluble taste.

The Gradumet is an inert, porous, plastic matrix, which is impregnated with micronized theophylline. The drug is released slowly from the Gradumet as it passes through the gastrointestinal tract. The expanded matrix is not absorbed and is excreted in the stool.

Preclinical safety data

Theophylline is embryotoxic and teratogenic and shows effects on male and female fertility in animals depending on dose. In rabbits the teratogenic effects occur at 5 times the human target therapeutic plasma concentration.

Storage

Protect from heat, light & moisture.

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THEOGRAD (Theophylline)

Qualitative and quantitative composition

Each Theograd Gradumet tablet contains 350 mg Theophylline.

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Physiological and method of administration

General guidelines

The theophylline dosage should be adjusted on the basis of individual efficacy and tolerability. Initially, the dosage should be adjusted to determine plasma theophylline concentrations (target range: 8-20 mcg/mL). Monitoring of serum theophylline is indicated particularly in the event of side effects or inadequate response.

When determining the starting dose, any premedication with theophylline or theophylline compounds needs to be taken into account as regards dose reduction.

The dose should be calculated on the basis of ideal body weight as theophylline does not distribute into fatty tissue. Theophylline elimination is commonly reduced in patients with heart failure, renal failure, severe hypoxemia, impaired liver function, pneumonia, viral infection (especially influenza), in the elderly and in patients on certain other drugs (see interactions). These patients therefore have lower dosage requirements and caution should be exercised when increasing the dose. There are also reports of reduced theophylline clearance after tuberculosis and influenza vaccination and a reduction in the dose may be necessary in such cases.

Doses should be spaced at regular intervals over a 24 hour period.

Theophylline Gradumet tablets should not be chewed or crushed.

Adults

The daily theophylline maintenance dose for adults is 11 to 13 mg per kg of body weight.

Smokers need a higher theophylline dose relative to body weight than non-smokers. This is because of theophylline metabolism which is accelerated in smokers.

Pediatric

Theophylline should not be used in children below 6 months of age (see
contraindications

Children from the age of six months require a higher body weight-related theophylline dose than non-smoking adults since in this population the clearance rate is higher.

Solid pharmaceutical drugs of Theophylline should not be used in children below 6 years of age. Other dosage forms are available that are more suitable for children aged less than 6 years.

The stated daily dose may need to be reduced when switching a patient from an instant release form to a slow release theophylle preparation.

Unless otherwise prescribed, the following dosage recommendations apply:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Daily dose (mg/kg body)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8</td>
<td>20-25</td>
<td>24</td>
</tr>
<tr>
<td>8-12</td>
<td>25-40</td>
<td>20</td>
</tr>
<tr>
<td>&gt; 10-16</td>
<td>50-60</td>
<td>18</td>
</tr>
<tr>
<td>&gt; 16 years</td>
<td>60-70</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Contraindications

Theophylline is contraindicated in:

- Hypersensitivity to the active substance or to any of the inactive ingredients
- Recent myocardial infarction
- Acute tachyphylaxis
- Children under 6 months of age

Gradual tablets are contraindicated in the presence of intestinal obstruction or any intestinal blockage.

Special Warnings and Precautions for use

Theophylline should be used with caution and only if absolutely necessary in the following cases:

- Unstable angina
- Patients at risk of tachyphylaxis
- Severe hypertension
- Hypertrophic obstructive cardiomyopathy
- Hyperthyroidism
- History of epileptic seizures
- Gastro- and/or duodenal ulcer
- Porphyria

Theophylline should be used with caution in patients with hepatic or renal function impairment.

Use of theophylline in the elderly, patients with multiple pathologies and patients who are seriously ill and/or in intensive care is associated with a higher risk of toxicity. Therapeutic drug monitoring should therefore be performed.

In case of insufficient effect of the recommended dose and in case of adverse events, theophylline plasma concentration should be monitored.

Acute febrile illness

Fever decreases the clearance of theophylline. It may be necessary to decrease the dose to avoid intoxication.

Interaction with Other Medicinal Products and Other Forms of Interaction

Interactions with other xenobiotics, beta-sympathomimetics, caffeine and similar substances have been reported with theophylline. Theophylline may have a shorter half-life and/or diminished bioavailability and efficacy in smokers and when given with parabenzylthio, the theophylline dose may need to be increased.

Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Theophylline Plasma Concentration</th>
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<tbody>
<tr>
<td>Phenylbutazone</td>
<td>Decrease clearance and decrease steady-state plasma concentration</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Decrease clearance and decrease peak plasma concentrations</td>
</tr>
<tr>
<td>Cimetidine</td>
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<tr>
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<tr>
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<tr>
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<tr>
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</tr>
<tr>
<td>Formoterol</td>
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Metabolism and nutrition disorders

- Hypothyroidism
- Hyperthyroidism
- Alcohol

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Fertility, Pregnancy and Lactation

Fertility

There are no clinical data on fertility in humans. Nonclinical data on theophylline reveal adverse effects on male and female fertility.

Pregnancy

The safety of theophylline, which crosses the placental barrier, has not been established as there are no adequate and well-controlled studies in pregnant women. Theophylline should not be used during pregnancy, especially the first three months unless strictly necessary. During the second and third trimesters of pregnancy, theophylline should not be used unless the benefits clearly outweigh the risks, as the drug may produce symptomatic effects in the fetus.

Theophylline plasma protein binding and clearance may diminish as the pregnancy progresses, therefore, dose reduction may be necessary in order to avoid adverse effects.

Theophylline treatment towards the end of a pregnancy may inhibit uterine contractions. Premature exposed neonates need to be monitored closely for signs of theophylline-induced effects.

Breastfeeding

Theophylline is excreted in breast milk. Therefore neonates and infants of nursing mothers taking theophylline should be monitored closely for signs of theophylline-induced effects (theophylline serum concentrations may be produced in the infant).

Nursing should ideally take place immediately before a dose of the drug. Nursing mothers requiring elevated therapeutic doses must stop breast feeding.

Effects on Ability to Drive and Use Machines

Even when taken as prescribed, this drug may affect the individual's ability to drive a vehicle, operate machinery or work safely under hazardous conditions. This applies particularly when the medication is taken in conjunction with alcohol or other drugs liable to impair judgment and motor skills.

Undesirable effects

Adverse reactions may be aggravated in patients with individual hypersensitivity or overdose (plasma theophylline concentration above 20 microg/ml).

The following side effects are seen in association with treatment with theophylline-containing drugs:

Immune system disorders

- Hypersensitivity

Metabolism and nutrition disorders

- Hypothyroidism, hyperglycaemia, electrolyte imbalance

Psychiatric disorders

- Agitation, restlessness, irritability, nervousness

Nervous system disorders

- Headache, insomnia, tremor, convulsions

Cardiac disorders

- Heart rate increased, heart rate irregular, palpitations, arrhythmia, ventricular arrhythmia, tachycardia, sinus tachycardia, supraventricular tachycardia, atrial tachycardia and atrial flutter, ventricular extrasystoles, atrial fibrillation or atrial flutter

Vascular disorders

- Hypotension, shock

Gastrointestinal disorders

- Diarrhoea, vomiting, diarrhoea, gastrointestinal disorder including gastrointestinal haemorrhage, abdominal pain, haematemesis.

Existing gastrointestinal reflux disease may be aggravated at night owing to relaxation of the esophageal sphincter. Aspiration may provoke asthma.

Musculoskeletal and connective tissue disorders

- Rhabdomyolysis

Renal and urinary disorders

- Urinary output increased, renal failure acute

Investigations

Blood calcium increased and blood creatinine increased, blood pressure decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local authorities.

Overdosage

Symptoms

Provided plasma theophylline levels remain within the therapeutic range (up to 20 microg/ml) and depending on individual sensitivity, the known side effects include gastrointestinal disorder (nausea, abdominal pain upper, vomiting, diarrhoea), central nervous system stimulation (restlessness, headache, insomnia, vertigo) and cardiac disorder (arrhythmia).

Other signs of theophylline overdose include convulsions, sudden blood pressure decreased, ventricular arrhythmia and severe gastrointestinal manifestations disorder (including gastrointestinal haemorrhage).

At plasma levels above 20 microg/ml, the symptoms are of the same type but more severe. At theophylline concentrations exceeding 30 microg/ml, nervous system disorder and cardiac disorder may take the aggravated form of convulsions, severe arrhythmia and cardiovascular insufficiency.

In individual patients with higher sensitivity to theophylline, severe adverse effects have been known to occur below the stated plasma concentrations.