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 measure 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 future 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 measure 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, hypocalcaemia, platelet consumption, and bleeding diatheses may occur. Hemodialysis is about as efficient as multiple-dose oral activated charcoal and has a lower risk of serious complications than charcoal hemoperfusion. Serum theophylline concentrations may rebound 5 to 10 mcg/ml after discontinuation of charcoal hemoperfusion or hemodialysis due to redistribution of theophylline from the tissue compartment.

Effects on the respiratory system:
- Relaxation of the smooth muscle tissue of the bronch and pulmonary vessels
- Improvement of mucociliary 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

Extra pulmonary effects:
- Lossening of perception of dyspnea
- Vascular dilation
- Smooth muscle relaxation (e.g., gall bladder and gastrointestinal tract)
- Inhibition of uterine contractility
- Positive cardiac inotropism and chronotropism
- Stimulation of skeletal muscle
- Increased urinary output
- Stimulation of exocrine and endocrine glands (e.g., increases hydrochloric acid secretion in the stomach, enhances catecholamine release from the adrenal glands)

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, prosstaglandin antagonism and translocation of intracellular calcium. However, these effects also only 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 (forte 375 mg theophylline) in fasted subjects and after ingestion of a high fat meal disclosed no evidence of food-drug interactions.

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

Peak theophylline SR forte concentrations at steady state (Cmax/observ) were 9.16 mcg/ml (geometric mean) in fasted subjects and 9.42 mcg/ml (geometric mean) in fasted subjects.

Theophylline's bronchodilatory action correlates with the plasma concentration. Optimum therapeutic effects in the presence of a calculable side effect of adverse effects are achieved at plasma levels of 8-20 mcg/ml.

About 60% of plasma theophylline is protein-bound in the therapeutically effective range (approximately 40% in neonates and adults with cirrhosis of the liver). The drug distributes from the blood stream into all compartments of the organism with the exception of fatty tissue. 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).

The main metabolites are 1,3-dimethyluric acid (approximately 40%), 3-methylxanthine (approximately 36%) and 1-methyl uric acid (approximately 17%). Of these, 3-methylxanthine is pharmacologically active, but not theophylline.

Hepatic first-pass metabolism of theophylline differs substantially between individuals, resulting in great inter individual variations in clearance, serum concentrations and elimination half-lives.

The major factors influencing theophylline clearance are: age, body weight; diet; smoking habits (theophylline metabolism is much faster in smokers); use of specific medications (see Interactions); disease and/or functional disorders of the heart, lung or liver; viral infections.

Kidney dysfunction may result in the accumulation of theophylline metabolites, since it is acutely active. Clearance is also lowered in the presence of physical stress and severe hypothyroidism and elevated in the presence of severe anemias. The elimination rate is initially concentration-dependent, but a saturation effect occurs at serum concentrations in the upper therapeutic range. Accordingly, small dose increases result in a disproportional increase in theophylline levels.

The plasma half-life of theophylline is also subject to great variation. It is seven to nine hours in healthy non-smoking adult asthmatic patients with no other intercurrent diseases, four to five hours in smokers, three to five hours in children and may be more than 24 hours in preterm infants and patients with pulmonary disease, heart failure or liver disease.

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.

How supplied

Theograd 350 mg gradumet Tablets are supplied in blister strips of 10x10s in carton. (No. 8489)

Theophylline Gradumet Tablets contain theophylline in a Gradumet sustained-release formulation for oral administration. Theophylline is a bronchodilator, structurally classified as a methylxanthine. It occurs as a white, crystalline, water-soluble, odourless, tasteless substance.

The Gradumet is an inert, porous, plastic matrix, which is impregnated with micronized theophylline. The drug is dispersed slowly from the Gradumet as it passes through the gastrointestinal tract. The expelled 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 Properties

Pharmacodynamic Properties

Pharmacotherapeutic group: Anti-Asthmatic medicines. Xanthines.

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

Theophylline's bronchodilatory action correlates with the plasma concentration. Optimum therapeutic effects in the presence of a calculable side effect of adverse effects are achieved at plasma levels of 8-20 mcg/ml.

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.

How supplied

Theograd 350 mg gradumet Tablets are supplied in blister strips of 10x10s in carton. (No. 8489)

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

SOLID 100038887 17 JULY 2014

Theophylline should not be used in children below 6 months of age (see Precautions).
Children from the age of six months require a higher body weight-related theophylline dose than non-smoking adults since in this population group the clearance rate is higher. Solid pharmaceutical forms 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 preparation.

**Interaction**

**Interaction with Other Medicinal Products and Other Forms of Therapy**

Theophylline should be used with caution in patients with hepatic or renal impairment. Reduced theophylline half-life and altered bioavailability and/or decreased clearance may occur in patients with liver disease.

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

Theophylline should be used with caution in patients with individual drug interactions. Use of theophylline in the elderly, patients with multiple pathologies and any individual with a decreased hepatic or renal function impairment. Use of theophylline in the elderly, patients with multiple pathologies and who are seriously ill and/or in intensive care is associated with a higher risk of toxicity. Therapeutic drug monitoring should be performed. Use of theophylline in the elderly and patients with multiple pathologies and who are seriously ill and/or in intensive care is associated with a higher risk of toxicity. Therapeutic drug monitoring should be performed.

**Contraindications**

Contraindications to theophylline include:

- Hypersensitivity to the active substance or to any of the inactive ingredients
- Repeated cardiomyopathy
- Acute tachyarrhythmia
- Children under 6 months of age

**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 tachyarrhythmia
- Severe hypertension
- Hypothroidism
- History of epileptic seizures
- Gastric or duodenal ulcer
- Porphyria

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

Usual use of theophylline in elderly patients with multiple pathologies and 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 effects, 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 Therapy**

Interactions with other xanthines, 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 pentobarbital, the theophylline dose may need to be increased.

**Drug Interactions**

**Use of theophylline in the elderly, patients with multiple pathologies and any individual with a decreased hepatic or renal function impairment.**

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

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

**Adverse Reactions**

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

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