

RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Theophylline toxicity

Theophylline is used as adjunctive treatment in severe persistent asthma and chronic obstructive airways disease. The use of theophylline is considered when the standard combination therapy of inhaled short and long acting bronchodilators and inhaled corticosteroids do not adequately control symptoms.

The mechanism by which theophylline acts is not entirely understood but a number of mechanisms have been proposed. Theophylline is thought to inhibit phosphodiesterase (thereby increasing cAMP levels), stimulate endogenous catecholamines, antagonise adenosine receptors and inhibit the release of inflammatory mediators from mast cells and leukocytes. As a result theophylline relaxes bronchial smooth muscle, stimulates the respiratory centre, and causes cardiac stimulation, diuresis and increased gastric secretion.

Theophylline has a narrow therapeutics index, with the usual recommended therapeutic plasma concentration ranging between 10–20 mg/L. The incidence and severity of adverse effects increases with increasing serum concentrations. Adverse effects are uncommon at serum concentrations of 5-10 mg/L; become more frequent around 15 mg/L and increase in frequency and severity as the serum concentration rises above 20 mg/L.

The severity of the symptoms also depends on whether the toxicity is acute, due to an overdose, or chronic. Chronic toxicity occurs when the oral dose exceeds the metabolic clearance. A number of factors affect the clearance of theophylline, including age, smoking, diet and drug interactions. Theophylline clearance decreases with increasing age and high caffeine intake, and increases with smoking. Theophylline is mainly metabolised by the enzyme CYP1A2, therefore its major drug interactions revolve around CYP1A2 inducers and inhibitors. CYP1A2 inducers such as carbamazepine, phenytoin and omeprazole increase the clearance of theophylline and thus decrease serum concentrations. CYP1A2 inhibitors such as erythromycin, ciprofloxacin and fluvoxamine decrease theophylline clearance and may result in elevated serum concentrations. Other drug interactions include increased risk of hypokalaemia when used with beta₂ agonists and diuretics and increased serum concentrations when theophylline is used in combination with high-dose allopurinol.

Theophylline toxicity can manifest as nausea, vomiting, agitation, tremor, hyperglycaemia, hypotension, electrolyte disturbances such as hypokalaemia, hypomagnesaemia, hypophosphataemia and hypercalcaemia, supraventricular and ventricular arrhythmias, and seizures.

Seizures are most likely to occur at peak theophylline concentrations above 100 mg/L but have also been reported to occur within the therapeutic range. Similarly, tachyarrhythmias can occur within the therapeutic range, but become more common at theophylline serum levels of 20-30 mg/L and above. These tachyarrhythmias are thought to be initiated and driven by excessive beta-adrenergic stimulation. The risk of seizures and arrhythmias is greater for older patients suffering from chronic toxicity.

Treatment of theophylline toxicity is mainly supportive, revolving around correcting any electrolyte abnormalities and controlling arrhythmias and seizures.

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FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
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