

# Theophylline

**T**heophylline, usually administered orally, is an effective bronchodilator which may be used in the management of both asthma and chronic obstructive pulmonary disease (COPD). It is widely available, and less expensive than many other bronchodilators. However, theophylline can be a difficult drug to use safely. It has serious side-effects, a narrow therapeutic window, and requires vigilant monitoring of plasma levels to avoid the risk of toxicity. Guidelines for both asthma and COPD, therefore, recommend that oral theophylline be reserved for patients with difficult-to-control symptoms in spite of standard asthma therapy, or patients who are unable to use or do not have access to inhaled therapy. Sub-therapeutic dosing can be clinically useful in atopic asthma, attenuating airway inflammation and with fewer side-effects than therapeutic doses<sup>1</sup>. Theophylline may have an anti-inflammatory action useful in the prevention of asthma. However, these preventive properties are regarded as considerably less effective than those of inhaled corticosteroids (ICS).

## MODE OF ACTION

Theophylline's exact mode of action remains unclear. It is a methylxanthine, similar to caffeine, and works by inducing relaxation in the bronchial smooth muscle. This may be due to a non-selective inhibition of phosphodiesterase, resulting in increased intracellular cyclic adenosine monophosphate (cAMP) levels. Theophylline does not have an instant effect. It takes some time for theophylline to build up in the blood stream, where it must

stay at a constant level to have a lasting effect. So when to take the drug and how much of the drug to take are matters that must be strictly monitored. There are many factors that influence blood levels of theophylline. It is cleared from the circulation by the liver. Clearance varies significantly between individuals and is affected by a number of other drugs (for example, diltiazem, verapamil, frusemide, ciprofloxacin, cimetidine, allopurinol, azithromycin, carbamazepine, clarithromycin, erythromycin, diuretics, lithium, oral contraceptives, phenytoin, prednisone, propranolol, rifampin, ephedrine, epinephrine, phenylephrine and phenylpropranolamine.) Theophylline's half life is reduced by smoking. As advice on smoking cessation is a central part of the management of both asthma and COPD it is important to be aware that theophylline doses may need to be reduced as patients succeed in reducing their tobacco consumption. Patients with alcoholism or any other type of liver disease or liver irritation will require very close monitoring and may not be good candidates for its use.

## SIDE-EFFECTS AND TOXICITY

Side-effects of theophylline include: tachycardia, palpitations, nausea and other gastro-intestinal disturbances, headache, CNS stimulation, insomnia, arrhythmias and convulsions<sup>2</sup>. Signs of toxicity include vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and

supraventricular and ventricular arrhythmias. There is a risk of hypokalaemia, which may be potentiated by combined use with high-dose beta<sub>2</sub> agonists<sup>3</sup>.

## PRESCRIBING DATA

Most sustained-release preparations should be given twice-daily (although some preparations are once-daily, administered in the evening). Sustained-release theophylline tablets or capsules should not be chewed because too much medicine may be released at once, causing toxic effects. It is recommended to 'start low – go slow', with regular review of serum levels and slow titration of dose to give steady state serum levels of 10-12 mg/L<sup>4</sup> (Box 1). Sometimes, up to 20mg/L may be tolerated<sup>4</sup>. Serum levels should be taken nine to ten hours after ingestion. Particular caution needs to be taken with the use of theophylline in elderly patients because of differences in pharmacokinetics, the increased likelihood of co-morbidities and the use of other medications. Careful note should be made of drug interactions (see mode of action).

### BOX 1

RECOMMENDED TITRATION OF THEOPHYLLINE DOSE FOR TWICE-DAILY PREPARATIONS <sup>4</sup>	
WEEK 1	200mg every 12 hours for 1 week
WEEK 2	If serum levels are low increase to 300mg every 12 hours for 1 week
WEEK 3 and beyond	If serum levels are low increase by 100mg every 12 hours each week till therapeutic range achieved.

## ◀ ORAL THEOPHYLLINE IN ASTHMA

In common with most international guidelines, the IPCRG recommends a stepwise approach to adult asthma management (Box 2)<sup>6</sup>.

BOX 2

STEPWISE APPROACH TO ASTHMA MANAGEMENT IN ADULTS	
STEP 1: Intermittent asthma; symptoms ≤ once per week	Rapid-acting, beta2-agonists. Over 60 years, consider anticholinergics as alternative.
STEP 2: Mild persistent asthma symptoms > once per week	Low-dose inhaled corticosteroids (ICS) (200-400 mcg of beclomethasone or equivalent).
STEP 3: Moderate persistent asthma	Combination of medium-dose inhaled glucocorticosteroid and a long-acting beta2-agonist. Alternatives are combinations of ICS with leukotriene receptor antagonists (preferred in those with concomitant rhinitis) or with sustained release theophylline.
STEP 4: Severe persistent asthma	Combination of high-dose ICS, plus a long-acting, inhaled beta2-agonist twice-daily, plus one or more of the following: sustained release theophylline and leukotriene receptor antagonist, oral beta2-agonist or oral corticosteroid.

## ORAL THEOPHYLLINE IN COPD

A recent review of 20 randomised clinical trials of theophylline used in moderate to severe COPD found the drug offered a modest benefit on forced expiratory volume in one second (FEV<sub>1</sub>) and forced

vital capacity (FVC)<sup>6</sup>. It also slightly improved arterial blood gas tensions. These modest benefits, however, should be weighed against the risk of side-effects and the need to monitor plasma levels.

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, 'theophylline is effective in COPD, but due to its potential toxicity, inhaled bronchodilators are preferred when available'<sup>7</sup>. The UK's National Institute of Health and Clinical Excellence (NICE) recommends that theophylline should be used in COPD only after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy<sup>8</sup>. The IPCRG's guidelines on COPD make no mention of theophylline<sup>9</sup>.

## USE OF THEOPHYLLINE IN DEVELOPING COUNTRIES – ASTHMA

Recommendations to use theophylline with caution are similar for developed and developing nations. Nevertheless, in some countries, considerations of availability and price will favour the use of theophylline as a first-line treatment to relieve symptoms, to treat acute attacks and as a mild preventer. A survey of 24 countries in Asia and Africa, carried out in 1997, found that theophylline was used to treat asthma 'usually or often' by 30 of the 41 respondents<sup>10</sup>. This compared to 12 respondents for inhaled bronchodilators and just two for inhaled corticosteroids. Theophylline was locally available in all 41 cases, whereas inhaled corticosteroids were available in just 15. The authors of this study expressed the concern that 'many asthma patients in developing countries are not receiving adequate treatment because the required drugs are not available in their area or are prohibitively expensive'. However, generic inhaled

corticosteroids can be very reasonably priced, even comparable with oral theophylline and are considerably more effective in asthma.

## USE OF THEOPHYLLINE IN DEVELOPING COUNTRIES - COPD

The World Health Organisation has published a stepwise approach to the treatment of COPD in developing countries (Box 3). This recommends that theophylline should be used at low doses only in Grade 3 patients, when symptoms are uncontrolled with inhaled ipratropium bromide and inhaled salbutamol.

BOX 3

STEPWISE APPROACH TO TREATMENT FOR COPD IN DEVELOPING COUNTRIES	
GRADE 1 (FEV <sub>1</sub> /FVC<70% and FEV <sub>1</sub> =60-79% predicted and variable symptoms)	Inhaled salbutamol 100µg as needed
GRADE 2 (FEV <sub>1</sub> /FVC<70% and FEV <sub>1</sub> =40-59% predicted and continuing symptoms)	Inhaled ipratropium bromide 2-6 puffs every 6 hours/day and inhaled salbutamol 100µg as needed
GRADE 3 (FEV <sub>1</sub> /FVC<70% and FEV <sub>1</sub> <40% predicted and/or continuing symptoms with unsatisfactory response to step 2.	Inhaled ipratropium bromide 2-6 puffs every 6 hours and inhaled salbutamol 100µg 2-4 puffs 4 times a day. Add theophylline at low dose if symptoms are not controlled

## IV THEOPHYLLINE

In severely ill patients or in patients responding poorly to inhaled beta2-agonist therapy, theophylline is sometimes used as a slow, intravenous injection, given over at least 20 minutes. ●

## REFERENCES

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