Theophylline

Introduction
Theophylline is listed in the 2004 WHO Model Formulary for the treatment of 'chronic asthma including nocturnal asthma'. Other drugs listed in the Formulary for the same indications are beclomethasone dipropionate, epinephrine (adrenaline), ipratropium bromide and salbutamol. Sodium cromoglicate and aminophylline are listed as complementary drugs.

Product and prescribing
Theophylline is listed as simple tablets (100mg), and as modified release (MR) tablets (200mg, 300mg). In patients with chronic asthma, the suggested dosage regimen for the tablet (in adults and children aged over 12 years) is 100-200mg, 3-4 times daily after food; and for the MR tablet (in adults), 300-450mg every 12 hours. In patients with nocturnal asthma, it is recommended that (in adults) the total daily dose be taken as a single evening dose as the MR tablet. The ideal plasma theophylline concentration suggested is 5-15mg/L (27.5-82.5 micromol/L), a range rather lower than the 10-20mg/L often recommended.

Evidence of value
Theophylline is an old drug and its value has rarely been formally tested in randomised controlled clinical trials. One such study, performed in patients with chronic obstructive pulmonary disease (COPD), showed that compared to placebo, theophylline improved the respiratory muscle performance by 29%. In a more recent trial in similar patients, theophylline was significantly better than placebo in terms of its effects on FEV1, FVC, WMD, Pa2, and PaCO2. In a further study, the combination of salmeterol with theophylline provided significantly greater improvement in pulmonary function, a greater decrease in symptoms (including dyspnea) and the need for salbutamol use, and fewer COPD exacerbations, than either drug given alone. In this study theophylline caused more side effects. In a cross over randomized three treatment blocks trial, theophylline (in a relatively low dose) had a smaller effect than zafirlukast on bronchial hyperresponsiveness as the primary outcome variable. In a parallel group designed study, inhaled budesonide was more effective than oral theophylline on asthma symptoms scores and bronchial reactivity. With theophylline, the symptoms decreased only slightly. In a recently published study, comparing beclomethasone with oral theophylline in pregnant women with moderate asthma, maternal and prenatal outcome measures were the same. Theophylline did, however, cause more unwanted effects.

The value of theophylline, as assessed by meta-analyses, has been modest and the product is rarely recommended in national guidelines. The problem has been its relatively modest efficacy compared to other products now available, balanced against the common occurrence of (sometimes serious) unwanted effects.
One analysis,\textsuperscript{12} underlines the value of theophylline as a steroid-sparing agent. Others\textsuperscript{10} recommend it especially in children who are critically ill and who have failed to respond to aggressive treatment with inhaled beta agonist, systemic corticosteroids and inhaled ipratropium. In recommendations generally, the importance of regular measurement of plasma theophylline concentrations is stressed,\textsuperscript{8, 14-17} although it should be recognised that the practicality of universally implementing such a strategy in developing countries is unrealistic.

Despite the various negative findings, theophylline continues to be recommended as part of treatment for the treatment of asthma and COPD in a number of guidelines\textsuperscript{14 -19} All recognise its modest effect and the cautions needed when it is used, but suggest it is given where other therapies have failed or are impractical.

**Unwanted effects**
Theophylline can cause nausea, vomiting, restlessness, anxiety, insomnia, headache, dizziness, aggravation of dyspnea, palpitations, cardiac arrhythmias, tremor and convulsions. These effects are essentially dose dependent, although to some extent their development depends on individual susceptibility. Theophylline interacts with a number of substances and those that inhibit hepatic microsomal enzymes are especially dangerous.

**Recommendation**
Theophylline has modest effects in asthma and its unwanted effects are troublesome, however it should remain on the WHO Model List of Essential Medicines, to be used as a second-line drug for the treatment of asthma in patients who do not respond to a beta 2 agonist plus an inhaled corticosteroid, and, where appropriate, an anti-cholinergic drug. The importance of therapeutic monitoring should be stressed, but even so, the product should continue to be available even where routine measurement of plasma concentration cannot be provided.

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(October, 8 2004)

**References**
3. Dempsey OJ et al, Effects adding ether a leukotriene receptor antagonist or low dose theophylline to a low or medium dose of inhaled corticosteroid in patients with persistent asthma Chest 2002;122:151
4. Dahl R et al, Effect of long-term treatments with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms, Respir Med. 2002;96:432
The medical literature was searched to identify clinical trials, systematic reviews, meta analyses or guidelines related to use of aminophylline in acute asthma, including nocturnal asthma, and chronic obstructive pulmonary disease. Table 1 lists the electronic databases, websites and journals searched.

Table 1. Electronic databases, websites and journals searched

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Databases and Medline were searched with the goal to find relevant randomized clinical trials, systematic reviews, meta analyses, Medical Subject Headings terms and words find in the texts, titles and abstracts. The search was done in English, German, Croatian and partially French language journals and publications:

- British medical journal
- The Lancet
- New England Journal of Medicine
- Arzneimittelbrief
- Arzneitelegramm
- Pharmaca
- British Journal of Clinical Pharmacology
- European Journal of Clinical pharmacology
- International Journal of clinical pharmacology, therapy and toxicology

Beside these journals a number of textbooks, handbooks and formularies have been analysed in above mentioned languages.