MEMORANDUM

From: Coordinator, PCS

To: The Secretary of the Expert Committee on the Selection and Use of Essential Medicines

Date: 3 February 2005

Our ref: 

Attention: Dr R. Gray, PAR

Your ref: 

Through: 

Originator: Ms J. Tempowski, PCS

Subject: PROPOSAL FOR REMOVAL OF THEOPHYLLINE AND AMINOPHYLLINE FROM THE ESSENTIAL MEDICINES LIST: TOXICITY OF THESE DRUGS

At the request of the Department of Medicines Policy and Standards, please find some rapidly-assembled information on the toxic risks of theophylline and aminophylline.

Poisoning with aminophylline/theophylline may arise from acute overdose, chronic intoxication, or an acute overdose against a background of therapy. Acute overdose may be accidental or deliberate. Chronic intoxication may result from dosing errors, or from drug interactions or intercurrent illness interfering with metabolism of theophylline. In this case the usual victims are very young infants or the elderly. A study of 356 theophylline poisoning cases referred to the Massachusetts Poisons Control System over a 10-year period found that 45.5% involved acute overdose, 40.4% involved chronic intoxication, and 14% acute-on-therapeutic intoxication.1

Aminophylline and theophylline have narrow therapeutic indices. The therapeutic range is 10-20 mg/L (55-110 μmol/L), and features of toxicity are likely to occur above this concentration.2 Life threatening features may occur with concentrations > 60 mg/L (>330 μmol/L). Patients with chronic theophylline intoxication have a greater risk for major toxicity at lower serum theophylline concentrations than those with acute intoxication, and the elderly are at particular risk.1,3

According to treatment guidelines from the UK National Poisons Information Service (NPIS), an acute dose exceeding 3 g of theophylline could cause serious toxicity in an adult, and 40 mg/kg in a child (NPIS, personal communication). This could be as few as 10-12 tablets for an adult and 1-2 tablets for a small child.4

The toxic effects of aminophylline/theophylline include severe and protracted vomiting, haematemesis, convulsions, cardiac arrhythmias (supraventricular or ventricular tachycardia, ventricular fibrillation), coma and death. Hypokalaemia (which may be severe), hypophosphataemia, hypomagnesaemia, metabolic acidosis and respiratory alkalosis are among the metabolic disorders seen.5,6

As most theophylline preparations are in sustained-release form, there may be a delay in onset of toxic effects of 12-24 hours after acute overdose. Patients may, therefore, require prolonged monitoring in hospital. The management of poisoning involves administration of
repeat-dose activated charcoal to enhance elimination, cardiorespiratory support and correction of electrolyte imbalance. Vomiting may be resistant to treatment, thereby preventing administration of activated charcoal. Management of cardiac arrhythmias may be difficult. Extracorporeal elimination techniques such as charcoal haemoperfusion or haemodialysis may be needed.5,6

References


Tim Meredith, M.D.