Comment on aminophylline/theophylline reviews

At the EML Committee meeting in 2003, theophylline and aminophylline were considered for possible deletion. Several reviews and submissions in relation to both products have been prepared for the Committee to consider at its meeting in March 2005. The recommendations vary: the external review (Dr Andy Gray) recommends deletion of aminophylline and retention of theophylline as a complementary drug, while other submissions recommend retention of both products.

The external reviews of efficacy of both theophylline and aminophylline are comprehensive and I agree with the conclusions of both, that both theophylline and aminophylline have limited evidence for efficacy in either the acute or chronic treatment of both asthma and COPD. In terms of comparative effectiveness, beta-agonists and corticosteroids (inhaled and/or oral) are superior. On this basis, therefore, neither theophylline nor aminophylline can be considered as an essential medicine.

Given that theophylline and aminophylline have only limited efficacy, their relative toxicity becomes a major issue. As noted in the reviews, both products have very narrow therapeutic margins. Although it is not well quantified in the systematic reviews of RCTs, there are numerous case reports, case series and studies of theophylline toxicity in the literature. Toxicity associated with both products is frequent and can be serious, ranging from nausea/vomiting/headache to cardiac arrhythmias, seizures and death. Although a ‘therapeutic range’ for plasma concentrations has been defined, this is not reliable; when theophylline is used chronically, it is possible for patients to have plasma drug concentrations within the ‘therapeutic range’ and at the same time have signs of severe toxicity. In patients with COPD for example, chronic toxicity can develop and manifest with cardiovascular or neurological symptoms with plasma concentrations much lower than those noted in acute toxicity. A similar problem of variability in plasma concentrations has been found in children (Visitsunthorn, 2001).

As noted in the reviews, in developed countries if the drugs are used at all, it is recommended that monitoring of theophylline concentrations is routinely used to try to minimise toxicity. Treatment of theophylline/aminophylline poisoning or overdose (either due to intentional self-poisoning or therapeutic misadventure) is difficult and can require charcoal haemoperfusion or haemodialysis to prevent death (Henderson JH, 2001; Okada S 2000; Shannon, 1997). One study estimated the overall mortality rate associated with theophylline poisoning to be approximately 10% (Dawson and Whyte, 1989).

A further problem is that a number of other medicines commonly used in patients with COPD or respiratory tract infections interact with both theophylline and aminophylline leading to increased plasma concentrations of both and thus an increased risk of toxicity in the absence (or presence) of therapeutic drug concentration monitoring facilities. Common examples include ciprofloxacin, cimetidine and erythromycin. One North American study estimated the additional hospital time and cost arising from these interactions (Hamilton 1992) as significant. Although theophylline and aminophylline
drugs may be superficially attractive as ‘cheap’, any cost-effectiveness analysis would need to take into account the cost of therapeutic drug monitoring and the cost of treatment of toxicity.

The definition of essential medicines is:

“Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness”.

Asthma and chronic airways disease are likely to be of increasing public health relevance, particularly given problems with smoking and air quality in developing countries. It is appropriate that, as has been the case with drugs for HIV/AIDS and malaria, that the EML include the best available treatments for these diseases. Given that (1) alternative medications – ie beta-agonists and corticosteroids - for asthma and COPD are superior, available and limited only in terms of cost of the inhaled formulations, and that (2) theophylline and aminophylline have limited effectiveness, have significant toxicity and require monitoring to be used safely, both should be deleted from the EML.

References


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