

Correspondence

Asthma therapy and airway inflammation

To the Editor:

In his article, "Therapy for airway inflammation in asthma" (*J ALLERGY CLIN IMMUNOL* 1991;87:914-9), D. W. Cockcroft, MD, views inflammation as the underlying process, and its treatment as primary therapy, in all asthma. He remarks, on the basis of three cited studies, that theophylline neither inhibits allergen-induced increases in airway responsiveness, nor produces sustained improvement in responsiveness when administered for a long time. These findings, he concludes, suggest that theophylline is not antiinflammatory. The article, however, omits mention of the published reports inconsistent with these positions, some of which may have postdated its preparation.

I believe that viewing theophylline as a mere adjuvant to cromolyn or corticosteroids for "bronchodilator manipulation" relatively late in outpatient treatment may cost asthma patients important therapeutic benefits.

The actions of theophylline are varied and complex. Apart from bronchodilation, improved diaphragmatic performance, and mucociliary clearance, they have been found to include antiallergic, steroid-sparing, and antiinflammatory effects, as well as inhibition of airway responsiveness.¹⁻⁶

Theophylline has been shown to antagonize airway responsiveness to methacholine, carbachol, and nebulized distilled water.^{2,3,5} It has also been observed to cause significant inhibition of the late asthmatic response to allergen challenge and to partially inhibit the increase in airway reactivity associated with the late reaction in some subjects.^{1,3} Pauwels et al.¹ found the protective effect against the late asthmatic response to allergen challenge particularly pronounced. The late phase is thought to be linked to inflammation. Theophylline has further been shown to attenuate the activity of various inflammatory cells and may also combat inflammation by directly affecting the epithelial lining and reducing plasma leakage via the microvasculature.^{1,6} In addition, Brenner et al.⁴ demonstrated that patients with severe asthma, stabilized on combined regimens of beta-agonists, inhaled and systemic corticosteroids, cromolyn, and maintenance theophylline, required significantly higher doses of systemic steroids on cessation of theophylline therapy. Its replacement by placebo resulted in marked and unacceptable worsening of symptoms within 24 to 48 hours.

Controlled-release theophylline therapy further protects against a major pathophysiologic feature of chronic asthma, that is, typical worsening of signs and symptoms at night and in the early morning, caused by powerful circadian influences.⁷ Indeed, inflammation itself may increase at night. The excessive day-night variation in lung function common in asthma and difficulties in delivering adequate treatment at night almost surely contribute to the sometimes dangerous early morning "dip" in airway patency. A once-daily evening chronotherapeutic regimen of a controlled-release theophylline preparation (Uniphyl tablets, Purdue

Frederick Co., Norwalk, Conn.), helps prevent this nadir, stabilizing airflow over the 24-hour day by providing maximum serum levels at night and in the early morning when most needed.⁷ Yet, as found in a recent survey of nearly 8000 patients, inhaled cromolyn or corticosteroids do not adequately control nocturnal asthma.⁷ Even nonchronotherapeutic theophylline therapy has been observed to reduce the number of night awakenings caused by asthma by a higher percentage than cromolyn (Dr. Cockcroft's reference no. 41).

Overall, theophylline affords extensive protection in chronic asthma, administered with or without corticosteroids or cromolyn. Its use may modify requirements of systemically administered steroids and hence the risks often associated with these drugs.⁴ Furthermore, there is increasing concern in the literature about the possible hazards of higher doses of inhaled steroids. Recent reports document interference with growth and bone function. Surely, we should be using theophylline, a drug of clearly documented clinical value, appropriately, in addition to steroids, to enhance our therapeutic options.

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Reply

To the Editor:

Dr. Goldenheim raises two partially related questions in his letter. The first is the question of an antiinflammatory