
Theophylline Is No More Obsolete Than “Two Puffs qid” of Current Beta₂ Agonists

For it so falls out that what we had we prize not to the worth whiles we enjoy it, but being lack’d and lost, why, then we rack the value, then we find the virtue that possession would not show us whiles it was ours.

Much Ado about Nothing, IV:1

Lam and Newhouse (see pages 1, 44) have summarized the problems and controversies surrounding theophylline therapy in the US. Writing from the therapeutically more flexible Canadian environment, they ask whether theophylline is not on the verge of becoming obsolete. I submit that the continuing popularity of theophylline in the US is, in part, due to the fact that the standard package insert regimen for a beta₂ adrenergic metered dose inhaler (MDI) is inadequate for many patients and is itself obsolete. Lam and Newhouse would agree on the latter point, since much of their argument hinges on individualizing dosing of beta agonists, and the use of high-potency inhaled corticosteroids—not yet approved in the US. Dose-response studies show that two puffs of presently formulated MDIs are suboptimal in patients with constant bronchospasm, both in terms of peak response and certainly in terms of the trough, trough being that recurring state of distress requiring another two puffs.¹⁴ For example, when properly controlled by placebo, the FEV₁ response to albuterol is nearly gone at four hours.¹⁵ Moreover, the ability of beta₂ agonists to inhibit bronchoprovocational stress falls off even more rapidly.¹⁶

Must we subject patients to such relentless, periodic discomfort? Fortunately, patients cheat. They use more puffs at a time, or more frequent puffs. Others end up using a nebulized aerosol. We now realize that the approved dose for liquid nebulization often delivers a larger effective dose to the airways, but can be matched by a larger dose from the MDI.¹⁶ The reason that such low doses were specified for the MDI may have included the only patients with mild asthma for study (a poor index of reality, but necessary for studies), a fear of overdosing gained from the asthma deaths in the UK in the 1960s associated with large doses of isoproterenol and prior to use of corticosteroids,¹⁰ and early animal studies examining the cardiac toxicity of isoproterenol and fluorohydrocarbons under hypoxic conditions.¹¹ Concerns linger, especially among physicians practicing from that era. Recent reports from New Zealand of an excess of deaths associated with fenoterol over albuterol, a compound with more beta, activity, suggest that this concern is not totally irrational.¹²,¹³

But is theophylline obsolete? In their comprehensive study of COPD patients,¹⁴ and that of others in asthmatic patients,¹⁵ theophylline adds significantly to the spirometry result both before and after qid dosing of the beta agonist. Most COPD patients do not respond to corticosteroids. I am puzzled why the authors disparage a pre-inhalation FEV₁, improvement of 10-15 percent in this population. Patients find significantly improved performance and quality of life, not necessarily reflected in pulmonary function measurements.¹⁴,¹⁶ We do not understand all the reasons. Improved diaphragmatic performance may be part of it.¹⁷ When the dose of theophylline is properly adjusted to 10-15 μg/ml, most patients tolerate it very well. It should be no surprise that patients welcome the comfort and convenience of a cushion of added pulmonary function and undisturbed sleep¹⁸,¹⁹ with a once- or twice-daily sustained release preparation. Whether theophylline adds significantly to anticholinergics in the COPD patient must be studied.

Unquestionably, the increased emphasis on antiinflammatory agents is improving care of the asthmatic, but there are several statements now often seen that I believe need editorial fine-tuning: 1) “Asthma is an inflammatory disease . . . with associated bronchospasm.” Whether inflammation is accountable for all asthma remains unproven. Treatment with cromolyn or even high doses of inhaled corticosteroids usually produces improvement, but does not eliminate non-specific airway hyperreactivity and the need for therapy with bronchodilators, particularly in the patient with more severe asthma.²⁰,²¹ 2) “Theophylline is a weak bronchodilator.” In one head-to-head comparison, 15 μg/ml theophylline was the equivalent of two puffs of albuterol at their peak effect.²² When the FEV₁ response to albuterol is averaged over 4 h, theophylline is equivalent. 3) “Theophylline causes behavioral problems in children.” Reference should be made to recent editorial moderation of this controversy.²³ In fact, the Furukawa group’s most recent study found that, with proper controls, the majority of abnormalities were due to the disease itself.²⁴ 4) “Theophylline is unnecessary in the treatment of acute asthma.” For most attacks, I agree. The asthma studies cited were in patients, most of whom were already receiving some theophylline, and added theophylline was the issue, with its possibility of overdosing.
Furthermore, the response was studied out to 3 h at most. What about the remaining course when beta-agonist dosing is less intense, but the danger from renewed bronchospasm still present?

Lam and Newhouse correctly cite excessive severe theophylline toxicity on a nationwide basis, and the following principles need constant emphasis: 1) For maintenance, initial oral dosing should be conservative (10 mg/kg IBW in adults) until adjusted to the 10-15 µg/ml range through early monitoring. Outliers with prolonged half-lives will eventually be seen. The elderly patient, particularly, requires care. 2) In the asthmatic patient, inhaled anti-inflammatory drugs are an essential part of treatment, as are anticholinergics in the patient with COPD, and they should generally be in place or tried before theophylline is considered. 3) Patients on therapy with theophylline seen in the emergency room should only be placed on maintenance therapy and not on a loading dose until their theophylline levels have been measured. These levels should subsequently be measured at least daily while patients are on IV therapy, which itself should not be prolonged.

The situation is bound to change if and when the new bid ultra-long acting beta2 agonists are approved, but even then, there will remain some patients who prefer to take theophylline or else must do so, and we should retain our facility with its use.

John W. Jenne, M.D., F.C.C.P.
Hines, Illinois

References
1 Mestitz H, Copeland JM, McDonald CF. Comparison of outpatient nebulized vs metered dose inhaler terbutaline in chronic air flow obstruction. Chest 1989; 96:1237-40
20 Petty TL, Rollins DB, Christopher K, Good JT, Oakley R. Cromolyn sodium is effective in adult chronic asthmatics. Am Rev Respir Dis 1989; 139:694-701
22 Dutoit JL, Salome M, Woolcock AJ. Inhaled corticosteroids reduce the severity of bronchial hyperresponsiveness in asthma but oral theophylline does not. Am Rev Respir Dis 1987; 136:1174-78
28 Ullman A, Svedmyr N. Salmeterol, a long acting inhaled B4 adrenoceptor agonist: comparison with salbutamol in adult asthmatic patients. Thorax 1988; 43:674-78