Is Theophylline Obsolete?

Be not the first by whom the new are tried, nor yet the last to lay the old aside. Alexander Pope, 1688-1744.

For almost 50 years, methylxanthines have been considered first-line therapy of reversible airflow obstruction in adults and children, despite their relatively weak bronchodilator effect, narrow therapeutic window, innumerable drug interactions, and toxic reactions. The great popularity of this class of drugs, which yielded sales of about US $1 \times 10^9$ worldwide in 1988, probably arose, in part, from the duration of action of the sustained release formulations at a time when adrenoceptor-agonist aerosols were relatively short acting.

In recent years, however, with management of asthma and chronic obstructive pulmonary disease (COPD) evolving toward therapy of the underlying inflammatory component rather than simply treating the bronchospasm, this class of drugs is gradually being relegated to the position of third or fourth-line therapy for patients with reversible airflow obstruction. Why, then, is theophylline on the threshold of obsolescence after so many years as a first-line medication?

The answer is probably that it has been superseded as a bronchodilator by inhaled adrenoceptor agonists and anticholinergics for both the maintenance therapy and treatment of acute exacerbations of asthma and COPD. Furthermore, with an increased appreciation of the importance of inflammation in the pathogenesis of asthma, inhaled bronchodilators have been relegated to second-line therapy for controlling asthma by increasingly potent topical steroids and cromolyn with an excellent therapeutic ratio. Thus, the so-called "step therapy" used in the past that began with a relatively low dose of inhaled β₂-sympathomimetic to which was added dose-optimized theophylline, is being supplanted in the control of asthma by dose-optimized inhaled steroids and adrenoceptor agonists. The latter are effective not only for maintenance therapy but also during acute life-threatening episodes together with steroids given in relatively large doses intravenously or even orally. There is now increasing evidence that the addition of intravenous aminophylline adds side effects to these treatment regimens but does not increase their efficacy.

For maintenance therapy of asthma, theophylline may be obsolete because it is merely a relatively weak bronchodilator that adds little but side effects to dose-optimized inhaled β₂-agents and does not address the underlying inflammation, a fundamental characteristic of the disease. In this context, bronchoconstriction might be considered an epiphenomenon, like pain in patients with appendicitis. Thus, first-line therapy for moderate chronic asthma should be dose-optimized inhaled steroids delivered via a metered dose inhaler (MDI) add-on device such as the AeroChamber to minimize local and systemic side effects or for very mild asthma, possibly inhaled cromolyn sodium (cromoglycate sodium) especially in children. Second-line therapy is β₂-agonists. Theophylline is rarely of additional value except, perhaps, as a steroid-sparing strategy in the maintenance therapy of patients with asthma requiring systemic steroids for control despite maximum tolerated doses of inhaled steroid, adrenoceptor agonists, and (rarely) anticholinergic agents. Where necessary, in individual patients, the benefit of theophylline should be confirmed by a properly structured N of one clinical trial to confirm both efficacy and safety.

Sustained action formulations (such as Theo-Dur or Uniphyll) previously used to control nocturnal symptoms of asthma and early morning "dipping," are almost never required if inhaled steroids are used in adequate doses to control the disease. Furthermore, the new relatively β₂-specific long-acting inhaled agents such as salmeterol promise to provide effective bronchodilation (or protection from bronchoconstriction) for a period of 12 hours or more, negating any remaining advantage of sustained release ingested theophylline or adrenoceptor agonists.

In pediatric practice, ingested theophylline or ingested adrenoceptor agonist bronchodilators have in the past been first-line therapy, probably because aerosol nebulizer systems are expensive and cumbersome, while at the same time, many of the more potent prophylactic anti-inflammatory agents were not available as nebulizer solutions.

The use of MDI with valved add-on devices, such as the AeroChamber and AeroChamber with Mask has facilitated MDI aerosol delivery of a variety of bronchodilators, cromolyn, and various inhaled ster-
oids in patients ranging in age from a few weeks to the very elderly, making nebulizers unnecessary. With an increasing appreciation of the role of airway inflammation in the pathogenesis of asthma by pediatricians, prophylactic steroid or cromolyn aerosol therapy is being increasingly applied in the management of childhood asthma, thus avoiding the common side effects of hyperexcitability and possibly learning disorders in children when theophylline is used.

The argument for obsolescence is not as readily made with respect to the use of theophylline for maintenance therapy in patients with COPD because the data are still conflicting to a considerable degree. Furthermore, the available studies, whether pro or con, suffer from a number of deficiencies, including small numbers of patients and comparison of theophylline with placebo-treated patients where selection bias is inevitable due to exclusion of up to 50 percent of patients due to side effects. In studies that have shown theophylline beneficial when added to adrenergic agonists, the major problem is failure to optimize the dose of the inhaled adrenergic agonist or anticholinergic agent prior to adding theophylline. Where adrenergic agonist or anticholinergic therapy has been virtually optimized, only modest additional benefit could be demonstrated when theophylline was added. Nevertheless, the number of patients in these studies is small and it may require a large (and expensive) multicenter trial to settle the question. Even when usually modest additional benefit in spirometry has been demonstrated, investigators have usually been unable to demonstrate benefit in terms of improved effort tolerance or decreased dyspnea when such information has been sought.

Unlike the highly effective inhaled agents, whose side effects are minimal, theophylline is a weak and potentially toxic bronchodilator with a narrow therapeutic window and numerous drug interactions that make its use complicated for the unwary or uninformed physician. Its cost of administration is as great or greater than that of other treatment modalities because of the need to monitor the serum theophylline level at regular intervals to assure safety and efficacy.

Thus, theophylline appears to be facing obsolescence because of major advances in the pharmacotherapy of the obstructive airway diseases by means of aerosol therapy and improved aerosol delivery systems. These aerosol bronchodilators and/or prophylactic anti-inflammatory drugs are generally more effective than theophylline in the management of asthma and COPD, enjoy a far superior therapeutic ratio at lower overall cost, and are thus likely with rare exceptions to replace theophylline in the treatment of reversible airflow obstruction in adults and children.

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REFERENCES

19. Lloberes P, Ramis L, Montserrat JM, Serra J, Campistol J.
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. For example, when properly controlled by placebo, the FEV₁ response to albuterol is nearly gone at four hours. Moreover, the ability of beta₂ agonists to inhibit bronchoprovocational stress falls off even more rapidly.

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. 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, and early animal studies examining the cardiac toxicity of isoproterenol and fluorohydrocarbons under hypoxic conditions. 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.

But is theophylline obsolete? In their comprehensive study of COPD patients, and that of others in asthmatic patients, 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. We do not understand all the reasons. Improved diaphragmatic performance may be part of it. 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 sleep 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 nonspecific airway hyperreactivity and the need for therapy with bronchodilators, particularly in the patient with more severe asthma. 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. 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. In fact, the Furukawa group’s most recent study found that, with proper controls, the majority of abnormalities were due to the disease itself. 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.

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