Use of Theophylline in the Treatment of COPD*

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It is ironic that many of the drugs used to treat COPD have been known since antiquity, yet we are still struggling to understand their basic mechanisms and how to use them. Theophylline is the best example of this dilemma, although anticholinergic agents and β-agonists share this irony. Methylyxan-thines have been used for centuries to treat obstructive lung disease, but in the last 20 years, theophylline has gone from a first-line drug in asthma and COPD to a third-line choice.1,2 Theophylline's bronchodilator effects are well known, but recent studies suggest that long-term theophylline use in patients with COPD may go beyond bronchodilation to improve various measures of patient functional state and well-being. It is timely, therefore, to reexamine its therapeutic use in patients with COPD.

The ultimate measure of theophylline's usefulness in the treatment of patients with COPD is its contribution to reducing disability and enhancing overall well-being and quality of life. The traditional method for describing the clinical usefulness of bronchodilators is the dose-related effect on organ physiology, ie, its ability to reverse airway obstruction. It is now apparent that patients taking theophylline may enjoy clinically important benefits in terms of functional status and quality of life, beyond simple bronchodilation, as a result of theophylline's impact on integrated organ performance. It is also important to understand the effect of theophylline in the context of the multidrug regimens used in the contemporary approach to treating COPD.3 These benefits must be weighed against the risks of toxic reactions at effective doses. Finally, we must understand how these factors are affected by patient characteristics such as age, sex, coexisting disease, and the concomitant use of nonrespiratory medication.

A review of the literature on theophylline suggests several caveats. Theophylline could have distinct effects in patients with different types of obstructive airways disease. It is important, therefore, to differentiate between studies involving patients with asthma vs COPD. Asthma and COPD have many common characteristics amenable to treatment by theophylline; for example, episodic bronchospasm and bronchial hyperreactivity are common in both,4 but there are important differences that make therapeutic generalization hazardous. Most patients with asthma have wide variations in airway obstruction and symptoms over time, and their bronchospasm responds well to corticosteroid therapy. In contrast, many patients with COPD have relatively constant obstruction and symptoms. Furthermore, most patients with COPD do not respond well to steroid therapy. At best only 40% of patients with COPD respond to oral corticosteroid therapy, and the response rate for inhaled steroids is probably lower.5,6 The nature of the patient population must therefore, be clearly defined. Other important considerations include chronicity of symptoms and treatment, the dose and blood levels of theophylline, and the end point of comparison (eg, pulmonary function, functional ability, etc). These observations provide the structure for this review.

Effects of Theophylline

Organ Physiology

Theophylline is an effective bronchodilator. Its short-term administration results in improvement in flow rates and lung volumes in asthmatics with bronchospasm that are correlated with serum levels in a classic dose-response relationship.7 The maintenance of a therapeutic blood level is the basis for the development of sustained-release preparations that are almost exclusively used in long-term regimens for COPD. Theophylline is also at least partially effective in blocking bronchial hyperreactivity to nonspecific, ie, methacholine and histamine,8 and antigen stimulation.9 Long-term theophylline use by patients with COPD results in improvement in other aspects of lung function, including vital capacity, FEV1, minute ventilation, and gas exchange.10 In addition to its effect on airflow resistance, theophylline may enhance the ventilatory pump. It is a respiratory stimulant in normal humans.11 Short-term theophylline administration has been shown to delay the onset of skeletal muscle fatigue in normal men12 and long-term administration will increase diaphragmatic muscle strength and delay fatigue in patients with COPD.13

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Theophylline has other organ-specific effects that may be beneficial to patients with COPD. Theophylline stimulates ciliated epithelial cells, facilitating bronchial toilet in patients with COPD. Theophylline improves cardiac function, pulmonary artery pressure, and renal function in patients with COPD. All of these nonpulmonary effects may contribute to improved overall functional capacity in patients with COPD.

**Functional Capacity**

The effect of theophylline on exercise capacity, the most common method for assessing integrated physiologic performance, has been extensively studied in different populations. Theophylline has little effect on various measures of exercise performance in young elite athletes, but a number of studies show that theophylline can have a beneficial effect on exercise in patients with COPD, which may be independent of effects on pulmonary function. Long-term theophylline use also improves the exercise capacity of patients with coronary heart disease and no lung disease.

The symptomatic response to theophylline has also been well studied. While the benefit of theophylline treatment on patients’ symptoms has been questioned, recent comparisons of theophylline treatment to placebo show improvement in dyspnea and measures of quality of life in patients with COPD. Indeed, theophylline has been shown to improve some measures of dyspnea in the absence of improvement in measures of pulmonary function, suggesting a complicated mechanism of action.

**Adverse Effects/Toxicity**

Theophylline, like any drug, has the potential for adverse effects. A recent analysis of the association of asthma mortality and morbidity in Saskatchewan is relevant to this question. While this study focused on β-agonists, the data revealed a crude odds ratio for death or near death associated with the use of theophylline of 3.7 with an adjusted odds ratio of 2.4 (1.4 to 4.3). This study focused on asthmatics, and may not be relevant to COPD. Furthermore, the increased odds ratio may be related, in part, to the severity of disease in those who died. Nevertheless, this study reinforces the notion that theophylline is potentially a dangerous drug.

Theophylline’s narrow toxic: therapeutic ratio is a major drawback to its use in elderly patients with COPD. This is especially important because the prevalence of COPD increases dramatically as the population ages. Aging-associated changes in liver function can result in as much as a tenfold decrease in the rate of the metabolism of theophylline in elders compared to children and young adults. As a result, the risk of chronic toxicity is especially high in the elderly. A prospective study from the Massachusetts Poison Control System found that for a given serum theophylline level, chronological age was the primary determinant of a life-threatening event in 72 patients with chronic theophylline toxicity over a 30-month period. Most patients had toxic reactions because they had increased their dose of theophylline slowly over a prolonged period of time in response to gradually increasing symptoms or because of prescribing errors. These two factors accounted for approximately two thirds of all causes of toxicity. Other studies show that for a given serum theophylline concentration, elderly individuals may have less improvement in FEV₁ and FVC compared with young adults, further increasing the risk of toxic reactions in elderly patients. Finally, the elderly are at risk for polypharmacy, and theophylline metabolism is affected by many commonly used drugs, providing yet another reason for special concern when using theophylline in this group of patients.

Theophylline has been implicated in affecting cognitive function in children for nearly a decade, but recent epidemiologic and controlled psychometric studies suggest that these affects are not clinically meaningful. Elderly patients with COPD would seem to be especially susceptible to subtle adverse effects of theophylline. In a recent study of elderly patients with COPD, we compared ipratropium, theophylline, and placebo in a crossover study design and were unable to demonstrate a significant change in cognitive performance on a battery of 11 tests of cognitive and motor function that measured learning and memory, attention, and language skills. Theophylline’s impact on sleep has also been debated. Theophylline may decrease the quality of sleep in normal individuals but patients with COPD tolerate high therapeutic doses of theophylline with no change in sleep characteristics and demonstrate improvements in lung function.

**Cost**

The overall cost of therapy is an important consideration in contemporary medical practice. Meaningful cost analysis goes beyond a per dose approach to evaluate the impact of a given therapeutic agent on overall health care cost. A recent Markov analysis comparing the strategies of treatment with theophylline or ipratropium in COPD found that ipratropium was only marginally better that theophylline in terms of measures of effectiveness, but the total cost per year, including hospitalization for toxic events, monitoring blood levels, etc, was significantly higher for patients using theophylline despite the fact
that ipratropium costs more on most formularies.34

Mortality

As is the case with most of the drugs used to treat the disease, there are no data showing that theophylline improves the life expectancy of patients with COPD.

Role in Treating COPD

Based on the available information, it is difficult to make a case for theophylline as monotherapy for the long-term management of COPD.35 The principal question, therefore, is what is theophylline’s role when used in conjunction with other drugs. Most studies of short- and long-term use of theophylline in combination with other drugs have reported beneficial effects on respiratory function in patients with COPD.36-39 Interestingly, there was no difference in symptom scores during each treatment period in several of these studies, although patients preferred the combination of theophylline and other bronchodilators when asked.40 This apparent discordance between respiratory function and symptoms may be simply a matter of insensitive measures for patient symptoms. This discordance was not seen in a study that reported the combination of theophylline and salbutamol to be superior to either alone in terms of valid functional and symptom measures, including walking distance in meters, dyspnea index, and a quality of life in patients with COPD.19 Finally, replacing theophylline with a placebo in patients receiving a long-term multidrug regimen, including ipratropium and a β-agonist, resulted in significant deterioration in pulmonary function, exercise capacity, subjective dyspnea level, and symptoms.41 From these and other studies, it is reasonable to conclude that theophylline is useful in combined drug regimens for COPD.

The appropriate dose in this context is a critical issue. The original dosing recommendations based on a classic logarithmic plot, targeted a therapeutic serum level of 10 to 20 µg/mL7 and tended to underestimate the benefits of lower serum levels. Recent recommendations suggest using lower doses and aiming for serum levels of 5 to 15 µg/mL, thereby reducing the toxicity of theophylline while maintaining beneficial effects.1 The appropriateness of these recommendations has been called into question by a recent study comparing placebo against low-dose (10 µg/mL) and high-dose (17 µg/mL) theophylline added to a combined drug regimen. This study found that the high-dose combination reduced trapped gas volume, increased walking distance, reduced fatigue scores, reduced dyspnea scores, and improved everyday activities and a quality of life index in more patients than the low-dose combination.42 This has challenged the usefulness of low-dose theophylline therapy in COPD and brings back old concerns about the toxicity.

Given these findings, where does this place theophylline in our approach to the long-term management of COPD? Theophylline has important potential benefits: (1) it is a pill; (2) it has an additive and perhaps unique effects (eg, strengthening muscles of respiration) in COPD; (3) it has a multisystem effect; and (4) sustained-release theophylline preparations are long lasting. Nevertheless, theophylline remains a potentially dangerous drug, especially in patients in whom it might be the most useful, ie, the elderly. As a result, more than ever, the use of theophylline must be individualized.

The approach suggested by Ferguson and Cherniack3 is a reasonable starting point. If a patient’s condition is not acceptable with maintenance ipratropium therapy and as-needed use of a short acting β-agonist, the addition of theophylline at a low dose to maintain a serum level of 8 to 12 µg/mL is appropriate. In light of recent data, however, if the patient’s condition is still not well managed, it would be appropriate to push serum theophylline levels to around 17 µg/mL. If there is no change in the patient’s condition, theophylline therapy should be discontinued, given the potential for chronic toxicity. It is important to evaluate the patient’s physiologic (eg, improved air flows or exercise capacity) and subjective (eg, reduced dyspnea or increased quality of life) response to treatment at each incremental step to identify beneficial effect. It is the task of the patient and treating physician to decide an appropriate indicator, but some measure of response should be employed to justify continuation of theophylline therapy in each patient, because once a patient is receiving theophylline, the treating physician is obligated to follow him/her closely, especially if the patient is receiving a high-dose regimen.

Finally, the impact of long-acting β-agonists on this scheme is unclear. Some of theophylline’s advantages can be found in a long-acting inhaled β-agonist, such as salmeterol. As other drugs in this class become available, theophylline may be further displaced as a useful agent in the treatment of COPD.

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