Theophylline as a Bronchodilator in COPD and Its Combination with Inhaled β-Adrenergic Drugs*

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The bronchodilating action of theophylline in COPD has been examined, with emphasis on its combined use with inhaled β₂ agonists. The suggestion is made that failure to recognize the nonlinearity of the dose-response curves for bronchodilators has resulted in underestimating their combined action. Recent studies suggest that systemic theophylline has somewhat different actions on the airways in COPD than inhaled β agonists, and that more bronchodilation may be possible when the two are used together than large doses of either one. By analogy, with asthma the suggestion is also made that the addition of theophylline is likely to provide a more constant bronchodilation, reducing peak-trough variations in flow. The most complete clinical comparison to date suggests that, in currently sanctioned doses, a regimen containing both theophylline and an inhaled β₂ agonist provides significantly greater bronchodilation than either drug alone, with fewer patient withdrawals. Further carefully designed studies are needed to resolve this issue, and particularly, to identify those patients who will derive the greatest benefit from a combined regimen.

The most tangible effect of theophylline, whether used in asthma or chronic obstructive pulmonary disease (COPD), is still bronchodilation. Numerous studies have shown that the mean improvement in forced expiratory volume in one second (FEV₁) from theophylline in COPD is only about 10 to 15 percent, which is consistent with the irreversible nature of obstruction to flow in this disease. However, theophylline is almost invariably used in COPD in conjunction with an inhaled β₂-adrenergic agonist, and we do know that most COPD patients claim to derive relief from the latter. Therefore, in this review, I will concentrate on studies of theophylline combined with these agents.

**Synergy vs Additivity?**

One of the oldest questions regarding theophylline is whether its effect is synergistic with β-adrenergic bronchodilators. The dictionary defines synergy as "the simultaneous action of separate agencies which, together, have a greater effect than the sum of their individual effects." Webster leaves the reader to worry about dose-response curves and other complexities. In reviewing studies of the synergy issue, the possibility exists that whether or not synergy exists, the addition of the two drugs contributes a component of bronchodilation otherwise achieved only by considerably increasing the dose of either one alone. The ultimate question is whether this added bronchodilation justifies theophylline's inclusion into the regimen, or whether one could accomplish the same thing by merely pushing up the dose of the inhaled drug.

**Dose Response Curves for Theophylline in COPD**

Dose-response curves for theophylline in COPD (or "chronic bronchitis") have not been done in as much detail. An important contrast with asthma was shown by Richer et al., who administered 600 mg of rapidly absorbed theophylline by mouth to stable asthmatics and patients with chronic bronchitis. Theophylline levels peaked at about 16 µg/ml. Over time, the response in peak expiratory flow rate (PEFR) almost paralleled theophylline levels in the asthmatics, but the bronchitis patients reached an abrupt limit to their response after an initial brisk rise (Fig 1). Their airways had evidently responded to an anatomic limit at this point, or else collapse phenomena were occurring.

Barclay et al. loaded and maintained theophylline in approximately 5 µg/ml increments in 12 chronic bronchitis patients until a plateau of response was reached in their forced vital capacity (FVC). Baseline FEV₁ averaged 1.0 L and FVC, 1.78 L. Although the step...
wise increases in FVC were not reported, the "plateau" concentrations beyond which further increases did not occur were listed. Seven of 12 patients plateaued at 17 μg/ml or more; two at 9 μg/ml; while plateaus were not reached up to 25 μg/ml in two others. After attaining the practical theophylline end point, 400 μg of salbutamol was inhaled by metered-dose inhaler. Figure 2 shows the FVC responses at these two points (study 1), with the theophylline end point about half the way to the final FVC. It should be realized that the final point represents the action of salbutamol on a background of theophylline. This study brings out the fact that individual variation exists in the response of the chronic bronchitis patients to theophylline, and that considerably more bronchodilation is possible by adding inhaled β₂-agonists.

In another study, Barclay et al. next studied ten bronchitis patients from the same group, all of whom received 200, 600 and 1,400 μg salbutamol, and some also received 3,000 μg, again as necessary to reach a plateau of response. Theophylline was then loaded and maintained in all at the previously individualized dose. Further slight increases in FVC occurred in only four subjects and this is shown. I have plotted the mean responses in Figure 2, abstracted from their article (study 2). From 0 to 600 μg salbutamol, the mean increase in FVC follows an abrupt rise and then there is a marked slowing in response. Two of ten patients responded maximally to 200 μg, the remainder showing continuing increases up to 1,400 μg. Four who had not plateaued received 3,000 μg. This study also shows individuality of response to the β-agonist as well as theophylline and establishes the superiority of large doses of inhaled salbutamol over theophylline for most patients.

These dose-response curves deal, for the most part, with peak responses rather than responses four to six hours later. One might expect that FVC responses at the latter point would show that all patients required more than 200 μg salbutamol to optimize.

PROBLEMS IN INTERPRETING SPIROMETRY WHEN ASSESSING SYNERGY VS ADDITIVITY

Assuming that a log-linear, or at least, nonlinear response exists for each class of bronchodilator in either asthma or COPD, one can reason that their combined effect, if only additive, should be less than the numerical sum of their individual effects. This is illustrated in Figure 3. The curves are hypothetical.

Here the dose of bronchodilator A is increased alone (curve 1) and on a background of constant bronchodilator B, (curve 2) such as would apply to a patient on a constant theophylline dose when the dose of inhaled β-agonist is increased. If, however, the comi-

![Figure 1. Effect of 600 mg rapidly absorbed theophylline producing mean peak levels of 16 μg/ml on PEFR in 31 patients with asthma (solid circles) and eight patients with chronic airway obstruction (solid triangles). (Reproduced with permission from Richer et al. 9)](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21564/)

![Figure 2. Mean responses of FVC to inhaled salbutamol and theophylline. In study 1, 12 chronic bronchitis patients first received theophylline at 5 μg/ml increments in serum until FVC plateaued, followed by 400 μg of salbutamol by metered dose inhaler. In study 2, ten of these patients first received salbutamol in consecutive doses to 1,400 μg total. Four who had not plateaued received 3,200 μg. In only four of the 12 patients did theophylline produce a further response, and these are shown. (Adapted from data contained in Barclay et al. 17)](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21564/)
nation of A and B results in numerical additivity (curve 3) then there is an element of synergism. Such numerical additivity could arise, for example, through interaction between the drugs in the relaxation process within the muscle, or could be occurring through physiologic consequences such as enhanced bronchodilation through qualitatively different effects on the airway such as hypothesized by Svedmyr and Svedmyr\(^5\) between an inhaled and infused bronchodilator.

**Combination Studies in Asthma**

There are few studies in which dose-response curves have been constructed for each drug and their combination. Wolfe et al\(^6\) did essentially this when they studied the effect of 2.5 and 5.0 mg terbutaline given orally, 200 and 400 mg aminophylline given orally, and their combinations at the low and high doses. In their published Figure 1, the combined effect of the two low doses was numerically equal to the sum of the individual responses, and the higher doses combined actually appear to exceed the sum of the individual responses.

Since I do not have the actual data, this analysis of the problem is only approximate. However, when the responses as taken off their figure are arbitrarily plotted on a two-cycle log scale (Fig 4) and some assumptions also are made about the intercept on the Y axis, one notes that the combined effect of either the low or high doses exceeds the response obtained by doubling either drug alone when referred to the equivalent dose of aminophylline or terbutaline. In fact, to equal the effect of the high dose combination, one would need over 3,200 mg aminophylline or 40 mg terbutaline. While the two-cycle log scale is probably an exaggeration of the non-linearity, it makes the point.

Marlin et al\(^7\) compared the individual responses to a single 375-mg dose of theophylline and a single inhaled dose of rimiterol, a \(\beta_2\) selective catecholamine. Their combined effect could be superimposed on the numerical sum of the individual effects. By the above reasoning, this is more than additive in a functional sense. There is an element of synergy.

Billing et al\(^8\) charted a dose-response curve to intravenously administered terbutaline in the presence of 0.0, 7.3 and 15.0 \(\mu\)g/ml theophylline also given intravenously. The absolute mean response in FEV\(_1\) to terbutaline at each theophylline level plateaued. Yet, the 15 \(\mu\)g/ml plateau was appreciably higher than the 7.3 \(\mu\)g/ml plateau. The authors deduced additivity rather than synergy. Yet, the presence of theophylline here seemed to add an element of response to terbutaline that might not have been otherwise achieved by any dose of the latter. This corresponds to the numerically additive curve of Figure 4.

Leopold and Handslip\(^9\) addressed the synergism issue by observing the effect of a 3 mg/kg intravenously administered dose of aminophylline on an intravenous dose-response curve to salbutamol. Theophylline levels were not maintained. The new dose-response curve was shifted to the left, equivalent to a fourfold increase in salbutamol dose, but with the same approximate slope. They concluded that no synergism existed. However, it is questionable whether the available precision could rule this out. In any case, however, the study nicely illustrates that, on a basal level of bronchodilation by theophylline, appreciably less salbutamol is required to achieve the same further level of bronchodilation.
**COMBINATION ACUTE STUDIES IN COPD**

It is possible that COPD is a disease that may have, in part, a different basis than asthma for bronchial tone. In the stable patients, the relative response to a β-adrenergic and anticholinergic agent differs in the two conditions, suggesting that cholinergic tone plays a relatively more important role in COPD.

A recent and thorough study of inhaled salbutamol and theophylline at high doses of each was performed by Filuk et al. They used 800 μg of salbutamol by metered-dose inhaler in 16 chronic bronchitis patients, both before and after a substantial dose of theophylline producing mean levels of 24.5 μg/ml. They wished to determine whether theophylline added anything to the salbutamol response. Their rigorous design, in which the order was then reversed, is a key to interpreting their results as shown in Figure 5.

The cases are divided into eight responders and eight nonresponders to salbutamol. We see the effect of the individual drugs on the improvement in FEV1, comparing the first half of each study, and then their combined effect. Curiously, one notes that the effect of salbutamol following theophylline is greater than its effect preceding theophylline (0.22 vs 0.16 L), despite being higher up on the dose-response curve where effects are more difficult to demonstrate. This suggests that, functionally, there is synergism of some sort between these drugs when given in this manner. The actual effects on spirometry and airway conductance are shown in Table 1.

The authors make the highly interesting observation that the effect of inhaled salbutamol on airway conductance (SGaw) relative to FEV1 and FVC is greater than the theophylline effect, and indeed, there is a considerable contrast between the two drugs. Also, both salbutamol and theophylline have an enhanced effect when given following the other drug, suggesting that there is a form of synergism regardless of the order. One wonders whether the more complete bronchodilation achieved occurs because the systemic drug acts on different portions of the airway than the inhaled drug, with mutual benefit between the two. The combined effect appears to exceed the maximum effect of either drug when pushed to its limit. This may not be a theophylline-specific effect but simply a function of the systemic route in asthmatics, as concluded by Svedmyr and Svedmyr in asthmatic patients.

An interesting perspective has been supplied by the study of Passamonte and Martinez in COPD. They also separated their patients into responders and nonresponders, using preliminary testing with inhaled isoproterenol. They then compared the responses to oral theophylline at levels of 15 to 20 μg/ml, averaging spirometric values over three days on the drug (Fig 6). Note that the difference in response to theophylline was considerably less than the difference to isoproterenol. Later, when metaproterenol given by inhalation was added to the theophylline regimens, the response to metaproterenol was relatively greater in the nonresponders to isoproterenol, suggesting that theophylline was facilitating the response, perhaps by better distribution of the drug, or possibly through some other form of augmentation, eg, within the muscle itself. Consistent with a differential effect between inhaled β-agonists and theophylline in non-

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**Table 1—Changes in FEV1 and SGaw When Salbutamol Precedes Theophylline (Protocol A) or Follows Theophylline (Protocol B) in COPD**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>FEV1</th>
<th>Δ FEV1</th>
<th>SGaw</th>
<th>Δ SGaw</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.74</td>
<td>0.16</td>
<td>0.042</td>
<td>0.017</td>
</tr>
<tr>
<td>Salbutamol, 50/min</td>
<td>0.90</td>
<td>0.13</td>
<td>0.059</td>
<td>0.004</td>
</tr>
<tr>
<td>Salbutamol, theophylline, 30/min</td>
<td>1.03</td>
<td>0.063</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.71</td>
<td>0.11</td>
<td>0.041</td>
<td>0.004</td>
</tr>
<tr>
<td>Theophylline, 30/min</td>
<td>0.82</td>
<td>0.22</td>
<td>0.045</td>
<td>0.017</td>
</tr>
<tr>
<td>Theophylline, salbutamol, 50/min</td>
<td>1.04</td>
<td>0.062</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted, with permission from Filuk et al."
dose-response curve 12-fold. Yet, he concluded that the clinical augmentation by theophylline on inhaled terbutaline was not true synergism, but rather enhanced distribution of the inhaled drug.

Other dose-response curves for human airways have been published by Guillot et al., although not in combination. Against acetylcholine adjusted to produce 80 percent maximum contraction, they found the EC50 for theophylline to average about 27 μg/ml (1.5 x 10^{-4}M), equal to a serum level of 67 μg/ml assuming 60 percent protein binding. About one fourth of their preparations could not be completely relaxed by any concentration of isoproterenol, but these preparations responded to theophylline, albeit at high concentrations.

In our laboratory, using cervical tracheal strips from mongrel dogs contracted with 10^{-4} M methacholine, we find the EC50 for theophylline to be comparable, averaging about 30 μg/ml in buffer. Our preliminary data suggest that 10 μg/ml theophylline decreases the EC50 for terbutaline or isoproterenol by a three- to four-fold factor (unpublished data). Thus, theophylline exerts an appreciable effect at levels well below its EC50 by essentially reducing the β agonist requirement for the same level of relaxation. Whether this is additivity or synergy we cannot say. However, using conventional criteria for synergism, Persson and Gustafsson recently found modest overadditivity (synergy) between theophylline and isoproterenol using guinea pig trachea.

THE "SMOOTHING" EFFECT OF THEOPHYLLINE ON BRONCHODILATION

Sustained-release forms of theophylline by themselves provide constant bronchodilation. While most studies of their action in combination with a β agonist during multiple dosing have concentrated on peak rather than on trough effects, an elevation of trough pulmonary function is surely as important in terms of patient comfort.

There are now several studies with asthmatic patients that have examined the entire bronchodilation response curve over a dosing cycle using separate and combined therapy. Kemp et al. found that maintenance theophylline appreciably increased the area under the curve (AUC) of the response when combined with inhaled bitolterol. A similar influence of theophylline was shown by Appel with aminophylline added to inhaled metaproterenol. In fact, a few patients found the addition of aminophylline to be strikingly helpful. Smith et al. found that the presence of theophylline appreciably increased the morning PEFR when added to inhaled terbutaline. Although these cited studies were done in asthmatic patients, the same principle must apply in COPD. As shown in Figure 7, Lee and Evans, in a single-dose study

**In Vitro Studies**

There is a paucity of studies examining the effect of adding theophylline to a β-adrenergic drug using in vitro smooth muscle preparations made from tissue from the airways. On normal human bronchi contracted with 10^{-7} M carbacholine, Svedmyr found that only 2 μg/ml theophylline produced an approximately fourfold reduction in the EC50 for isoproterenol, and that 30 μg/ml theophylline shifted the

**Figure 6.** Comparative FEV1 response to 180μg isoproterenol (I) or maintenance theophylline (T) in COPD patients, averaged over three days. Note that the nonresponders to isoproterenol (n = 12) have a relatively greater response to theophylline than the responders (n = 9). (Reproduced with permission, from Passamonte and Martinez.)

responders is the study of Eaton et al. The action of theophylline was tested in COPD patients preselected for their relative unresponsiveness to an inhaled bronchodilator (less than 15 percent in FEV1). When the theophylline levels were pushed to 17 to 22 μg/ml, there was a mean increase in FEV1 of 21.3 percent over placebo.

These three studies in COPD raise the question whether theophylline is a relatively more effective drug than an inhaled β-agonist in such nonresponders, despite the correlation between the two. The study by Passamonte and Martinez also suggests that the response to an inhaled beta agonist in nonresponders may be appreciably improved by theophylline.

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Theophylline showed that 400 mg theophylline appreciably raised the trough FEV₁ to inhaled metaproterenol, although the effect on the peak response appeared negligible.

PROTECTION AGAINST INDUCED BRONCHOSPASM

Theophylline and other bronchodilator drugs play a protective role against induced bronchospasm in the hyperreactive airways of the asthmatic patient, and almost certainly in COPD. Ramsdell et al. showed a sizeable group of patients with chronic bronchitis and found them to have hyperreactivity (hyperresponsiveness) to inhaled methacholine, despite a negligible effect of isoproterenol on their FEV₁. Inhaled isoproterenol quickly reversed the bronchospasm induced by methacholine, and can be assumed to have a protective effect in this situation. We will hear from Dr. Ahrens on this topic later in the symposium.

CLINICAL TRIALS IN COPD

If theophylline had an obvious subjective effect in COPD and clearly improved work capacity, perhaps this symposium would not have been held. Admittedly there is controversy regarding its benefit, and its risk-benefit ratio. For example, two groups have vigorously emphasized theophylline’s failure to add subjective relief or to provide sufficient objective evidence of improved work performance in COPD patients as a whole. Eaton et al. found only small effects on work scales, insignificant for the entire group but striking for two of 14 patients, all of whom had severe COPD. Both investigative groups have emphasized the importance of detecting those patients who will truly benefit from the drug, rather than administering it to everyone. One cannot argue with this premise. We need better practical methods of establishing its benefit in the individual patient. Perhaps someone will devise a means for the clinician to stage a simple but statistically accurate means of doing this, perhaps through multiple placebo-controlled periods with a few subjective and objective tests.

The most complete population study to date has been published by Taylor et al. from Belfast. These investigators originally undertook the study in the belief that theophylline would not help inhaled salbutamol treatment in chronic bronchitis. Quite the opposite emerged. Twenty-four patients were given either salbutamol, 200 µg four times a day, theophylline, in a sustained-release form, or placebo separately and in combination. Each treatment period lasted four weeks. Patients kept a record of morning and bedtime peak flows. Formal spirometry was done between 9:30 and 11 AM one on each limb, 1.5 to 3.0 h after a morning dose. Patients were disqualified ("treatment failure") if they developed sufficient shortness of breath on one of the regimens to contact their physician for a change in therapy.

Twelve patients were able to complete all treatment periods and had complete pulmonary function studies as tabulated in Table 2. Note that the salbutamol-theophylline regimen produced the best spirometry. Moreover, when analyzed from the standpoint of PEFR record and "treatment failure" (by a formula not described), the salbutamol-theophylline regimen was clearly the best. There was only one failure for theophylline-salbutamol, eight for salbutamol alone, six for theophylline alone, and nine for placebo.

While the authors could not show a significant subjective preference for the combined regimen on any scale except morning wheeze, theophylline in combination with salbutamol emerged as the regimen most likely to prevent episodes requiring the attention of the physician. Such a regimen, prohibiting more than a stated dose of the salbutamol, is probably unrealistic. Patients with unrestricted access to their metered dose inhaler might have been happy with that modality alone. However, the study is still useful in comparing these regimens.

Table 2—Pulmonary Function 1.5 to 3.0 Hours Post-Placebo, Theophylline, and Salbutamol in Chronic Bronchitis

<table>
<thead>
<tr>
<th>Before Therapy</th>
<th>P/P</th>
<th>T/P</th>
<th>S/P</th>
<th>T/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (L)</td>
<td>1.15</td>
<td>1.14</td>
<td>1.27</td>
<td>1.22</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.50</td>
<td>2.55</td>
<td>2.69</td>
<td>2.74</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>4.60</td>
<td>5.01</td>
<td>4.90</td>
<td>4.79</td>
</tr>
<tr>
<td>RV (L)</td>
<td>3.88</td>
<td>4.12</td>
<td>3.80</td>
<td>3.86</td>
</tr>
<tr>
<td>TV/TLC (%)</td>
<td>58.3</td>
<td>58.1</td>
<td>54.6</td>
<td>56.1</td>
</tr>
</tbody>
</table>

*Adapted with permission from Taylor et al.
†Abbreviations: P/P, placebo/placebo; P, placebo; T, theophylline; S, salbutamol.

Theophylline as a Bronchodilator in COPD (John W. Jenne)
Reduction in the Work of Breathing

Another parameter reflecting bronchodilator effectiveness is the work of breathing (WOB) done on the lung. We have examined the effect of theophylline at a mean serum level of 12.3 μg/ml on WOB in patients with severe COPD whose mean FEV₁ had an average FEV₁ / FVC response of 15 percent. We measured the effect while standing and while walking 1.2 mph on a level treadmill for two minutes. Theophylline significantly reduced the WOB only while walking, by an average of 16 percent (Fig 8). However, in terms of the reduction in added work upon walking over standing, the reduction was about 30 percent. This reduction undoubtedly occurs with any effective bronchodilator, but the study does show a rather surprising effect of theophylline, and brings out the considerable work involved during what would seem to be modest exertion in such patients. Whether this work limits their performance on maximal physical stress compared to other factors such as overall physical conditioning remains to be shown. However, it may figure in their comfort.

One potentially useful observation from this study for individualizing the predicted response was our finding that those patients preferring theophylline to placebo had the greatest improvement in FVC compared to FEV₁. This is reminiscent of studies by Bellamy and Hutchinson with inhaled salbutamol. The FVC may be the clinically relevant parameter.

The optimal use of bronchodilators in COPD is still evolving, and other modalities such as the nonabsorbable anticholinergics will soon be available as an additional variable for study. What I have tried to do here is to bring out some provocative aspects of the use of theophylline and to raise some questions. The overall risk-benefit ratio for this drug has not been settled. It further may be reduced by efforts to improve individualization, to assist the clinician to become better informed about its practical pharmacokinetics, and to adopt safe guidelines for commencing and monitoring therapy. Pharmaceutical companies could play a larger role in this endeavor, and may have to, in order to maintain its safe and proper role in COPD.

References

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