Conversion of COPD Patients from Multiple to Single Dose Theophylline*
Serum Levels and Symptom Comparison

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The objective of the present study was to determine if patients with COPD who were taking Theo-Dur bid or tid (total dose 400 to 900 mg per day) could be safely switched to Uni-Dur, 800 mg given qd at bedtime. Twenty-eight patients were enrolled in the study, and 23 completed the study. The mean daily dose of theophylline prior to the study was 828 mg, while the mean dose after three weeks of Uni-Dur therapy was 753 mg. The mean serum theophylline level 10.5 ± 3.6 h after the last Theo-Dur dose was 10.5 mg/L. After three weeks of Uni-Dur therapy, the mean theophylline level at 8:00 AM was 14.6 mg/L, while the mean theophylline level at 8:00 PM was 9.9 mg/L. This latter level did not differ significantly from that obtained at the start of the study 10.5 ± 3.6 h after the last dose of Theo-Dur. After three weeks of Uni-Dur therapy, the peak expiratory flow rate, the FEV₁, and the FVC were not significantly changed from those at the initial evaluation. Twenty-one of the 23 patients ended up receiving 800 mg Uni-Dur qd. From this study, we conclude that once daily theophylline dosing with Uni-Dur compared with bid or tid dosing with Theo-Dur produces similar theophylline levels and pulmonary function, and most COPD patients who are taking 400 to 900 mg Theo-Dur daily can be managed with 800 mg Uni-Dur once daily at bedtime.

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Theophylline has been an important drug in the long-term treatment of COPD for many years. However, concentration-related side effects dictate that the serum concentration of theophylline be maintained within a narrow therapeutic range. Until recently, this required frequent dosing of theophylline which limited its use.

The introduction of sustained release theophylline formulations has increased the use of theophylline by decreasing the required dosing frequency. In the last decade, more than 30 brands of SR theophylline products have been released. Ideally, one would prefer a theophylline preparation that needed to be given only once per day because this would be expected to improve compliance. Although two brands (Theo-24, Uniphyl, Theo-Dur and Slo-bid) have been approved for once-a-day administration by the FDA, and an additional two (Theo-Dur and Slo-bid) have been approved for once-a-day dosing for patients who metabolize theophylline slowly, none of these products is capable of reliably maintaining serum concentrations within the 10 to 20 μg/ml therapeutic range around the clock in most patients with COPD.

The objective of the present study was to determine if patients with COPD who were taking Theo-Dur twice or three times per day could be safely switched to Uni-Dur given once a day at bedtime. In particular, we wondered if all patients taking 400 to 900 mg per day could be treated with a single dose of 800 mg per day. This is the dose of another SR theophylline preparation which has been used in several studies as a once-a-day preparation. Uni-Dur is a newly developed SR tablet theophylline preparation. Uni-Dur appears to have advantages over the three preparations that have been released for 24-hour dosing. With Uni-Dur, there is less fluctuation in serum levels, its absorption is nearly complete, and it is not affected by food.

METHODS

Patient Selection

In order to be eligible for the study, patients were required to be above age 18 and to have COPD as demonstrated by spirometry. Patients were also required to be taking 400 to 900 mg Theo-Dur in two or three divided doses per day at a stable dose level for at least two weeks. Patients who smoked more than ten cigarettes per day or who were taking erythromycin, troleandomycin, cimetidine, or quinoline were excluded. Women of childbearing potential and patients with any current significant renal, cardiovascular, neurologic, gastrointestinal, or hepatic disease were excluded. Prior to the study, each patient signed a written informed consent which had been approved by our Institutional Review Board. All patients were recruited from the pulmonary clinic at the Veterans Administration Medical Center, Long Beach, California.

Protocol

This was an open label, repeated dose study. At the time of the initial evaluation, patients provided a complete medical history and underwent a complete physical examination. The patients also underwent spirometry at least 6 h after their last adrenergic agonist. A serum sample for determination of theophylline levels was obtained at approximately the time their next Theo-Dur dose was due to be taken. Theophylline levels were determined by fluoro-
ence polarization immunoassay method.

The patients continued taking the other bronchodilators they were receiving prior to the study. The total dose of theophylline was replaced by a single dose of Uni-Dur up to 800 mg (but not more than 13 mg/kg) daily, at 8 PM. Those taking a total of 600 to 900 mg were given 800 mg while those taking 400 to 500 mg were given 600 mg of Uni-Dur. In this latter group, the dose was increased to 800 mg after three days of treatment if there was no drug intolerance.

Uni-Dur was provided in bottles of scored 400 and 600 mg tablets. The patient was requested to call the physician if there was any question of intolerance. At these times, the physician decided whether the patient should return to the hospital for examination and/or for a serum theophylline level.

The patient returned one week after the start of Uni-Dur treatment for a serum theophylline level and spirometry at 8 AM after omitting adrenergic agonists for at least 6 h. At this time, the patient rated his/her symptoms as improved, unchanged, or worse, while the physician rated the overall change and auscultatory changes as improved, unchanged, or worse. If the serum theophylline level was greater than 20 μg/ml, the dose was reduced.

After at least seven days of dosing with 800 mg of Uni-Dur (or a lower dose if it was effective in controlling symptoms and was the dose that was tolerated), and after a total of three weeks of Uni-Dur treatment, the patient returned for their final evaluation. The patient rated specific symptoms and night wakenings and overall response as improved, unchanged, or worse. The physician rated overall change as improved, unchanged or worse, and the auscultatory changes as present or absent. A serum theophylline level and spirometry were obtained at 12 and 24 h after the previous 8 PM Uni-Dur dose. Adrenergic agonists were omitted for at least 6 h prior to the spirometry.

A diary was maintained by each patient who recorded daily symptoms and use of medication. Patient symptoms were graded on a scale of 0 to 3, zero being none and 3 being severe. Each patient was instructed to measure the peak expiratory flow rate once in the morning and once in the evening. The results of these measurements were recorded in the patient diary.

Statistics

All data are expressed as the mean ± the standard deviation unless otherwise noted. A measure of the variability of the serum theophylline levels while the patients were taking Uni-Dur was obtained by calculating the fluctuation in the theophylline level. For this study, the fluctuation was defined as the difference between the level 24 h postdose and the level 12 h postdose divided by the level 24 h postdose. This analysis assumes that the level 24 h postdose is the trough level and the level 12 h postdose is the peak level.

Comparisons of the different theophylline levels and results of the pulmonary function tests were analyzed using two way analysis of variance. If the F value was significant, then the least significant difference between means was calculated. Probability values < 0.05 were considered significant. Linear regression analysis was performed to examine the relationship between changes in pulmonary functions and changes in theophylline levels.

RESULTS

Twenty-eight patients were enrolled in the study and 23 patients completed the study. The explanations for why the remaining five patients did not complete the study are as follows. Two patients were dropped from the study because they had exacerbations of their COPD and required hospitalization. One patient developed pneumonia the day he was entered in the study and never took the first dose of Uni-Dur. One patient, who did not have a telephone in his residence, never returned after the first visit and repeated efforts to contact him were unsuccessful. After one patient enrolled in the study, it was discovered that he had been taking oxtriphylline rather than Theo-Dur, and therefore, he was dropped from the study.

The average patient who completed the study (Table 1) was older (mean age 67) and had moderate or severe COPD. The COPD in most patients was predominantly due to emphysema. All but one of the patients who completed the study were men. The characteristics of the five patients who entered but did not complete the study did not differ significantly from those who completed the study. Concurrent medications for the 23 patients who completed the study included inhaled beta adrenergic stimulants (20), oral beta adrenergic stimulants (10), inhaled corticosteroids (6), oral corticosteroids (6), and ipratropium bromide (12).

Prior to the study, all patients were taking Theo-Dur; 17 patients were taking 900 mg/day, one was taking 800 mg/day, and five were taking 600 mg/day. At the end of the study period, 21 patients were taking 800 mg; one, 400 mg; one, 600 mg of 24-h theophylline. The patient who ended up receiving 400 mg per day was 74 years old and only weighed 130 pounds, but his serum levels on day 21 were less than 10 μg/ml both at 8:00 AM and at 8:00 PM. The patient who ended up receiving 600 mg was 78 years old and weighed 175 pounds. His AM theophylline level on day 21 was 15 μg/ml, while his PM level as 11 μg/ml.

The mean theophylline level prior to the study while the patients were taking Theo-Dur after the most recent dose was 10.5 ± 5.0 μg/ml (Fig 1). The mean time between the most recent dose of theophylline and the serum sampling was 10.5 ± 3.6 h. At this time, 10 of the 23 patients (43 percent) had subtherapeutic (< 10 μg/ml) theophylline levels. After the patients had been taking Uni-Dur for one week, the mean serum theophylline level 12 h after the most recent dose had increased significantly (p < 0.01) to 14.6 ± 5.6 μg/ml. The number of patients with subtherapeutic levels had decreased to four, but two of the patients had high (26 and 27 μg/ml) levels. One of these patients had a subtherapeutic level at the original evaluation, and it was felt that he took both Theo-Dur

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|                      | Mean             | Standard Deviation |
| Age, y               | 67               | 5.9 |
| Weight, kg           | 76               | 3.9 |
| FEV1, L              | 1.04             | 0.37 |
| FVC, L               | 2.39             | 0.58 |
| FEV1/FVC, %          | 44               | 15  |
| Theophylline level   | 10.5             | 5.0  |

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and Uni-Dur for the first seven days of the study. After seven days, the mean daily dose of Uni-Dur was 782 ± 57.6 mg which did not differ significantly from the initial mean daily dose of Theo-Dur (828 ± 127 mg). One would expect the theophylline levels to increase on Uni-Dur since the levels on Uni-Dur represented a maximum level while the levels on Theo-Dur represented a minimum level due to the timing of obtaining the samples.

When the patients returned for their final evaluation after three weeks of Uni-Dur therapy, the mean morning theophylline level (14.6 μg/ml) was nearly identical to that after one week of Uni-Dur therapy. In addition, the mean daily dose of theophylline, 773.9 ± 91.5, was very similar to that two weeks previously. As expected, there was a significant fall in the mean theophylline levels to 9.9 ± 4.3 by 8 PM on this day. The mean serum theophylline level 24 h after the previous dose of Uni-Dur did not differ significantly from that when the next dose of Theo-Dur was due, and the number of patients who had subtherapeutic levels was identical. For the 21 patients taking 800 mg Uni-Dur, there was not a significant correlation between the weight of the patient and the serum theophylline level either 12 h (r = 0.06, ns) or 24 h (r = 0.08, ns) after the last dose of Uni-Dur.

The median fluctuation in the serum theophylline levels was 54 percent, with a range of 0 to 275 percent. Only four of the patients had a fluctuation above 100 percent. There was a significant inverse correlation between the degree of fluctuation and the weight of the individual (r = -0.60, p < 0.01).

There were not significant differences in the FEV₁ or the FVC in the mornings of the three study days (Table 2). Between 8 AM and 8 PM on day 21, there was a significant decrease in both the FEV₁ and the FVC. The change in FEV₁ and FVC on day 21 did not correlate with changes in theophylline levels (r = 0.22). Interestingly, the mean peak expiratory flow rate in the morning (225 ± 47 L/min) on day 21 was slightly lower than it had been the previous evening (236 ± 53 L/min). In addition, when the mean peak expiratory flow rates on days, 18, 19, and 20 were analyzed, the mean flow rate was always lower in the morning than it was in the evening. Accordingly, we believe that the decrease in the FEV₁ on day 21 is not clinically significant.

Evaluation of patient diaries showed 18 of 23 patients had no change in their symptoms, four showed a decrease, and one had increased symptoms. The only adverse reactions reported by the patients which were possibly significant were one instance of mild indigestion and one instance of mild nervousness. Neither reaction occurred in patients who had theophylline levels above 20 μg/ml. Physician evaluation showed 17 of 23 patients had no change in clinical status, three had improved, and three had decreased clinical status.

**DISCUSSION**

The present study demonstrates that Uni-Dur has promise as a theophylline preparation that can be given once a day at bedtime at the same dose to most older patients with COPD who smoke less than ten cigarettes per day. The serum levels of theophylline and the pulmonary function levels are comparable while the patients are receiving Uni-Dur once a day or Theo-Dur two or three times per day.

It is probable that compliance in taking theophylline preparations would be improved if they only needed to be taken once per day. If theophylline preparations are given on a once per day basis, they should probably be given in the evening. Patients with reversible airways obstruction tend to have diurnal variation such that their lowest flow rates are in the morning. Previous studies in asthmatics have shown that the diurnal variation is minimized when theophylline is given once per day in the evening. The explanation for this is that evening dosing with slow-release theophyll-

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Table 2—Pulmonary Function and Theophylline Levels for 23 Patients who Completed the Study

<table>
<thead>
<tr>
<th>Time</th>
<th>Day 0, 8 AM</th>
<th>Day 7, 8 AM</th>
<th>Day 21, 8 AM</th>
<th>Day 21, 8 PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td>1.04 ± 0.37</td>
<td>1.04 ± 0.36</td>
<td>0.99 ± 0.3</td>
<td>0.89 ± 0.33</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.39 ± 0.58</td>
<td>2.51 ± 0.68</td>
<td>2.53 ± 0.62</td>
<td>2.29 ± 0.65</td>
</tr>
<tr>
<td>Theophyl (µg/ml)</td>
<td>10.5 ± 5.0</td>
<td>14.6 ± 5.6</td>
<td>14.6 ± 5.1</td>
<td>9.9 ± 4.3</td>
</tr>
</tbody>
</table>

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line provides maximum serum theophylline levels early in the morning when expiratory flow rates are expected to be the lowest.

It appears that Uni-Dur provides more stable serum theophylline levels than do any of the currently available slow-release theophylline preparations. In the present study, the median fluctuation in serum theophylline level was 54 percent; and only four of the individuals had fluctuations above 100 percent. Uni-Dur certainly had less fluctuation than Theo-Dur. Previous studies with evening dosing with Uniphyl have demonstrated higher fluctuations. In a study of nine asthmatics, Neuenkirchen and co-workers reported a mean fluctuation of 300 percent. In a group of patients very similar to ours, Rivington et al reported that the fluctuation was 76 percent. Higher levels of fluctuation have also been reported with Theo-24 given once a day.

Since individual data are not available for most of the prior studies, the percentage of fluctuation from the previous studies was calculated as the difference between the mean peak and the mean trough concentration divided by the trough concentration. If this method of calculation was used for the present study, the fluctuation would be 47 percent. It should be noted that our figures probably underestimate the true fluctuation since we only had two theophylline levels to analyze. However, we believe that our figures provide a good approximation to the true fluctuation because prior studies have shown that with once a day dosing with Uni-Dur, the trough level immediately precedes the next dose, and the peak level is 12 h after the previous dose.

The slow-release theophylline preparation used in the present study appears to have other advantages over the available theophylline preparations. In contrast to Uniphyl with which evening doses provide higher peak and mean serum theophylline levels, the peak and mean serum theophylline levels are almost identical with morning and evening dosing with Uni-Dur. In addition, the absorption of Uni-Dur appears to be less affected by the ingestion of food, than does the absorption of Uniphyl or Theo-24.

Since many factors are known to influence the absorption and clearance of theophylline, the administration of the same dose of a theophylline preparation to most patients in a population might appear impractical. However, there have been several studies in which the same dose of theophylline has been given to all patients. The present study documents that almost all patients who are taking 400 to 900 mg theophylline can have therapeutic levels on a daily dose of 800 mg. When patients are changed to once daily Uni-Dur, we recommend that a serum theophylline level be obtained after one week of if the patient develops any symptoms of theophylline toxicity. We recommend that the daily dose be given in the evening since the pulmonary function of patients with COPD tends to be lowest in the early morning, and therefore, this is when the highest serum level of theophylline is needed.

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