Comparison of 12-Hour and 24-Hour Sustained-Release Theophylline in Outpatient Management of Asthma*

Dan S. Tilles, M.D.;† and Charles A. Hales, M.D.;‡

A once-daily sustained-release preparation of theophylline (Theo-24) was compared to a twice-daily (bid) preparation (Theo-Dur). Fourteen subjects with asthma requiring daily therapy with theophylline were evaluated in a 30-day prospective study. Pulmonary function and serum levels of theophylline were measured. With the twice-daily preparation the mean variation over 12 hours between the maximum concentration (Cmax) and minimum concentration (Cmin) for theophylline was 3.0 μg/ml ± 0.3 μg/ml, and there was no significant change in tests of pulmonary function. With the once-daily preparation the mean variation over twenty four hours between Cmax and Cmin was 7.4 μg/ml ± 1.1 μg/ml, with a small but significant associated change in the forced expiratory volume in one second (84.1 vs 79.6 percent of predicted). Several of the subjects had large differences between Cmax and Cmin with the once-daily preparation. For some, Cmin was quite low while at the same time Cmax was high enough so that further increases in the dose of the once-daily preparation would not have been possible. Thus, consideration of the variation from Cmax to Cmin is necessary in adjusting a patient's dose of the once-daily preparation and may present problems in changeover from the twice-daily preparation if the mean blood level of theophylline is already high.

While theophylline is considered one of the most effective drugs available for treating acute and chronic asthma, its use in patients has been hampered by several problems. Chief among them are the interpatient variations in the bioavailability of theophylline, the drug's narrow therapeutic range, and the failure of patients to comply with daily multidose regimens.14 The introduction of sustained-release once-daily preparations of theophylline attempts to alleviate poor compliance by patients. These preparations, which are designed for delayed constant release of the drug into the gastrointestinal tract, are said to permit the maintenance of steady-state serum concentrations of theophylline for extended periods.5 Compliance by patients is improved, since the drug is taken fewer times in a day,5,7 and the abrupt peaks and troughs in serum concentrations typical of therapy with immediate-release theophylline may be avoided.5,8,9

Nevertheless, recent studies with two once-daily preparations (Theo-24 and Uniphyl) have shown substantial peak-to-trough variations.11,12 To learn more about the clinical efficacy of these new preparations of theophylline, we conducted a comparative prospective evaluation of patients with a diagnosis of asthma. Patients were transferred from a twice-daily (bid) sustained-release preparation (Theo-Dur) to treatment with a once-daily preparation (Theo-24). The purpose of the study was to determine whether a single daily dose of a once-daily preparation (Theo-24) provides 24-hour relief from asthmatic symptoms, adequately maintains pulmonary function, and produces steady-state serum levels of theophylline comparable to those attained with the twice-daily preparation (Theo-Dur). In addition, we evaluated these parameters on the switch-over day and during 72 hours after transferring these patients from bid to qd therapy, in order to see what the effective switch-over dose should be.

MATERIALS AND METHODS

Patients

All subjects had a history of chronic asthma for at least six months requiring long-term administration of theophylline. All subjects were otherwise healthy, and criteria for exclusion included the following: acute or chronic pulmonary disease of any type other than asthma; tobacco smoking; history of coronary artery disease; uncontrollable hypertension; significant renal or hepatic disease; and use of drugs known to interfere with metabolism of theophylline. The subjects all had a normal complete blood count, urinalysis, serum electrolyte levels, hepatic function, and chest roentgenogram. The study was approved by the Human Studies Committee of the Massachusetts General Hospital, and informed consent was obtained. Subjects were maintained on their usual dosage of theophylline, as well as their other medications, including inhaled bronchodilators. Two subjects were receiving long-term therapy with corticosteroids. No restrictions were placed on diet or usual daily activities. Patients ate about an hour before testing and were asked what they ate.

*Sustained-release Theophylline in Asthma (Tilles, Hales)

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Design of Study

The overall approach to the study was to place patients first on the twice-daily preparation for six days at 8 AM and 8 PM, in order to ensure a stable baseline for symptoms, pulmonary function tests, and theophylline levels. The patients were subsequently switched to the once-daily preparation at 8 AM and were followed for the same parameters for 24 days. In addition, to allow direct comparison of the two drugs, pulmonary function and theophylline levels were measured at four-hour intervals over a 12-hour period immediately prior to and then subsequent to ingestion of the twice-daily preparation on the first day and the once-daily preparation on the 15th day. We also measured pulmonary function and theophylline levels at 8 AM on the seventh day after six days of the twice-daily preparation (12 hours after the last dose of the twice-daily preparation) and again at 8 AM (24 hours after the once-daily preparation) on the seventh to tenth days and the 30th day, in order to observe the effect of switching from the twice-daily preparation to the same total dose of theophylline in the once-daily preparation.

A 12-L rolling-seal spirometer (P.K. Morgan) and an on-line computer (Apple II-plus) were used to measure flow-volume loops. The loop with the highest sum of the forced expiratory volume in one second (FEV1) and vital capacity (VC) was used, and the FEV1, VC, FEV1/VC ratio, peak expiratory flow rate (PEFR), and flow rate at 25 percent of the vital capacity (V25%) were recorded from it. The functional residual capacity (FRC) was measured in a variable-pressure body plethysmograph (Warren E. Collins, Inc). The prediction equations of Curoto et al3 were used for all spirometric tests except V25%, for which the equations of Cherniack and Ruber20 were used. For pulmonary volumes (FRC) the equations of Goldman and Becklake21 were used. All results of pulmonary function tests are expressed as percent predicted. Serum concentrations of theophylline were measured using the enzyme multiplied immunosassay technique (EMIT-Syva Co) with a lower detection limit of 2.5 µg/ml.

Subjects were also required to maintain a prewritten diary with a checkoff type of format. Each day, they recorded whether their asthma had disturbed their sleep or daily activities and whether they believed that their asthma was well controlled. The subjects also recorded use of an inhaler and whether they experienced cough, shortness of breath, wheezing, or chest tightness. These responses were compared for equal numbers of days following the first day and the 14th day, in order to evaluate any differences between the twice-daily and once-daily preparations, respectively.

Three subjects (two women and one man) were dropped from the entire analysis. One subject developed pneumonia and another a severe viral illness. The third took the wrong dose of medication due to an error in the prescription. Two additional subjects were included only in the switchover analysis, since they failed to take their medication at the correct time on the 14th day.

Data were analyzed using a computer-based system (CLINFO Data Management and Analysis System: Bolt, Beranek and Newman, Inc). The null hypothesis was tested using the Wilcoxon rank sum test due to the nonparametric character of the data. All results are expressed as the mean±SE. Significance was set at p<0.05.

Results

Table 1 illustrates baseline pulmonary function, dose of theophylline, and age and sex of the subjects.

First Day vs 15th Day

Theophylline Levels. Figure 1 illustrates the mean serum levels of theophylline plotted over time. While there were no significant differences between the two preparations at any of the points of time between 8 AM and 8 PM (the first 12 hours after each preparation), the minimum concentration (Cmin) was significantly lower with the once-daily preparation than with the twice-daily preparation (Table 2). The Cmin with the once-daily preparation was almost always the 8 AM time point (24 hours after administration), whereas the Cmin with the twice-daily preparation was either the 8 AM or 8 PM time point, which were not significantly different. The mean difference in maximum-to-minimum serum concentration of theophylline during the 24-hour dosing interval between 8 AM and 8 AM (Cmax - Cmin) was significantly greater with the once-

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\text{Table 1—Demographics} \\
\begin{array}{|c|c|c|c|}
\hline
\text{Subject, Age (yr)*} & \text{Daily Dose of Theophylline, mg} & \text{Weight, kg} & \text{FEV1 percent of predicted} \\
\hline
1, F, 26 & 600 & 50.3 & 105 \\
2, M, 25 & 900 & 82 & 92 \\
3, F, 35 & 600 & 54 & 96 \\
4, M, 25 & 1,200 & 81 & 72 \\
5, F, 25 & 400 & 63.9 & 82 \\
6, M, 30 & 1,400 & 76 & 110 \\
7, M, 52 & 1,000 & 70 & 50 \\
8, F, 30 & 700 & 53 & 84 \\
9, F, 29 & 600 & 68 & 103 \\
10, M, 50 & 600 & 80.2 & 70 \\
11, M, 63 & 400 & 88 & 78 \\
12, F, 60 & 600 & 55.5 & 102 \\
13, F, 63 & 600 & 97.5 & 96 \\
14, M, 60 & 800 & 75.7 & 52 \\
15, M, 33 & 800 & 78.6 & 81 \\
16, F, 61 & 600 & 93.4 & 66 \\
17, F, 40 & 1,000 & 65 & 97 \\
18, F, 30 & 900 & 53.4 & 104 \\
19, F, 53 & 600 & 70 & 62 \\
\hline
\text{mean±SE} & 753±60 & 71.3±3.2 & 80±6 \\
\hline
\end{array}
\]

*Mean age, 42±3 years.

and 8 PM (the first 12 hours after each preparation), the minimum concentration (Cmin) was significantly lower with the once-daily preparation than with the twice-daily preparation (Table 2). The Cmin with the once-daily preparation was almost always the 8 AM time point (24 hours after administration), whereas the Cmin with the twice-daily preparation was either the 8 AM or 8 PM time point, which were not significantly different. The mean difference in maximum-to-minimum serum concentration of theophylline during the 24-hour dosing interval between 8 AM and 8 AM (Cmax - Cmin) was significantly greater with the once-

\[
\begin{align*}
\text{Figure 1. Mean serum levels of theophylline levels at 0, 4, 8, and 12 hours after dose for twice-daily preparation (circles) and for once-daily preparation (triangles) on first day and 15th day, respectively.} \\
\text{No significant differences were noted over the first 12 hours.}
\end{align*}
\]
Table 2—Serum Levels of Theophylline: Twice-Daily Preparation vs Once-Daily Preparation

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cmax, μg/ml*</th>
<th>Cmin, μg/ml†</th>
<th>Cmax – Cmin, μg/ml</th>
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*Highest theophylline concentration on first and 15th days (0, 4, 8, or 12 hours after dose).
†Lowest theophylline concentration on first and 15th days (0, 4, 8, or 12 hours after dose).
‡p<0.05 vs twice-daily preparation.

Pulmonary Function. There were no differences between the once-daily preparation and the twice-daily preparation with regard to pulmonary function (including FEV₁, VC, PEFR, and V25%) at any of the points of time from 8 AM to 8 PM (the first 12 hours after each preparation). Figure 2 illustrates mean FEV₁ (percent predicted) plotted over time. The values for FEV₁ for all the time points (n = 4) for all of the subjects (n = 14) were added (n = 56), and the mean was obtained for each preparation for the 12-hour period following dosing (first day vs 15th day). The mean FEV₁ with the once-daily preparation was 84 percent vs 83 percent of predicted with the twice-daily preparation, and similarly meaned values for VC were 98 percent vs 97 percent, respectively. However, when the subjects were receiving the once-daily preparations, the corresponding FEV₁ at Cmin (24 hours after administration) was significantly lower (80 percent) than the FEV₁ at the maximum serum level of theophylline (Cmax) (84 percent), demonstrating an effect of theophylline. This variation was not seen with the twice-daily preparation, where the Cmax-to-Cmin differences for theophylline were much smaller.

Switch-Over Data

Analysis of the data on the seventh day, when subjects were switched from the twice-daily to the once-daily preparation, revealed a small but significant increase in FEV₁ (5 percent) at eight hours, which returned to baseline by 24 hours (Table 3). There were no changes noted on the ninth or tenth days (8 AM), compared to the 24-hour level on the eighth day. The theophylline level eight hours after the once-daily preparation was significantly increased from 10.0 μg/ml ± 0.9 μg/ml to 13.5 μg/ml ± 1.0 μg/ml and then significantly declined to 6.3 μg/ml ± 0.5 μg/ml at 24 hours. Levels of theophylline did not significantly change on the ninth or tenth day (8 AM), compared to the 24-hour level on the eighth day (Table 3).

Follow-Up Data

After three weeks of the once-daily preparation (30th day), there were no significant changes in pulmonary function or theophylline level (8 AM).

Response of Patients

There were no significant differences in the number of nights disturbed by symptoms of asthma (21.8 ± 8.4 percent for twice-daily preparation vs 15.1 ± 7 percent for once-daily preparation), the days considered bad or during which subjects were unable to conduct their usual activities (8.3 ± 7.1 percent for twice-daily preparation vs 9.7 ± 5.8 percent for once-daily preparation), the amount of inhaler use (15.4 ± 3.5 puffs per day for twice-daily preparation vs 13.7 ± 3.1 puffs per day for once-daily preparation), or the days without symptoms (31.1 ± 7.7 percent for twice-daily preparation vs 37.1 ± 10.3 percent for once-daily preparation). Subjects reported no increase in symptoms consistent with asthma or toxic effects of the drug on the switch-over day. There were no important differences in side effects. Specifically, five of 14 subjects thought that they had more side effects with the once-daily preparation, while two of 14 thought that they had more side effects with the twice-daily preparation, and seven of 14 thought that there was no difference in side effects produced by either preparation.
Table 3—Switch-Over Data

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<th>Subject</th>
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<th>Theophylline Level, µg/ml</th>
<th>FEV₁, percent of predicted</th>
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*Subjects are switched over to once-daily preparation at same total daily dose as with twice-daily preparation at 8 AM.
†p<0.05 vs 7th day, 8 AM.
‡p<0.05 vs 7th day, 4 PM.

DISCUSSION

A 24-hour sustained-release preparation of theophylline was compared to a 12-hour preparation in 14 patients who while on treatment had mild to moderate asthma. The Cmax-to-Cmin differences were greater with the once-daily preparation than with the twice-daily preparation, and this was associated with small but significant changes in pulmonary function. This was primarily due to the decreased pulmonary function in association with the theophylline level at Cmin with the once-daily preparation, which was almost invariably at 24 hours after taking the preparation at 8 AM. The diurnal variation in normal and asthmatic subjects results in worse flow rates in early morning compared to midday.

The twice-daily preparation prevented this fall from being significant, whereas the once-daily preparation with its significantly lower early-morning theophylline level did not. Another once-daily preparation of theophylline (Uniphyl), which also has a 7 µg/ml Cmax-to-Cmin variation over 24 hours, has been given in the evening and has blunted the early-morning fall in pulmonary function. The once-daily preparation used in this study might be expected to do the same if given in the evening, so that the highest level of theophylline would occur in the early morning, when flow rates are worse. The switch-over data imply that in our subjects, it was safe to directly switch from the twice-daily preparation to the once-daily preparation by using the same total daily dose of theophylline. There was no evidence that the 24-hour preparation, which actually has a measurable release of several hours more than that, built up a higher concentration over time. No patient had a clinically significant decline in pulmonary function, and there were no symptoms of toxic effects of the drug; however, our subjects did not have high theophylline levels with the twice-daily preparation to begin with. Had they started with peak levels at the upper end of the therapeutic range (eg, 15 µg/ml to 20 µg/ml), a milligram-for-milligram switch from the twice-daily to the once-daily preparation would probably have produced toxic effects in some of the subjects (eg, subjects 7 to 9, 12, and 19). Thus, one should proceed with caution when switching patients who have theophylline levels in the mid-teens with the twice-daily preparation to the once-daily preparation. The Cmax-Cmin difference was significantly greater for the once-daily preparation when compared to the twice-daily preparation. It is possible that the Cmax-Cmin difference was underestimated for the twice-daily preparation. First of all, these patients did not have their usual dosage of theophylline altered to achieve a serum level toward the higher side of the therapeutic range. If this had been done, the Cmax-Cmin difference might have been closer to the range of 3.5 µg/ml to 5.5 µg/ml which has been reported in previous studies. Secondly, we did not measure serum levels of theophylline hourly and may have missed the true Cmax and Cmin. Thirdly, the Cmin level for the twice-daily preparation might be lower at night when no levels were drawn. Scott et al noted lower values for Cmin for asthmatic children when

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nighttime dosing (8 PM) with the twice-daily preparation was compared to morning dosing (8 AM); however, among our subjects, there were no differences in theophylline level at 8 AM or 8 PM with the twice-daily preparation. The theophylline levels with the once-daily preparation may have been affected similarly, and therefore we believe that the measured Cmax-Cmin difference reflects inherent differences in the pharmacokinetics of these two preparations of theophylline.

Several of the subjects (subjects 1, 7 to 9, 12, and 19) had very large Cmax-Cmin differences with the once-daily preparation. These subjects were not optimal candidates for the once-daily preparation, since their values for Cmin were well out of the therapeutic range, whereas their values for Cmax were close to the maximum recommended therapeutic level of 20 μg/ml. Clearly, if these subjects at another point required an increase in their dose of the once-daily preparation, they would be at risk of developing toxic effects of theophylline. Indeed, if the need arose, one had the option of increasing the dosage of the twice-daily preparation in subjects 7 to 9, 12, and 19, in an effort to improve pulmonary function. With the once-daily preparation, this would not have been possible and clearly would have been important, since the FEV1 at Cmin was significantly lower than at Cmax. In addition, the subjects with these wide peak-to-trough differences would be more likely to develop toxic effects of theophylline as a result of a small change in their metabolism. The wider Cmax-Cmin differences with the once-daily preparation that we found agree with a previous study by Hendeles et al.11 It is of interest that in our series, five of six subjects with a large Cmax-Cmin difference while receiving the once-daily preparation were women. In this small series, this was not a statistically significant finding, but this tendency should be noted.

Since this study was not double-blind, it is hard to evaluate our data from the diaries on symptoms. Clearly, there were biases that could have favored the once-daily preparation. First of all, the subjects could have been biased by the investigators’ greater enthusiasm for the once-daily preparation, since it was a new drug. In addition, the advantage of taking theophylline once daily may have decreased the amount of reporting of symptoms while subjects were receiving this preparation. These two facts, coupled with previous observations that asthmatic subjects are less sensitive to early-morning falls in pulmonary function,12 probably explains the failure of patients receiving the once-daily preparation to report more symptoms in association with their small deterioration in flow rates in the morning compared to the twice-daily preparation.

We should also point out that our subjects in general had well-controlled asthma. Indeed, 50 percent had baseline values for FEV1 that were greater than 80 percent of predicted. This could tend to eliminate any differences between the two preparations; however, subjects receiving the once-daily preparation showed significantly more airway obstruction at Cmin than at Cmax. Theophylline was thus likely playing a useful role in these patients, and a population of sicker asthmatic subjects would not behave any differently from our group of mild and moderate asthmatic subjects. Furthermore, the change in FEV1 (from Cmin to Cmax) was no greater among subjects whose baseline FEV1 was less than 80 percent of predicted compared to those above 80 percent. In addition, the Cmax-Cmin difference was equivalent among subjects whose baseline FEV1 was less than 80 percent of predicted compared to those above 80 percent.

Recently published data have suggested that the ingestion of a meal with high fat content with large doses of the once-daily and the twice-daily preparations may alter their absorption and, therefore, potentially cause toxic effects.11,24,45 While we did not control our subjects’ intake of food, we did find that our subjects reported eating a much lighter breakfast compared to the breakfast with a larger fat intake provided by Hendeles et al.11 This may account for the lack of clinical toxic effects among our patients, although our data do not address the potential impact of high-fat meals on the pharmacokinetics of theophylline.

In summary, in subjects with stable asthma, the once-daily preparation can be safely exchanged for the twice-daily preparation at an equivalent dose in patients with medium levels of theophylline; however, the once-daily preparation has a much wider variation in maximum-to-minimum concentration than the twice-daily preparation, and thus caution is advised in switching patients to the once-daily preparation when the level of the twice-daily preparation is in the high therapeutic range, as toxic effects could occur.

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