Bioavailability of a Once Daily-Administered Theophylline Preparation*

A Comparison Study

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To evaluate the bioavailability of a new theophylline preparation suitable for once-a-day (od) oral administration, we performed a nonrandomized crossover study in which the absorption of the OD and a standard twice-a-day (bid) preparation were compared. Eight stable asthmatic patients, after having achieved steady-state, received an average of 975 mg of OD preparation at 8 PM. The protocol was later repeated with the same subjects receiving 487.5 mg of the bid preparation at 8 PM and again at 8 AM using the same total dose. The maximal mean serum concentrations were 15.5±1.6 (SEM) µg/ml for the od preparation on the 8th hour and 12.7±2.2 for the bid regimen. The trough level was 7.4±1.2 µg/ml for the od regimen and 10.6±1.6 for the bid regimen. With either regimen, therapeutic theophylline levels could be observed throughout the 24-hour study period. Anhydrous theophylline may be administered as a single daily dose agent.

Theophylline preparations are widely used in the treatment of asthma. Although most available oral preparations are well absorbed,¹ and the dose of theophylline is often adjusted for the patient’s weight, the desired serum theophylline concentration is difficult to achieve. Reasons include: genetically-determined differences in individuals’ rates of hepatic metabolism;² effects of disease states upon the distribution or elimination of theophylline;³ effects of other medications upon theophylline concentration;⁴ and, differences in the actual content of theophylline between the many marketed theophylline-containing preparations.

Since many available preparations require two, three, or even four daily doses, omission of one or more daily dose by patients may account for low serum theophylline levels in those patients. Although no available study has examined the compliance of asthma patients’ intake of daily prescribed medications, Kinsman et al⁵ showed an unsatisfactory compliance to PRN medications.

Therefore, the marketing of a theophylline preparation suitable for once daily oral administration may be of clinical use. Our study compares the bioavailability of a newer sustained release anhydrous theophylline suitable for once daily administration (od) to that of a currently available preparation taken twice a day (bid).

METHODS

Patient Population

Eight adult asthmatic patients (four men, four women) were selected from the University Hospital clinic population for study. All signed informed consent. All responded to provoking agents (physical or chemical) by wheezing and reported nocturnal symptoms. None had cardiovascular, renal or hepatic disease. Six were receiving theophylline preparations prior to the study; two received "over the counter" theophylline-containing medications. Two had previously received corticosteroids. One had mild wheezing at the time of study. None smoked.

Pulmonary Function Testing

All patients had been regularly evaluated with spirometry and peak expiratory flow rates in the pulmonary clinic. These patients had serial spirometry to document reversible airways obstruction, and met the American Thoracic Society definition of asthma.⁶ Each subject was entered into the protocol only when testing showed his maximal expiratory flow and volume to approximate his own best airway function as determined by his previous records.

Protocol

We studied two treatment regimens: 1) od anhydrous theophylline (Uniphyll, Purdue Frederick Company); 2) bid anhydrous theophylline (Theo-Dur, Key Pharmaceuticals, Inc). All subjects participated in both regimens.

Patients were asked to omit all dietary xanthine derivatives for two-three days (chocolate, cola, coffee, tea). On the fourth day, patients received 800 mg Uniphyll, to be taken each evening at 8 PM. Serum theophylline was measured at 4 PM three-four days after the administration of od theophylline. The nightly dose was increased by 200 mg in those subjects whose 4 PM serum level was less than 5 µg/ml. This was done repeatedly until the 5 µg/ml concentration was attained. Steady state was defined as a level of 5 µg/ml drawn four hours before trough (8 PM). A level of 5 µg/ml was selected because it represents a minimal level which will achieve bronchodilation.⁷

When the desired steady-state dose for each subject was established, patients were admitted to the medical service for study. Patients received pulmonary function testing, complete blood

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566
Table 1—Demographic and Functional Characteristics of Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Duration (yr)</th>
<th>FEV₁ Most</th>
<th>FEV₁ Least</th>
<th>Impaired</th>
<th>Impaired</th>
<th>Mean</th>
<th>± SEM</th>
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<tbody>
<tr>
<td>n=8</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>29</td>
<td>87</td>
<td>22</td>
<td>1.87</td>
<td>3.30</td>
<td>48</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>± SEM</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>0.38</td>
<td>0.30</td>
<td>9</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in one second; %Pred = percentage of predicted value; SE = standard error of the mean; duration = length of time with asthma.

counts, and basic chemistry screening (SMA24 which includes serum albumin, globulin, alkaline phosphatase, BUN and creatinine to rule out liver or renal disease). No patient with an abnormal SMA24 result was included in the study. Intravenous cannulas were inserted for blood sampling. A 4 PM (pre-trough) sample was obtained. Between 6-8 PM, a xanthine-free hospital dinner was served. We noted conflicting reports regarding the effect of food on absorption of sustained release preparation. The former study shows "dumping" of theophylline while fasting; the latter, with food ingestion. Therefore, since patients do not eat at the same time each day, we did not adhere to a rigid time schedule for eating and taking the medication. At 8 PM each patient received OD theophylline in the dose that had already been established during the out-patient preparation described above.

Serum levels were obtained at 8 PM (time zero or trough), and again at times 2, 4, 6, 8, 10, 12, 14 and 16 hours after the administration of theophylline. Peak expiratory flow was measured at time zero and four hours after the dose.

The bid regimen was administered to the same patients 90 days after the od regimen. During the three-month (90 days) interval, patients returned to their previous out-patient therapeutic programs. For the bid regimen, the Theo-Dur dose for each patient was identical to his Uniphyl dose, but given in two divided doses. Patients were switched over to Theo-Dur from their usual medication. Three to four days later, blood levels were obtained at 4 PM.

Admission and steady state criteria were similar to the OD regimen. Serum theophylline levels were drawn at 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 hours after the dose of Theo-Dur.

This protocol was reviewed and approved by the institutional review board of the University of Medicine and Dentistry of New Jersey, New Jersey Medical School.

Data Analysis

Demographic, functional, and pharmacologic data were reported as mean and standard error of the mean (SEM). Paired t statistics were used to compare data from the same subject during od and bid regimens. Pharmacokinetic data included: area under the plasma drug concentration curve (AUC) in µg/ml hour; average half life of elimination (Te) in hours; half life of absorption (Ta) in hours; mean maximum concentration, µg/ml (Cmax); and the time at which maximum plasma concentration was achieved (Tmax). The AUC for both regimens were calculated for 24 hours by the trapezoidal rule. Data points for the od regimen extended to 16 hours. To obtain a 20- and 24-hour data point, we used the 4 PM pre-trough and the 8 PM trough levels drawn at the time of admission. Thus, we assume that the patient took his appropriate dose at 8 PM on the previous evening. Data points for absorption, elimination and maximum concentration for the bid regimen were calculated from 12 hour periods. The AUC 0-24 for the bid regimen is the combined sum (AUC₂₄₋₀ + AUC₃₂₋₀). Bioavailability was expressed as ratio of od AUC over bid AUC. Ta, Te, Cmax and Tmax represented for the bid are from the 12-24 hour data since 0-12 and 12-24 hour values were similar (Table 3).

Serum theophylline was determined by a fluorescence polarization immunosassay (FPIA-TDs theophylline systems assay).

RESULTS

Demographic and functional characteristics appear in Table 1. Subjects were young and, on the average, overweight. Comparison of the FEV₁, when patients were ill (1.87 ± 0.38 liters or 48 percent pred) with FEV₁ when stable (3.30 ± 0.30 liters or 81 percent pred) demonstrated reversible airways obstruction.
Table 2—Steady-state Serum Theophylline Levels (µg/ml)

<table>
<thead>
<tr>
<th>Time in hours</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>22</th>
<th>24</th>
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<tbody>
<tr>
<td>Anhydrous theophylline (Uniphyl 975 mg od)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.4</td>
<td>10.5</td>
<td>12.7</td>
<td>15.3</td>
<td>15.5</td>
<td>15.0</td>
<td>15.3</td>
<td>15.1</td>
<td>13.6</td>
<td>—</td>
<td>(11.2)</td>
<td>—</td>
<td>(7.4)</td>
</tr>
<tr>
<td>± SEM</td>
<td>1.2</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.6</td>
<td>1.7</td>
<td>1.8</td>
<td>1.7</td>
<td>1.6</td>
<td>—</td>
<td>(0.9)</td>
<td>—</td>
<td>(1.2)</td>
</tr>
<tr>
<td>Anhydrous theophylline (Theo-Dur 487.5 mg bid)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>10.6</td>
<td>10.5</td>
<td>10.8</td>
<td>11.8</td>
<td>12.7</td>
<td>11.8</td>
<td>11.9</td>
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<td>13.7</td>
<td>13.7</td>
<td>12.5</td>
<td>12.5</td>
<td>11.5</td>
</tr>
<tr>
<td>± SEM</td>
<td>1.6</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>2.2</td>
<td>1.9</td>
<td>1.8</td>
<td>2.0</td>
<td>2.1</td>
<td>2.3</td>
<td>1.9</td>
<td>1.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

od = every 24 hours; bid = every 12 hours; ( ) = theophylline level of previous day

Mean serum theophylline levels appear in Table 2 and Figure 1. The mean dose to achieve steady-state, defined here as a 4 PM pre-trough level greater than 5 µg/ml, was 975 mg daily. Five patients received the standard 800 mg while three received doses ranging from 1,000 to 1,600 mg. Paired statistical analysis showed that mean serum theophylline levels between the od and bid regimen at each hour of testing (data point) did not show any statistical difference except at the 8th hour (Table 2) when od resulted in a mean serum theophylline level (15.5 ± 1.6) higher than bid (12.7 ± 2.2). This level corresponded to the mean maximum point of fluctuation for the od regimen (p value of less than .01).

The mean trough levels during the od regimen (7.4 ± 1.2) and bid regimen 10.6 ± 1.6 µg/ml (0 hour) and 11.5 ± 1.8 µg/ml (24th hour) were not of statistically significant difference (p value of more than .05).

Theophylline pharmacokinetic characteristics of the xanthine preparations studied. AUC, or the amount of drug available to the systemic circulation, is graphically presented in Figure 1. Note that the od AUC (0-24) of 302 units and bid AUC (0-24) of 293 units, are comparable. There was no statistical difference between od AUC and bid AUC. The bioavailability ratio of the od to bid regimen was 103 percent.

Mean TA for the od regimen was 3.18 hours; for bid, 1.3 hours (p value of less than .05). TE for the od regimen, 10.6 hours, is similar to that previously reported for sustained release theophylline.10 TE of the bid regimen, by contrast, was greater (21.6 hours; p value of less than .05) than TE of the od regimen. Cmax and Tmax for the od regimen exceeded Cmax and Tmax for the bid regimen. Cmax (Table 3) values differ from the mean 8th hour level shown in Table 2 in that the Cmax value represents the average of the maximal value recorded for each individual subject regardless of the time at which that level was obtained. Cmax difference was not statistically significant. Tmax difference could be accounted by the regimen schedule (od vs bid).

Determination of peak expiratory flow rates (PEFR) appear in Table 4. PEFR were in the low-normal ranges at the beginning of and during each regimen.

Side Effects

Three patients described side effects during the od regimen: two patients had headaches, one had insomnia. Five patients presented complaints during the bid regimen: four had nausea, one had insomnia. None described nocturnal wheezing or dyspnea with either regimen. Blood pressure and pulse rate were within normal limits at the beginning of each regimen and remained so throughout both clinical trials.

Discussion

Our study shows that the administration of an od

Table 3—Steady-state Pharmacokinetic Data

<table>
<thead>
<tr>
<th></th>
<th>AUC0-24</th>
<th>T0-24</th>
<th>Tmax-24</th>
<th>Cmax0-24</th>
<th>Tmax0-24</th>
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<tbody>
<tr>
<td>Mean</td>
<td>302.4</td>
<td>10.6</td>
<td>17.1</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>± SEM</td>
<td>0.30</td>
<td>1.2</td>
<td>1.5</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td></td>
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<tr>
<td>Theo-Dur</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>292.9</td>
<td>21.6</td>
<td>15.1</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>± SEM</td>
<td>0.6</td>
<td>3.6</td>
<td>2.2</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

AUC = area under the plasma concentration curve; µg/ml hr (0-24) = for od dose; nighttime 12-hour period (12-14) = for bid dose; TA = average half-life of absorption in hours; Te = half-life of elimination in hours; Cmax = maximum theophylline concentration (µg/ml); Tmax = time at which maximum plasma concentration was reached; n = number of subjects.

Once Daily-administered Theophylline (Mangura et al)
theophylline preparation and the administration of a currently available bid product are both efficacious. For the eight subjects studied here, equivalent doses of the two preparations yielded similar serum theophylline levels and bronchodilation with few adverse effects.

For this study we established an arbitrary dose for each patient. This dose was selected to achieve a minimal pre-trough serum level of 5 μg/ml. Since the total theophylline doses for both regimens were identical, comparisons between regimens could be made. Given the average weight of our patients (87 kg), our average dose of 975 mg represented 11.21 mg/kg/day.

Since the subjects in our study achieved steady-state on an out-patient basis before the 24-hour protocol was performed, the 975 mg dose should be considered a maintenance dose. It appears that the serum levels achieved for our patients were higher than might have been predicted from the doses given and the patients' weights (six of eight patients were overweight). This observation might have been predicted from previous observations concerning theophylline administration to obese subjects.10 Body clearance of theophylline is similar in obese and lean subjects only when ideal body weight is considered. Therefore, while loading doses should be calculated according to actual weights, maintenance doses must be estimated from ideal body weights in obese individuals. The therapeutic serum theophylline levels seen in our patients suggest that an adequate steady-state level had been achieved in our patients prior to the overnight study and that the serum levels might have been predicted had ideal body weight been considered.

The bioavailability of the od and bid preparations were identical (302 units vs 293 units), and mean levels were similar on either regimen. The mean trough level of 7.4±1.2 μg/mg with the od regimen was low; otherwise, levels were comparable between od and bid throughout the 24-hour period. The 8th hour mean concentration, which corresponded to the point of mean maximum fluctuation, was higher in the od than the bid regimen (Table 2; 15.5±1.6 vs 12.7±2.2 μg/ml).

When the eight patients received the od regimen, levels of 10 μg/ml were maintained for 20 of 24 hours, or 85 percent of the 24-hour period; with the bid regimen, similar (between 10-20 μg/ml) levels were maintained 24% of the 24-hour period (100 percent).

The half-life of absorption was, as expected, longer for the once-a-day preparation than for the bid product. The half-life of elimination was similar for the od preparation to that previously reported for theophylline. Unexpectedly, TE for the bid product was prolonged. TE is computed from the terminal phase of the serum level versus time curve, shown in Figure 1. This finding may reflect the fact that the TE calculated is valid only with agents which are given intravenously or rapidly absorbed.

In summary, two theophylline preparations were compared using identical doses. Although the mean trough level of the od regimen was below that of the bid, both regimens resulted in comparable mean serum theophylline levels throughout the rest of the 24-hour study period. The bioavailability of od regimen relative to the bid regimen was 103 percent. These findings agree with those of Fanta and McFadden.13

ACKNOWLEDGMENT: The authors thank Drs. Frederic Potulski, Michael Russioniello; medical students Eric Korsh, Barry Butler, Larry Livornese and Patricia Davis for their assistance; Mrs. Jean Norwood for the patient preparation of this manuscript; and Dr. Lee B. Reichman for thoughtful review of the manuscript. Dedication: To the memory of Rosemary A. Cellene, M.D., F.A.C.P. (1933-1985)

REFERENCES

Table 4—Peak Expiratory Flow Rates During the Study Trials

<table>
<thead>
<tr>
<th>Peak Expiratory Flow (L/min)</th>
<th>t₄</th>
<th>t₄</th>
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<tr>
<td>Anhydrous theophylline od (Uniphyll) n=8</td>
<td>350±39 SEM</td>
<td>390±26</td>
</tr>
<tr>
<td>Anhydrous theophylline bid (Theo-Dur) n=8</td>
<td>336±41</td>
<td>340±46</td>
</tr>
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</table>

Values represent the mean and SE of the mean for 8 patients. n = number of subjects; t₄ = time at start of dose; t₄ = time at 4 hours post dose; expiratory flow = liters per minute.
Sampling and Evaluating Airborne Asbestos Dust

This five-day Occupational Safety and Health Course will be held November 3-7, sponsored by the University of Southern California, Institution of Safety and Systemic Management, 3500 South Figueroa Street, Los Angeles 90007 (213:743-6523).

Symposium on Noninvasive Vascular Diagnostic Techniques

Temple University and the Institute for Medical Studies will present this program October 30-November 1 in Washington, D.C. For information, contact Kim Stroich, 30131 Town Center Drive, Suite 215, Laguna Niguel, CA 92677 (714:495-4499).