Theophylline in Obstructive Sleep Apnea*
A Double-Blind Evaluation

Eithne Mulloy M.B., B.Ch.; and Walter T. McNicholas, M.D., F.C.C.P.

Twelve patients with documented obstructive sleep apnea were enrolled in a double-blind placebo controlled crossover trial of oral theophylline, (Uniphyllin) 500 mg, taken at night for four weeks. Overnight polysomnography, using standard techniques, was performed at the end of each treatment period. The total number of apneas (A) and hypopneas (H) decreased significantly while receiving theophylline compared to placebo, from 398 (69), mean (SEM), to 283 (72), p<.01. Sleep quality was, however, significantly worse while receiving theophylline. Obstructive A and H were very much decreased with theophylline (p<.001), and even when the data were adjusted for the more disturbed sleep with theophylline, this decrease remained significant; the obstructive A and H index fell from 49 (8.7) on placebo to 40 (9) while receiving theophylline, p=.02. There was no difference in the numbers of central or mixed A and H, and mean A and H duration was unchanged on the two study nights. Oxygen desaturations >4 percent were less with theophylline treatment (p=.02), but mean overnight SaO2 was unchanged. We conclude that theophylline may be beneficial in patients with OSA, but part of the improvement is due to a deterioration in sleep quality.

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A = apnea; H = hypopnea; OSA = obstructive sleep apnea; REM = rapid-eye-movement; RIP = respiratory inductance plethysmograph

Previous reports of pharmacologic therapy in obstructive sleep apnea have given mixed results, although protriptyline has been reported to be of benefit. The methyloxanthines have a respiratory stimulant effect, which appears to be at least partly central. They increase alveolar ventilation and the ventilatory responses to both oxygen and carbon dioxide. They improve Cheyne-Stokes respiration, and are beneficial in neonatal apnea, and improve diaphragmatic contractility.

Many of these factors have a potential impact on the pathophysiology of OSA, which appears to involve both central and upper airway factors. Central factors may include instability of ventilatory control during sleep, and an exaggerated periodic breathing pattern, both being factors which might be influenced by theophylline therapy. Local factors include decreased tone in the upper airway muscles during sleep, predisposing to oropharyngeal occlusion. Should theophyllines have a stimulant effect on upper airway muscles similar to that on the diaphragm, this might have a beneficial effect in OSA. To date, however, there are no reports on the effect of theophylline on upper airway muscles.

Based on the above considerations, there are strong theoretical reasons to propose that theophylline may have a beneficial effect in patients with OSA. We, therefore, examined the effects of oral theophylline in a group of patients with previously diagnosed OSA, using a placebo-controlled randomized crossover study design.

METHODS

Patient Selection

Twelve male patients with recently diagnosed OSA (>15 apneas or hypopneas per hour of sleep) were enrolled in the study. Patients with a history of cardiac or hepatic disorders were excluded, as were those taking hypnotics or sedatives, or any medication known to interfere with the absorption or metabolism of theophylline. Patients with a substantial alcohol intake (>20 units per week) were also excluded. The study was approved by the Hospital Ethics Committee, and all patients gave informed consent prior to entry into the study. Initial evaluation included a clinical history, physical examination, and pulmonary function tests (spirometry with reversibility to inhaled salbutamol, flow-volume loops, and single breath diffusing capacity).

Trial Medication

Patients were randomly allocated to receive either the trial medication, theophylline, or matching placebo. One patient already receiving theophylline had a two-week washout period without treatment. Thereafter, they took 80 mg theophylline or placebo nightly at 10 PM (for the first week of treatment, the dose of theophylline was 200 mg to reduce the likelihood of side effects). Treatment was continued for four weeks, and the patients then underwent a sleep study before crossing over to the other treatment arm. The trial was double blind in nature.

Sleep studies

Overnight sleep studies were performed at the end of each treatment arm using standard polysomnographic techniques, and staged in 30-s epochs by a single, blinded, observer. Respiration was measured by a respiratory inductance plethysmograph (RIP) which was calibrated using the isovolume technique. When calibrated against a spirometer, this device has been shown by many investigators to provide a relatively accurate means of noninvasively measuring respiration, and thus, is well suited to studying respiration during sleep. The device can also distinguish

*From the Department of Respiratory Medicine and the Respiratory Sleep Laboratory, University College, and St. Vincent's Hospital, Dublin, Ireland. Manuscript received April 3; revision accepted July 9. Reprint requests: Dr. McNicholas, St. Vincent's Hospital, Dublin 4, Ireland

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central from obstructive apneas, by showing the presence or absence respectively of equal and opposite ribcage and abdominal movement, where an apnea is indicated by a net tidal volume of zero.

In the present study, apnea was defined as the absence of movement in the sum channel of the RIP lasting at least 10 s. Hypopnea was defined as a period of 10 s or more when the tidal volume fell abruptly to less than 50 percent of the average tidal volume during the last epoch of stable respiration, associated with a drop in \( \text{SaO}_2 \) of at least 4 percent from baseline. The termination of these hypopneas was usually associated with an EEG arousal. The above variables were recorded continuously on a polygraph recorder. Oxygen saturation was also recorded continuously using an ear oximeter. Significant oxygen desaturation was taken as greater than 4 percent. *

Serum theophylline levels were taken at 10 PM (prior to taking the trial medication) and at 8 AM during the sleep study nights, and a full blood count was also taken at the end of each treatment limb.

The data were analyzed using the nonparametric Wilcoxon signed rank test. Simple regression analysis was used to correlate quantitative variables. A p value of less than 0.05 was regarded as significant.

**Results**

Nine patients completed the trial, and the anthropometric and spirometric data for these patients are presented in Table 1. They were all above ideal body weight for height, and two were morbidly obese. They had established OSA of varying severity prior to entry into the study, with an A + H index ranging from 25 to 100. Some of the patients also had mixed and a small number of central apneas, but all had predominantly obstructive disease. All had excessive daytime sleepiness of varying severity.

Serum theophylline levels taken the morning after the sleep study (10 h after the last dose) were all greater than 8 \( \mu \)g/ml in the active phase of the trial, with a mean morning theophylline level of 14.3 (1.6) \( \mu \)g/ml (mean [SEM]).

The effects of theophylline on disordered breathing during sleep are shown in Table 2. The total number of A and H decreased significantly on theophylline (p = 0.01) but increased wakefulness during sleep while on theophylline resulted in the A + H index (apneas and hypopneas per hour of sleep) not being significantly reduced, although there was a trend towards reduction (p = 0.14). Obstructive A and H however were markedly reduced with theophylline (p < 0.001), and this reduction remained significant (p < 0.05) when the data were adjusted for differences in sleep quality (Fig 1). There was no change in the numbers of mixed or central events, but these numbers were relatively small. There was a greater decrease in the number of apneas rather than hypopneas, suggesting that theophylline may convert the former to the latter. There was no change in the mean A + H duration, and there was no selective effect of theophylline on REM or nonREM-related apneas or hypopneas.

The effects of theophylline on sleep architecture are shown in Table 3. Sleep tended to be more disturbed, with a shorter sleep period time, increased wakefulness, and reduced stage 2 sleep with theophylline as compared to placebo, although the per-

### Table 1 — Anthropometric and Spirometric Data of Trial Patients*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SEM)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>48 (3.3)</td>
<td>35-64</td>
</tr>
<tr>
<td>Weight, % ideal</td>
<td>145 (12)</td>
<td>105-205</td>
</tr>
<tr>
<td>FEV1</td>
<td>84 (7.1)</td>
<td>46-114</td>
</tr>
<tr>
<td>FVC</td>
<td>90 (5.1)</td>
<td>70-115</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>77 (2.0)</td>
<td>66-84</td>
</tr>
</tbody>
</table>

*Spirometric data are presented as percentage of normal predicted values for age and height.

### Table 2 — Effects of Theophylline on Respiratory Events During Sleep

<table>
<thead>
<tr>
<th>Variable</th>
<th>Theophylline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. A + H</td>
<td>253 (72)</td>
<td>368 (60)†</td>
</tr>
<tr>
<td>A + H index</td>
<td>51 (10)</td>
<td>59 (8.9)</td>
</tr>
<tr>
<td>Total no. obstructive A + H</td>
<td>220 (59)</td>
<td>330 (63)‡</td>
</tr>
<tr>
<td>Total no. central A + H</td>
<td>23 (14)</td>
<td>30 (14)</td>
</tr>
<tr>
<td>Total no mixed A + H</td>
<td>40 (15)</td>
<td>37 (16)</td>
</tr>
<tr>
<td>Obstructive A + H index</td>
<td>40 (9)</td>
<td>48 (8.7)*</td>
</tr>
<tr>
<td>Central A + H index</td>
<td>3.8 (2.3)</td>
<td>4.1 (1.7)</td>
</tr>
<tr>
<td>Mixed A + H index</td>
<td>7.4 (3.1)</td>
<td>6.0 (2.7)</td>
</tr>
<tr>
<td>Mean A + H duration, s</td>
<td>22 (1.3)</td>
<td>22 (1.7)</td>
</tr>
</tbody>
</table>

*p < 0.05.
†p < 0.01.
‡p < 0.001.

**Figure 1.** Frequency per hour of sleep for obstructive apneas and hypopneas in each individual patient on placebo and theophylline phases of trial (see text for details).
percentage of REM sleep was unchanged. Only two patients had any slow wave sleep on either night. There was no significant correlation, however, between those patients who had the highest percentage of wake time during sleep with theophylline and those who had the greatest improvement in A + H index.

Mean nocturnal SaO₂ was unchanged with theophylline (Table 4), but the number of falls in SaO₂ of greater than 4 percent from baseline was significantly less with theophylline as compared to placebo (p = 0.02).

Three patients who completed the trial had mild to moderate COPD, but were not receiving any treatment, and none had a significant improvement in FEV₁ after salbutamol inhalation. Two of the COPD patients and one other had hypertension, but only one was taking medication for this (a thiazide diuretic). There was no evidence of a preferential beneficial effect of theophylline on sleep apnea in those patients with coexisting COPD. None of the patients had any other significant illnesses.

Three of the initial 12 patients enrolled in the study failed to complete the trial. One patient was withdrawn because of inability to tolerate the placebo phase of the trial. He had moderately severe OSA and COPD and had previously been receiving theophylline for his OSA. He suffered greatly increased daytime sleepiness, dyspnea, and general malaise while receiving placebo, which improved markedly when he resumed theophylline therapy. Another patient, who also had coexistent COPD, suffered intercurrent pneumonia while taking the active phase, and the third patient was unable to tolerate the full dose of theophylline because of nausea and palpitations.

Side effects complained of during the theophylline phase of the trial included nausea (five patients), dyspepsia (two), headaches (two), depression (one), and a feeling of being hungover (three). However, these symptoms tended to lessen with time while receiving treatment, and only one patient was unable to tolerate the full dose of theophylline sufficient to require withdrawal from the trial.

**DISCUSSION**

The main finding of this study was that theophylline significantly reduced the number of apneas and hypopneas during sleep with obstructive apneas being preferentially reduced. When these data are corrected for the deterioration in sleep quality while receiving theophylline, the frequency of obstructive apneas and hypopneas remains significantly lower with theophylline than placebo. These findings differ from those of Espinoza and colleagues,¹ who in a placebo-controlled trial of a single overnight infusion of aminophylline, demonstrated a significant reduction in the number of central but not obstructive events during sleep. They postulate that this finding may be due to the central respiratory stimulant effects of theophylline. This difference in findings from our study may in part be related to the relative numbers of these events; all our patients had predominantly obstructive or mixed apneas, with very few purely central events. Another possible explanation is that long-term oral treatment with theophylline may have different effects than acutely administered intravenous aminophylline treatment.

Other reports on the efficacy of theophylline therapy in OSA have given conflicting results, but all have suffered from a number of deficiencies. Peter and colleagues⁷ reported a significant reduction in sleep apneas in a placebo-controlled trial of long-acting oral theophylline. However, no figures are given to support this conclusion, and the nature of the sleep apnea is not specified. Mayer and co-workers⁸ also reported a significant reduction in sleep apnea with theophylline, but again, the nature of the sleep apnea is not specified, and the study was not placebo-controlled. Guilleminault and Hayes⁹ found no change in either severity of OSA or quality of sleep with theophylline therapy, but this trial was neither placebo-controlled nor double-blinded, and serum levels of theophylline were not measured.

Potential mechanisms by which theophylline could improve OSA remain to be established, but may include both central and local upper airway factors. While the recognized effects of theophylline on periodic breathing¹⁰,¹¹ might appear to have therapeutic

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**Table 3—Quality of Sleep**

<table>
<thead>
<tr>
<th></th>
<th>Theophylline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep period time*</td>
<td>417 (20)</td>
<td>448 (16)†</td>
</tr>
<tr>
<td>% Wake time</td>
<td>22 (5.5)</td>
<td>9 (1.6)†</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>333 (33)</td>
<td>409 (19)‡</td>
</tr>
<tr>
<td>% REM sleep</td>
<td>11 (1.7)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>EEG arousals/h sleep</td>
<td>16 (4.8)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Sleep stage changes/h sleep</td>
<td>21 (3)</td>
<td>15 (2)†</td>
</tr>
</tbody>
</table>

*Sleep period time, time in minutes from first onset of sleep to final awakening in AM. Total sleep time, SPT less intervening periods of wakefulness. Wake time and REM sleep are presented as % SPT.
†p<0.05.
‡p<0.01.

**Table 4—Effect of Theophylline on Nocturnal Oxygen Saturation**

<table>
<thead>
<tr>
<th></th>
<th>Theophylline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SaO₂</td>
<td>89 (2.4)</td>
<td>88 (2)</td>
</tr>
<tr>
<td>Lowest SaO₂</td>
<td>64 (6.6)</td>
<td>65 (6.1)</td>
</tr>
<tr>
<td>REM SaO₂*</td>
<td>84 (4.7)</td>
<td>83 (3.9)</td>
</tr>
<tr>
<td>Desats &gt;4%</td>
<td>272 (78)</td>
<td>351 (79)†</td>
</tr>
</tbody>
</table>

*REM SaO₂ mean SaO₂ during REM sleep. Desats, >4% = number of falls in SaO₂ of >4% from baseline.
†p<0.05.
implications only for central sleep apnea, Onal et al have shown that OSA has some similarities with periodic breathing, and thus, may be influenced by an agent such as theophylline. Theophylline also has a stimulant effect on central respiratory drive, which may stimulate upper airway muscles in addition to the diaphragm. Since theophylline has also been reported to increase skeletal muscle in addition to diaphragmatic contractility, the drug may also have a direct stimulant effect on the upper airway muscles.

Based on our findings, we can postulate that theophylline may have a preferential augmenting effect on upper airway muscle contraction, similar to that reported with protriptyline, since augmentation of diaphragmatic contraction without simultaneous augmentation of the contraction of upper airway dilating muscles would likely predispose to upper airway occlusion. Such occlusion has previously been demonstrated in patients with central alveolar hypoventilation treated with an electrophrenic pacemaker. Such patients may develop OSA under these conditions because of unopposed contraction of the diaphragm during electrical stimulation. To date, however, there are no reports on the effect of theophylline on upper airway muscle contractility. The fact that medroxyprogesterone acetate, however, a recognized central respiratory stimulant, has been shown to be helpful in central but not OSA, supports the notion that theophylline's effects in OSA are not simply central.

We demonstrated a significant deterioration in sleep quality with theophylline therapy, similar to previous reports. This finding represents a significant drawback to theophylline therapy in OSA. However, we found that this effect varied widely, with the percentage of wake time during sleep while receiving theophylline varying from 4 to 55 percent. It is noteworthy that the percentage of REM sleep was unchanged, although it was low on both study nights. The possibility has been raised that long-term theophylline treatment may, by increasing sleep fragmentation, actually worsen OSA, as it has been shown that arousal responses are reduced following sleep deprivation and fragmentation, and apnea length increases. Our findings do not support this possibility, since only one patient had a deterioration in his A + H index while receiving theophylline, and this difference was small. The mean A + H duration and the arousal frequency were also unchanged.

In the majority of OSA patients with mild to moderate disease, who may also have relatively mild daytime symptoms, pharmaceutical therapy, if effective, is likely to remain an important therapeutic modality, since other more invasive forms of therapy, such as nasal CPAP, may be less appealing to the patient. Pharmaceutical therapy may also have a role as an adjunct to other forms of treatment such as weight reduction. Unfortunately, protriptyline, which is the most commonly used medication at the present time, has inconsistent benefits, and has not been shown to significantly improve the apnea index, although it does appear to reduce daytime sleepiness and improve nocturnal oxygenation. These benefits differ from our findings with theophylline, where apnea frequency but not daytime sleepiness or nighttime oxygen saturation improved. It is possible, therefore, that the two agents given together may have an additive beneficial effect, thus possibly allowing a lower dosage of each agent, with consequent lesser risk of side effects. The dosage of theophylline used in the present study was that recommended for optimum bronchodilator effect. The possibility exists that a lower dose might have had similar beneficial effects on obstructive sleep apnea, but with a lesser degree of sleep disruption. This possibility remains to be proven.

It was not possible to predict which patients would have the greatest benefit from theophylline, and those with the greatest improvement in the A + H index were not necessarily those with the greatest sleep disruption, as these variables were not significantly correlated. Furthermore, we were unable to demonstrate any preferential benefit of theophylline in patients with coexisting OSA and COPD. However, our patient population was not specifically chosen to assess this possibility in that only three patients had coexisting COPD. Further studies will be required to address this question.

In conclusion, we feel that theophylline has a role to play in the treatment of patients with OSA where nasal CPAP or surgery is either not indicated or unacceptable to the patient. Unfortunately, there is, as yet, no reliable method of predicting which patients with OSA are likely to benefit most from theophylline, although we feel, based on our data, that it may be those with mild disease. The treatment of choice remains nasal CPAP in more severe cases of OSA.

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tive sleep apnea do not change during medroxyprogesterone acetate therapy. Chest 1989; 96:262-66
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