Treatment of Nocturnal Asthma with Pulsed-Release Albuterol*  

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The treatment of nocturnal asthma remains a challenge. We investigated the use of a pulsed-release albuterol in ten patients with nocturnal symptoms of asthma. In a randomized, double-blind, placebo-controlled, crossover designed study, we tested the use of 8 mg of pulsed-release albuterol sulfate (Proventil Reptabs) vs placebo. The pulsed-release albuterol significantly blunted the overnight drop in FEV₁, improved peak flow readings in the morning, and decreased subjective awakenings from sleep. We conclude that pulsed-release albuterol is an effective therapeutic option in patients with nocturnal asthma.

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The nocturnal worsening of asthma is a common phenomenon that remains a therapeutic challenge. A commonly used approach has been the evening use of sustained-release theophylline. This regimen results in maximal theophylline concentrations during the nocturnal period of increased bronchoconstriction and is therefore helpful in many asthmatic patients; however, the use of theophylline has well-known drawbacks. Therapeutic serum levels must be established, and many drugs given concomitantly may affect theophylline metabolism. Side effects of tremor, jitteriness, and nausea may occur at therapeutic serum levels. Theophylline has also been shown to adversely affect sleep quality.

Other therapies have also been used with variable success. An alternative approach has been the evening use of oral β-adrenergic agents. Sustained-release preparations of albuterol and terbutaline have been demonstrated to improve nocturnal asthma in many patients. The unavailability of such sustained-release preparations in this country has previously forced physicians to use rapidly-acting formulations (durations of action from 5 to 8 h) for this purpose. Although this has been well tolerated by most patients, the brief duration of action has left many patients without effective bronchodilation during the critical early morning hours.

Albuterol sulfate has recently become available in this country in a pulsed-release formulation (Proventil Reptabs). The sequential "pulsed" release of this formulation is designed to extend the duration of action up to 12 h. Such an extended duration of action would be expected to better control the nocturnal worsening of asthma. Therefore, we evaluated the use of a single bedtime dose of pulsed-release albuterol sulfate (Proventil Reptabs) to control symptoms and improve airflow in asthmatic subjects with nocturnal worsening. We also sought to determine the effects of pulsed-release albuterol on sleep architecture in these patients.

MATERIALS AND METHODS

Subjects

Ten adult patients (ages, 18 to 65 years) with a documented history of asthma per the ATS definition were recruited from the outpatient population. They were not receiving steroids, cromolyn, or oral β-adrenergic agonist therapy, nor had they used such medication during the previous three months. These patients therefore had mild to moderate disease and were treated with sustained-release theophylline and inhaled β-adrenergic agonists only. Nevertheless, the patients reported nocturnal or early morning symptoms of bronchoconstriction and demonstrated decreases in either peak expiratory flow rate (PEFR) or FEV₁ of at least 20 percent in the morning compared to bedtime.

Subjects were excluded from the study if they had a history of significant heart disease; other pulmonary disease, including chronic airflow limitation (chronic bronchitis; emphysema; bronchiectasis); an acute upper respiratory infection or sinusitis; current or recent (less than three months) cigarette usage; clinical instability in the opinion of the physician-investigator; pregnancy or delivery within one year; or nocturnal or irregular work shifts.

Experimental Protocol

Serum theophylline levels were obtained at 8 am prior to entry into the study. If a level was less than 10 μg/dl, theophylline dosage was adjusted at three-day intervals to attain a level in the range of 10 μg/dl to 20 μg/dl. Each subject was also maintained on a stable regimen of inhaled albuterol four times daily unless additional doses were needed acutely for increasing asthmatic symptoms. All patients also abstained from caffeine-containing beverages for the duration of the study. At entry into the protocol, each subject was given a medication (either placebo or 8 mg of pulsed-release albuterol sulfate [Proventil Reptabs] assigned randomly and in a double-blind fashion) to be taken once daily, at 10 pm, for a total of ten days. During this time, subjects maintained a symptom log and recorded at least thrice daily PEFRs. On the tenth study day, each subject underwent a nocturnal sleep study and was monitored using all techniques described in the section, "Study Techniques."

Following the initial sleep study, each subject was crossed over to the alternative medication in the protocol. After an additional ten
days of maintaining a symptom log and monitoring thrice daily PEFRs, each subject again underwent a sleep study as outlined subsequently.

**Study Techniques**

Sleep studies were routinely started by 11 PM and terminated at 6 AM. During each sleep study, parameters 1 to 4 in the following list were monitored and recorded:

1. **Sleep Staging.** Sleep was staged per the standard criteria of Rechtschaffen and Kales, using continuous recordings of electrooculographic, electromyographic, and electroencephalographic activities. These activities were recorded using a 16-channel chart recorder (Grass Instruments model 78D).

2. **Oxygen Saturation.** All subjects were monitored using an ear oximeter (BIOX III). The \( \text{SaO}_2 \) was continually recorded throughout each study using the chart recorder.

3. **Cardiac Rate and Rhythm.** Cardiac activity was recorded continually throughout each study from a standard chest electrode using the chart recorder.

4. **Spirometry.** Spirometry (Collins Eagle II) was performed at "bedtime," at the time of awakening in the morning, and at any nocturnal awakening due to symptoms of increasing bronchoconstriction. Each reported measurement consisted of the "best" (highest FEV\(_1\)) of three consecutive efforts.

5. **Symptom Scoring.** During the study, each subject was also required to maintain a daily symptom log. These symptoms included the following: general daytime asthma symptoms; nighttime wheezing, coughing, and tremor; sleep quality; and nocturnal awakenings with asthma. The symptoms were scored as follows: 0 = no symptom or occurrence; 1 = mild or occasional; and 2 = severe or frequent; while sleep quality was scored as 0 = good, 1 = slightly disturbed, and 2 = frequent awakenings. This log included PEFR measurements made before and after the bronchodilator at least three times daily: upon morning awakening, midafternoon, at bedtime, and at any nocturnal awakening associated with symptoms of bronchoconstriction and necessitating treatment. The PEFRs were measured with a peak flowmeter (mini-Wright).

**Data Analysis**

Total sleep time, sleep efficiency, sleep latency, sleep stage distribution, total number of arousals (awakenings lasting less than 15 s), total number of awakenings (awakenings lasting more than 15 s), total number of sleep stage changes, mean oxygen saturation, and mean heart rate were calculated from each nocturnal sleep study. These data were analyzed by paired t-tests. Variables that were measured daily were summarized by averaging the measurements for the last three days in each period. This effectively emphasized the longer term effect of treatment and reduced the possibility of a carryover effect between periods. All other variables were measured at the end of each treatment period. The variables of cough and tremor were not analyzed, since almost all of their values were zero.

All variables (and summary variables) were analyzed using the methods described in Jones and Kenward. In particular, the model was a repeated-measures analysis of variance which included terms for period, carryover, and treatment effects. This allowed for separate tests of significance for systematic differences over time, different residual treatment effects between the two treatment sequences, and differences between the placebo and albuterol treatments, respectively.

**Results**

Eight men and two women were recruited into the study. The mean age of the ten subjects was 31.4 ± 2.4 years. The mean AM theophylline level was 12.9 µg/dl ± 0.8 µg/dl. All subjects completed the protocol. The results of spirometry are shown in Table 1. When using placebo, subjects experienced a significant overnight drop in FEV\(_1\); this effect was blocked by using pulsed-release albuterol sulfate (p<0.05). The change in morning FEV\(_1\) and FVC compared to

**Table 1—Spirometric Data**

<table>
<thead>
<tr>
<th>Measurement, L</th>
<th>Albuterol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedtime FEV(_1)</td>
<td>2.62 ± 0.32</td>
<td>2.73 ± 0.26</td>
</tr>
<tr>
<td>Morning FEV(_1)</td>
<td>2.31 ± 0.23</td>
<td>1.84 ± 0.23†</td>
</tr>
<tr>
<td>Bedtime FVC</td>
<td>3.62 ± 0.36</td>
<td>3.85 ± 0.19</td>
</tr>
<tr>
<td>Morning FVC</td>
<td>3.33 ± 0.23</td>
<td>2.99 ± 0.27†</td>
</tr>
<tr>
<td>Δ Bedtime FEV(_1) – morning FEV(_1)</td>
<td>0.31 ± 0.17</td>
<td>0.89 ± 0.18‡</td>
</tr>
<tr>
<td>Δ Bedtime FVC – morning FVC</td>
<td>0.29</td>
<td>0.87‡</td>
</tr>
</tbody>
</table>

*Data are means ± SE.
†p<0.005 for morning vs bedtime FEV\(_1\), or FVC.
‡p<0.05 for placebo vs albuterol.

![Figure 1. Overnight drop in FEV\(_1\) (in liters) in ten subjects while using placebo and pulsed-release albuterol sulfate (Proventil Repetabs). Mean FEV\(_1\) change is represented by dashed line.](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21652/ on 04/08/2017)
The evening values was also moderated by the pulsed-release albuterol (p<0.005 for both FEV₁ and FVC). Figure 1 demonstrates that the overnight drop in FEV₁ was significantly lower when the subjects used pulsed-release albuterol sulfate, when compared to placebo.

Results from the patients' diaries are shown in Tables 2 and 3. Subjective improvement was noted in nighttime wheezing when taking the pulsed-release albuterol (p<0.05); however, most notably, the subjects reported awakening from sleep less frequently during the study period when using the pulsed-release albuterol. Other symptoms were unchanged by the drug, although there was a tendency towards fewer nighttime metered-dose inhaler puffs (p = 0.10). Peak flow recordings (Table 3) demonstrated significant improvement in peak flow readings taken before and after the bronchodilator in the morning, and before the bronchodilator in the evening when taking the pulsed-release albuterol.

The sleep study results are depicted in Table 4. No significant differences were noted in any of the sleep characteristics between drug and placebo. Not surprisingly, heart rate was significantly higher with pulsed-release albuterol when compared to placebo (73 beats per minute with drug; 66 beats per minute with placebo).

**DISCUSSION**

Nocturnal asthma remains a common therapeutic challenge. Up to 75 percent of the patients with asthma have symptoms of nocturnal awakenings or decreased airflow in the morning, as compared to the evening. This pattern of nocturnal bronchoconstriction contributes to the disruption of sleep in affected patients.

An increased evening dose of theophylline has been suggested as treatment for nocturnal asthma, and some of these preparations have been demonstrated to improve morning spirometry in mild asthma. However, this therapy may not be the treatment of choice in all patients. Serum levels must be checked periodically to assure proper dosing of this drug. Once daily dosing may not be adequate to control daytime symptoms in more severe asthma. Interaction with other prescribed medications may occur and may result in toxic levels of theophylline. Many patients are unable to tolerate theophylline products, even if maintained within therapeutic levels, due to tremulousness or GI upset. Finally, theophylline has been shown to adversely affect sleep quality.

A number of other drugs used in the treatment of asthma have been studied for use specifically in nocturnal asthma. Several authors have investigated the use of ipratropium bromide. Studies by Cox et al., Hughes, and Catterall et al. noted a significant but small improvement in overnight reductions in peak flow when ipratropium was used by asthmatic subjects at bedtime. Coe and Barnes were able to demonstrate a similar improvement in PEFR in nine of 18 subjects using oxitropium at bedtime. Anticholinergics therefore seem to be somewhat effective in improving nocturnal asthma in some patients.

Horn et al. studied inhaled albuterol (salbutamol) and beclomethasone in patients with nocturnal asthma. These investigators found that eight of 14 subjects showed improvement in overnight reductions in PEFR with the inhaled β-adrenergic agonist alone, with further improvement occurring after addition of the inhaled steroid; however, spirometry, symptoms, and sleep parameters were not measured.
Ketotifen, a newer antihistamine, has been shown to improve sleep quality in subjects with nocturnal asthma, but not to affect nocturnal SaO₂ or morning FEV₁.¹⁷

Morgan et al⁵ⁿ investigated the use of nebulized cromolyn sodium (sodium cromoglycate) in patients with nocturnal asthma. These investigators⁵ⁿ found that although the lowest nocturnal oxygen saturation was minimally improved in these patients (SaO₂ dropped a maximum of 6 percent with the drug and 8 percent with placebo), morning FEV₁ was unchanged by this medication.

The timing of doses of oral corticosteroids was evaluated by Reinberg et al.¹⁹ Their data indicated that morning dipping was improved but not eliminated when steroids were given at 8 AM and 3 PM. Soutar et al²⁰ infused hydrocortisone into subjects with nocturnal asthma. Although these investigators²⁰ were able to prevent a nocturnal fall in plasma corticosteroid levels, they were unable to affect the overnight decrease in PEFRs in five of their six subjects.

Previous studies⁴ⁿ⁻⁶ⁿ of nocturnal asthma demonstrated the efficacy of a 16-mg bedtime dose of a long-acting oral β-adrenergic agonist preparation, with few side effects. When a slow-release formulation of albuterol (Ventolin Spanperts) was compared to aminophylline,¹⁶ both drugs were found to significantly improve morning peak flows, while albuterol also improved the evening peak flow. Gastrointestinal intolerance was a problem for 23 percent of the subjects using aminophylline and for 19 percent of those using albuterol. Fairfax et al²⁰ also compared albuterol (Ventolin Spanperts) to nighttime aminophylline and noted significantly higher mean peak expiratory flow rates on waking with both drugs; however, this albuterol preparation is unavailable in this country. The introduction of an oral pulsed-release formulation of albuterol sulfate (Proventil Repetabs) to the United States has provided the alternative of a long-acting albuterol preparation for the treatment of nocturnal asthma. The release mechanism of this pulsed-release formulation essentially works as a tablet within a tablet (Fig 2). An outer color coat surrounds a subcoat which contains 2 mg of albuterol. These two coats rapidly dissolve within the stomach and immediately release 2 mg of the drug. Beneath the drug's subcoat is a "barrier coat" which is not soluble in the acid pH of the stomach. When the remaining portion of the tablet enters the more basic environment of the small intestine (after about 6 h), the barrier coat dissolves, exposing the "core tablet," which contains the remaining 2 mg of albuterol. This core tablet then dissolves, releasing the remainder of the albuterol.

Our study was designed to determine if a single bedtime dose of 8 mg (two tablets) of pulsed-release albuterol sulfate (Proventil Repetabs) is effective in improving airflow limitation and sleep quality in nocturnal asthma, and to evaluate any side effects produced by 8 mg of this drug. Our data indicate that an 8-mg dose is very effective in improving the overnight increase in airflow limitation, as measured by the overnight fall in FEV₁ and PEFR. The pulsed-release albuterol also improved the number of nighttime awakenings due to asthma noted by the subjects. The pulsed-release formulation did not adversely affect sleep quality, and no increase in side effects was noted. The increase in heart rate of 7 beats per minute noted during the sleep studies is, we believe, unlikely to be clinically significant or disturbing to patients. We conclude that a single bedtime dose of 8 mg of pulsed-release albuterol sulfate (Proventil Repetabs) is effective in improving symptoms and airflow impairment in patients with nocturnal asthma, and should be considered a therapeutic option in these patients.

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