

A double-blind comparison of inhaled budesonide, long-acting theophylline, and their combination in treatment of nocturnal asthma

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In 61 patients with nocturnal asthma, the effects of budesonide, an inhaled steroid (Pulmicort®; 200 µg twice daily), long-acting theophylline (Theodur®; 200 mg twice daily), and their combination were compared. After a 2-week placebo run-in period, the patients were entered into double-blind, crossover periods of 3 weeks. Patients were allowed to use inhaled β_2 -agonists as required throughout the study. Morning and evening peak expiratory flow rate (PEFR) (percentage of predicted normal $\pm$ SEM) was significantly higher during the budesonide (morning $77 \pm 1\%$; evening $80 \pm 1\%$) and combination therapy (morning $79 \pm 1\%$; evening $81 \pm 1\%$) than the theophylline treatment (morning $74 \pm 1\%$; evening $76 \pm 1\%$; $P < 0.01$, respectively). Significantly fewer sleep disturbances and fewer nighttime inhalations of β_2 -agonists were required during budesonide and combination therapy than theophylline treatment. No statistically significant differences were seen between combined therapy and budesonide alone. Budesonide, an inhaled steroid, was significantly better than the bronchodilator, theophylline, in controlling nocturnal asthma, but no additional improvement in efficacy was seen when the drugs were used in combination.

P. Youngchaiyud¹, C. Permpikul¹,
T. Suthamsmai¹, E. Wong²

¹ Siriraj Hospital, Mahidol University, Bangkok, Thailand; ² Astra East Asia Regional Office, Singapore

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Ellick Wong, PhD
5 Shenton Way, #31-01
UIC Building
Singapore 0106

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Nocturnal asthma occurs when symptoms and airway function worsen overnight or in the early morning. Earlier reports have shown that over 70% of asthmatic patients are woken at least once a week (9, 18). Treatment of nocturnal asthma is particularly important because many asthmatic deaths occur at night (5), and sleep disturbance impairs daytime performance. Nocturnal asthma has been associated with an exaggeration of the normal circadian rhythm in airway caliber, with the result that the airways become hyperresponsive at this time (1). It has previously been shown that inhaled steroids improve bronchial hyperresponsiveness (13, 14) and are of benefit in the treatment of asthma (2, 12). Previously, additional benefits have been shown in the treatment of asthma when inhaled steroids and β_2 -agonists were used in combination (8, 9, 12, 16, 19).

The purpose of this double-blind, crossover study was to compare the effects of budesonide (Pulmi-

cort®), an inhaled steroid, long-acting oral theophylline (Theodur®), and the combination of these drugs in patients with nocturnal asthma.

Material and methods

Patients

Adult patients of either sex attending the outpatient clinic at Siriraj Hospital, Bangkok, Thailand, were selected for the study. The inclusion criteria were mild to moderate asthma, with at least 15% reversibility in peak expiratory flow rate (PEFR) after β_2 -agonist inhalation, a history of nocturnal or early morning asthma (this was defined as being woken up by symptoms of asthma at least three times in any week during the run-in period), or having a night to morning reduction in PEFR of at least 20% on three occasions in any week during the run-in period. Patients were excluded from the study if they had re-

ceived steroids in the previous 4 weeks, if they had significant bronchopulmonary disease other than asthma, if they had any other significant disease that might interfere with the study or place them at risk, or if a respiratory tract infection had been present within the last 2 weeks. Also excluded were patients who had poor inhalation, were uncompliant during run-in, or were pregnant or intended to become pregnant, and those who had previously been included in this study. Informed consent was obtained from all patients.

Experimental design

This was a randomized, double-blind, double-dummy, crossover study. All patients entered a 2-week run-in period on placebo, which was followed by randomized treatment with budesonide alone, theophylline alone, and the combination. The order of treatment followed a 3×3 Latin square design, comprising four treatment periods of 3 weeks each, with six possible treatment sequences. The theophylline treatment was given for two consecutive 3-week periods, the first 3 weeks serving as a washout period for a possible carry-over effect of budesonide should it be allocated before theophylline. Data from this period were not included in the efficacy analysis. The dose regimens were budesonide (Pulmicort) 200 μ g twice daily, given via a spacer device (Nebuhaler[®]), and theophylline (Theodur) 200 mg twice daily, taken at 0800 and 2000 daily. All tablets and inhalers, with matching placebos, were packed and labeled by Astra, Sweden.

During the run-in period, inhaled β_2 -agonists were the principal medication. Disodium cromoglycate and ketotifen were allowed if dosages were kept constant, but steroids and xanthine derivatives were not permitted in the study. Inhaled β_2 -agonists were used, as required, as additional medication throughout the study; the number of inhalations used was recorded on diary cards.

Measurements

Clinic visits were scheduled in the early morning before intake of trial drugs, and patients were asked to avoid using inhaled β_2 -agonists 3–4 h before the visit. During each clinic visit, after run-in and every third week of treatment, spirometry measurements (PEFR, forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), forced expiratory flow (FEF) 25–75%) were done, and the percentages of predicted normal values for PEFR and FEV₁ were calculated from the predicted normal values for Asians (7). Symptoms and signs of asthma were also recorded at each clinic visit; rhonchi, wheezing, and dyspnea were scored on a scale of 0–3 (0 = absent,

1 = mild, 2 = moderate, 3 = severe). Chest oppression was scored as 0 (absent) or 1 (present). Adverse events were elicited by an open question at each visit. At the end of the study, patients were asked which treatment period they preferred. All tests were done in the same laboratory by the same technician, and the patients were seen at each visit by the same investigator.

Patients also completed diary cards throughout the study. Morning and evening PEFR were measured before taking the medication with Wright's mini-peak-flow meter, the best of three blows being recorded. Daytime (0600–2000) and nighttime (2000–0600) asthma symptoms (rated as mild, moderate, or severe), sleep disturbances (0 = no awakenings, 1 = awake once, 2 = awake 2–3 times, 3 = awake 4–6 times), and use of β_2 -agonist inhalers (number of puffs) were also recorded.

Statistical analysis

For measured variables, parametric models for fixed effects ANOVA were used. If a significant difference was found between treatments in the ANOVA, pairwise comparisons of the adjusted means of treatments by *t*-tests followed. As a test for carry-over effects, a preliminary analysis of the efficacy variables was done in which this effect was taken into account in the model. If no significant carry-over effects were found, they were not included in the final ANOVA model. Scored variables were transformed to ranks, after which the fixed-effects ANOVA model was applied to the rank-transformed data (6). Diary card variables were analyzed with the means calculated for the last 10 days of each treatment period. A value of $P < 0.05$ was considered to be statistically significant.

Results

Patients

A total of 70 patients (26 male, 44 female) with mean age of 33 years (range: 16–66 years) and body weight of 56 kg (range: 37–84 kg) entered the study. Five of the patients were smokers.

Nine patients had acute exacerbations during the study and they were therefore excluded from the efficacy analysis. The acute exacerbations occurred during the run-in period (four patients) and during treatment with theophylline alone (four patients) and budesonide alone (one patient). The five patients who developed acute exacerbations during treatment could be considered to be treatment failures because they attended the hospital emergency room and received parenteral adrenaline or aminophylline, and systemic steroids.

Efficacy data

The ANOVA model including the carry-over term showed no significant carry-over effect, and this was discounted in the final analysis.

Diary card data. Base-line values for diary card variables are given in Table 1. Morning and evening PEFR (percentage of predicted normal) during treatment are shown in Fig. 1. Statistically significant differences between treatments were observed for morning ($P < 0.0001$) and evening ($P < 0.0005$) PEFR. The highest PEFR values were seen after the combined therapy, and the lowest values were seen with theophylline alone. Pairwise comparisons of the adjusted means for combination therapy and theophylline were significantly different for morning ($79.2 \pm 0.8\%$ and $74.3 \pm 0.8\%$; $P < 0.0001$) and evening ($80.5 \pm 0.8\%$ and $75.7 \pm 0.8\%$; $P < 0.0001$) PEFR, as were the adjusted means for budesonide and theophylline in the morning ($77.4 \pm 0.8\%$ and $74.3 \pm 0.8\%$; $P < 0.01$) and evening ($79.6 \pm 0.8\%$ and $75.7 \pm 0.8\%$; $P < 0.005$) PEFR. No statistically significant differences were observed between budesonide and combination therapy for morning and evening PEFR. The overnight change in PEFR calculated from the recorded PEFR values was generally small (budesonide: $1.68 \pm 0.7\%$; theophylline: $0.21 \pm 0.7\%$; combination: $0.45 \pm 0.7\%$); the difference between treatments was not statistically significant.

Table 1. Base-line spirometry values and asthma symptoms and signs

	Clinical data		Diary data	
	Mean	(SEM)	Mean	(SEM)
<i>Spirometry values</i>				
PEFR (l/min)	337.5	(12.44)		
FEV ₁ (l)	1.75	(0.08)		
FVC (l)	2.32	(0.10)		
FEF 25–75% (l/s)	1.57	(0.10)		
PEFR (% of predicted normal)	71.7	(2.21)		
FEV ₁ (% of predicted normal)	67.3	(2.44)		
PEFR morning (l/min)			324.6	(11.90)
PEFR evening (l/min)			332.8	(11.73)
Overnight change in PEFR (%)			0.46	(1.41)
PEFR morning (% of predicted normal)			69.2	(2.24)
PEFR evening (% of predicted normal)			70.9	(2.20)
<i>Symptom and sign scores</i>				
Rhonchi	0.16	(0.06)		
Wheeze	0.16	(0.06)		
Dyspnea	0.18	(0.06)		
Chest oppression	0.11	(0.04)		
Daytime symptoms			1.05	(0.12)
Nighttime symptoms			1.21	(0.11)
No. of β_2 -agonist inhalations during day			2.31	(0.26)
No. of β_2 -agonist inhalations during night			1.85	(0.19)
No. of nights with sleep disturbance in 10 nights			6.60	(0.37)

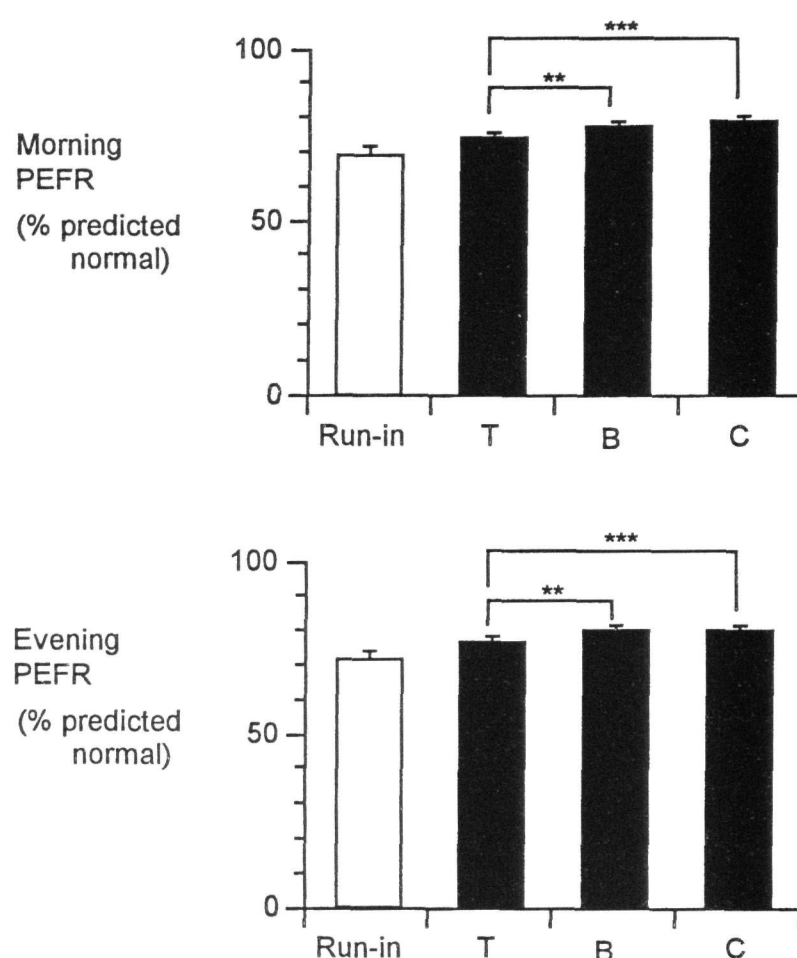


Fig. 1. Mean morning and evening PEFR for each treatment period; run-in, theophylline (T), budesonide (B), and combination (C) therapy. Values are means $\pm$ SEM. *** $P < 0.001$, ** $P < 0.01$.

Symptoms and signs recorded in the diaries during treatment are shown in Fig. 2. Analysis of variance showed significant differences between treatments for daytime symptoms ($P < 0.01$), nighttime symptoms ($P < 0.05$), number of inhalations during the day ($P < 0.0001$), number of inhalations during the night ($P < 0.0001$), and number of nights with sleep disturbances ($P < 0.01$). During the run-in period, all patients experienced some sleep disturbance. The quality of sleep was improved during treatment: 10 patients during the theophylline treatment, 21 patients during budesonide, and 25 patients during the combination therapy had no sleep disturbances. Budesonide and combination therapy had statistically significantly lower scores for all the variables above than theophylline alone. During budesonide treatment, daytime and nighttime symptom scores were lower than those during combination therapy; the differences were not statistically significant. For the other symptoms, the combination therapy had the lowest scores. No statistically significant differences were seen between budesonide and the combination therapy for these symptoms.

Clinic visit data. Base-line values for spirometry measurements and scores for asthma symptoms and signs are given in Table 1.

Analysis of spirometry PEFR showed a significant difference between treatments ($P < 0.05$). The

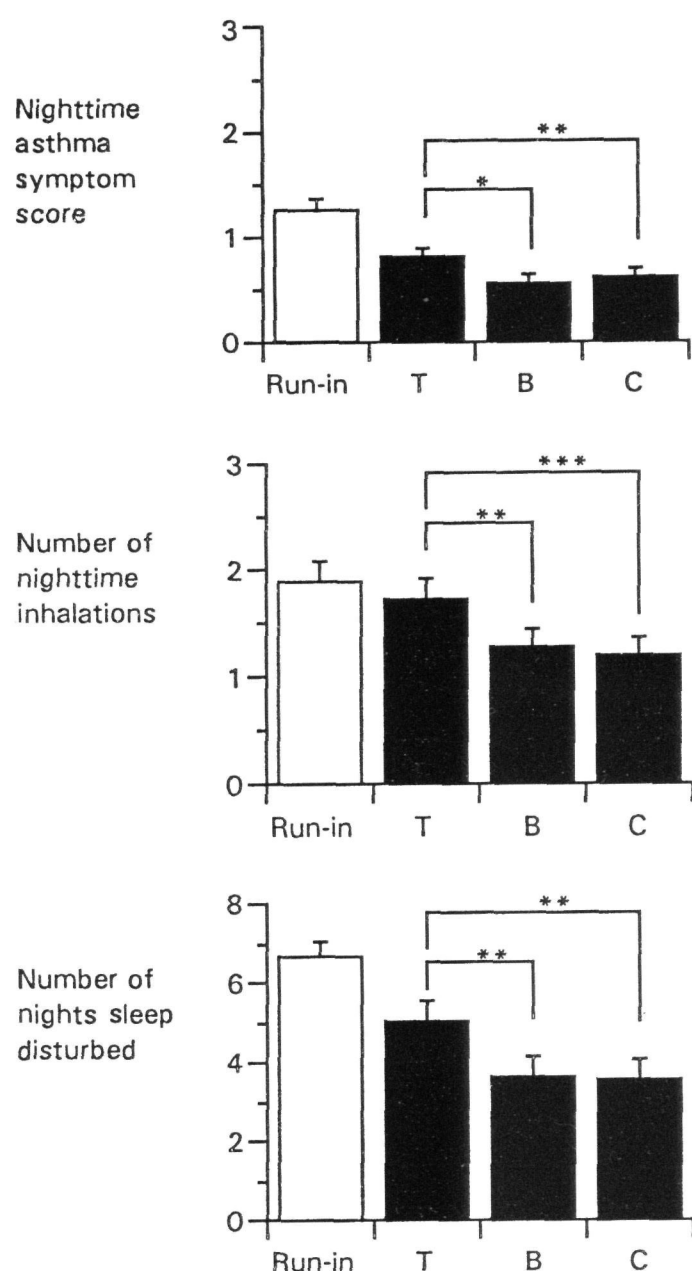


Fig. 2. Nighttime symptom score, number of β_2 -agonist inhalations, and number of nights with sleep disturbances during run-in; theophylline (T), budesonide (B), and combination (C) therapy. Values are means $\pm$ SEM. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$.

highest mean PEFR was seen after combination therapy and the lowest after theophylline alone. Pairwise comparisons of the adjusted means showed that combination therapy had significantly higher values for percentage of predicted normal PEFR than theophylline alone ($84.9 \pm 1.3\%$ and $80.2 \pm 1.3\%$; $P < 0.05$), but no significant difference was seen between budesonide and theophylline for PEFR ($82.0 \pm 1.3\%$ and $80.2 \pm 1.3\%$; NS). No significant difference was seen between budesonide alone and the combination therapy for PEFR.

For the other spirometry measurements, analysis of variance showed statistically significant differences for FEV₁ ($P < 0.01$), FVC ($P < 0.05$), and FEF 25–75% ($P < 0.005$). Pairwise comparisons of the adjusted means showed that theophylline had significantly lower values for percentage of predicted normal FEV₁ than combination therapy ($69.8 \pm 1.3\%$ and $75.6 \pm 1.3\%$; $P < 0.005$), FVC (2.36 ± 0.04 I and 2.50 ± 0.04 I; $P < 0.01$), and FEF

25–75% (1.72 ± 0.05 I/s and 1.97 ± 0.05 I/s; $P < 0.005$). Budesonide alone improved FEV₁ significantly more than theophylline alone ($73.5 \pm 1.3\%$ and $69.8 \pm 1.3\%$; $P < 0.05$). No statistically significant differences for any of these variables were seen between budesonide alone and combination therapy.

Symptoms and signs recorded at the clinic visits are shown in Tables 1 and 2. Symptom scores were highest during theophylline treatment and lowest during combination therapy. A statistically significant difference between treatments was observed for wheeze ($P < 0.05$). Treatment differences for other symptoms were not statistically significant.

Treatment preference

At the last clinic visit, patients were asked which treatment they preferred. Twenty-two patients (36.1%) preferred the combination therapy, 20 (32.8%) preferred budesonide, and 19 (31.1%) preferred theophylline.

Adverse events

Of the 66 patients who were treated with the double-blind study drugs, three reported adverse events during the combination therapy, two during budesonide alone, and 11 during theophylline alone. Adverse events are listed in Table 3.

Discussion

Asthma has been conventionally treated with bronchodilators to give symptom relief. However, the underlying cause of asthma is inflammation of the airways, which results in their being more responsive to stimuli (11). This hyperresponsiveness of the bronchi is further aggravated at night by exaggeration of normal circadian rhythms (1, 4), leading to the worsening of symptoms associated with nocturnal asthma. It is now recommended that inhaled steroids also be used in the treatment of nocturnal asthma (2, 10, 16) because they have been shown to reduce bronchial hyperresponsiveness (13, 14) and decrease nocturnal dip (12).

This study showed that budesonide alone was

Table 2. Clinic visit symptom and sign scores

	Theophylline	Budesonide	Combination	P
Rhronchi	0.10 $\pm$ 0.04	0.07 $\pm$ 0.03	0.05 $\pm$ 0.03	NS
Dyspnea	0.13 $\pm$ 0.04	0.10 $\pm$ 0.04	0.08 $\pm$ 0.04	NS
Wheeze	0.20 $\pm$ 0.06	0.08 $\pm$ 0.04*	0.07 $\pm$ 0.03*	0.033
Chest oppression	0.15 $\pm$ 0.05	0.10 $\pm$ 0.04	0.03 $\pm$ 0.02	NS

Values are means $\pm$ SEM. * $P < 0.05$, as compared with theophylline.

Table 3. Occurrence of adverse events

Treatment	Adverse event	No. of patients reporting events
Theophylline	Headache	2
	Insomnia	3
	Nausea	5
	Tremor	4
	Feeling hungry	1
	Dizziness	2
Budesonide	Tremor	2
	Headache	1
Combination	Nausea	2
	Dizziness	2
	Feeling hungry	1

more effective than theophylline alone in the treatment of nocturnal asthma. This agrees with a previous study in which budesonide was shown to have greater efficacy than theophylline in the treatment of asthma (3). Previously, the efficacy of budesonide has been shown to be improved when used in combination with an oral β_2 -agonist in nocturnal asthma (8) and mild asthma in children (19). In the present study, combination therapy with budesonide and theophylline proved more effective than theophylline alone, but the effect was similar to budesonide alone.

Budesonide and the combination therapy reduced the number of nights that patients were awakened by asthma symptoms; this constitutes an important benefit to the quality of life of asthma patients. Theophylline treatment was significantly less effective in this respect. However, the patients did not perceive this difference; they were evenly divided as to the treatment they preferred. The occurrence of adverse events also did not seem to have influenced the patients' preference in treatment.

The dose of theophylline in this study was selected on the basis of previous experience of the investigators that this dose provided adequate blood levels of theophylline and was clinically effective in most patients. The dose chosen was the minimum recommended dose, which was unlikely to result in high serum concentrations (15). It is possible, though, that the lower efficacy seen with theophylline alone would have been improved by increasing the dose. However, the occurrence of adverse events was already high during the theophylline period, and an increase in dose would probably have worsened this situation. Theophylline is known to have a small therapeutic window, and commonly causes, among other side-effects, tremor and insomnia (15). Our study also found similar side-effects of theophylline; there were more adverse events seen during theophylline than budesonide therapy. The occurrence of adverse events was lower when theophylline was given in combination with budesonide. Similarly,

previous study has shown that theophylline given together with a β_2 -agonist reduces the incidence of tremor and palpitations (17). In the present study, no serious adverse events occurred with any of the treatments.

In conclusion, budesonide improved lung function and reduced asthma symptoms during nighttime significantly more than theophylline alone. No significant additional effect was seen with combination therapy.

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