

Terbutaline controlled-release tablets and ipratropium aerosol in nocturnal asthma

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The effect of oral terbutaline (controlled-release [CR] tablets) was compared with that of inhaled ipratropium bromide (aerosol) in 21 patients with nocturnal asthma. In a randomized, double-blind, crossover study, the patients were treated with terbutaline CR 10 mg twice daily, ipratropium 40 µg four times daily, and the two drugs in combination. Each treatment was given for 3 weeks. Before the start of the study, the patients participated in a 1-week run-in period. The mean nocturnal decline in peak expiratory flow rate (PEFR) was 29% in the run-in period and was reduced to 22% in the terbutaline CR period, 27% in the ipratropium period, and 23% in the period with the combination of the two drugs. The mean night PEFR was significantly ($P < 0.05$) higher in the period with terbutaline CR, as compared with the period with ipratropium. The mean morning PEFR was also highest in the terbutaline CR period. The mean evening PEFR was significantly ($P < 0.05$) higher during treatment with terbutaline CR alone and with the combination, as compared with treatment with ipratropium alone. Treatment with terbutaline CR alone or the combination was preferred by as many patients as was treatment with ipratropium alone. When present, adverse reactions were judged to be mild or moderate.

Treatment with terbutaline CR alone and the combination significantly improved the evening and night PEFR, as compared with treatment with ipratropium alone.

Key words: anticholinergic; β_2 -agonist; ipratropium; nocturnal asthma; terbutaline CR.

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Introduction

There is a normal circadian variation in bronchial tone (8). Lung function parameters, such as forced expiratory volume in 1 s ($FEV_{1.0}$, l) and peak expiratory flow rate (PEFR, l/min), are lowest in the night or in the early morning. In many asthmatic patients, this nocturnal decline is more pronounced.

Studies on combination therapy with inhaled β_2 -agonists and anticholinergic drugs have indicated additive bronchodilating effects (8). Anticholinergic drugs show a slower onset of action, as compared with β_2 -agonists. It has been suggested that higher doses of anticholinergics have a prolonged effect and may be useful for patients with nocturnal asthma (1, 2).

The aim of the present study was to compare the effect of oral terbutaline (controlled-release [CR] tablets) with that of inhaled ipratropium (aerosol) and their combination in patients with nocturnal asthma.

Material and methods

Twenty-eight adult outpatients (10 men, 18 women) with bronchial asthma participated in the study. To be included, patients had to show a nocturnal decline in PEFR of at least 20% or to wake up at night because of asthma (requiring aerosol treatment) on at least three occasions during a run-in period of 1 week. The nocturnal decline was determined by the formula:

$$\frac{PEFR_e - PEFR_n}{PEFR_e} \times 100$$

where e indicates the evening value and n the lowest value the following night or morning.

All patients received written and verbal information about the study and gave their informed consent to participation. The study was approved by the Ethics Committee at Turku University.

The study consisted of three consecutive treat-

ment periods, each lasting for 3 weeks: terbutaline CR tablets (Bricanyl® Depot, AB Draco, Sweden) 2 × 5 mg twice daily; ipratropium bromide aerosol (Atrovent®, Boehringer Ingelheim, Germany) 2 × 20 µg four times daily; and the two drugs in combination. The treatments were given in a randomized, double-blind, crossover fashion by a double-dummy technique. The tablets were pre-packed, with each dose in a separate chamber. Terbutaline CR tablets were administered at 0800 and 2000, and ipratropium aerosol at 0800, 1200, 1600, and 2000.

The patients' mean age was 38.6 years (range 18 to 59 years), mean weight 66.2 kg (range 50 to 88 kg), and mean height 164.8 cm (range 152 to 179 cm). The mean duration of their asthma was 4.8 years (range 0.25 to 20 years). During the run-in week, patients continued with their ordinary medication (six patients were on oral theophylline and two on oral β_2 -agonist). During the study, patients were not allowed to use any oral β_2 -agonists other than the study drug but were allowed to use inhaled β_2 -agonists when needed. Xanthines were to be avoided during the study. None of the patients used steroids before or during the study.

The patients measured PEFR daily on two to three occasions – every evening at 2000 before medication, at night if awake because of asthma, and immediately after rising in the morning before drug intake. The time of measurement, their asthma symptoms and possible adverse reactions (according to a four-point scoring system, 0–3), and the use of extra aerosol inhalations were noted in diary cards.

On the last day in each treatment period, the patients visited the clinic for change of study medication. At the end of the study, patients were asked which treatment period they preferred, with respect both to effect and adverse reactions.

In order to avoid possible carry-over effects, the determination of the nocturnal decline in PEFR and the evaluation of the study were based on the last 2 weeks in each treatment period.

For the statistical analysis, both a parametric test (two-way analysis of variance-additivity, one observation per cell) and a nonparametric test (Friedman's) were used.

Results

Twenty-one patients completed all three treatment periods and seven were withdrawn for various reasons. One patient was withdrawn for asthma deterioration during the terbutaline CR period, one patient for salmonellosis, and five patients for poor compliance (did not take their study medication or concomitant medication on a regular basis). Thus,

the statistical calculations were based on 21 patients (6 men, 15 women).

During the run-in week (on ordinary medication), 18 patients woke up during the night because of asthma, showing a sufficient decrease in PEFR. The mean nocturnal decline in PEFR over this week for all 21 patients was 29.1% (SD 14.6).

The mean night PEFR (measured only if awake because of asthma) was higher during all three treatments, as compared with the run-in week (Table 1). The differences were not statistically significant except for terbutaline CR ($P < 0.001$). During treatment with terbutaline CR, the mean night PEFR was also significantly ($P < 0.05$) higher than with treatment with ipratropium. During treatment with the combination of the two drugs, the mean night PEFR was numerically but not significantly higher than during treatment with ipratropium alone. The differences between the three treatments were also reflected by the number of patients waking up during the night because of asthma: 13 patients in the terbutaline CR period, 15 patients in the period with the combination, and 17 patients in the ipratropium period. The mean morning PEFR showed the same pattern, with the highest PEFR increase in the terbutaline CR period ($P < 0.01$), followed by the period with the combination therapy ($P < 0.05$), and the lowest value in the ipratropium period (NS) (Table 1). The mean evening PEFR was significantly ($P < 0.05$) higher during the periods with terbutaline CR alone or the combination than during the period with ipratropium alone and during the run-in week (Table 1).

During the study periods, the mean nocturnal decline of PEFR was lowest during treatment with terbutaline CR and with the combination of the two drugs, as compared with treatment with ipratropium

Table 1. Peak flow values at night, in the morning, and in the evening as well as nocturnal decline in PEFR: mean values $\pm$ SD over the last 2 weeks in each treatment period

	Run-in	Terbutaline CR 10 mg X 2	Ipratropium 40 µg X 4	Combination
PEFR night l/min, n = 10	258 ± 39 (n=8)	298 ± 41	262 ± 72	284 ± 62
		***	*	
PEFR morning l/min, n = 21	356 ± 83	394 ± 79	379 ± 73	389 ± 72
		**		
PEFR evening l/min, n = 21	416 ± 91	438 ± 79	423 ± 80	438 ± 78
		*	*	*
Nocturnal decline* in PEFR l/min, n = 21	122 ± 63	96 ± 74	117 ± 83	101 ± 82
		*	*	*

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

* nocturnal decline = $PEFR_{\text{morning}} - PEFR_{\text{evening}}$; e = evening; n = lowest value following night or morning.

alone (Fig. 1). The differences between the treatments were not statistically significant. During all three treatment periods, the mean nocturnal declines were lower than during the run-in week.

The nocturnal asthma symptoms, as well as the asthma symptoms during the day, were experienced as mild to moderate during all three treatments. Even though there were no statistically significant differences between the treatments, there was a tendency towards a lower mean score for asthma symptoms during treatment with terbutaline CR alone (Table 2). Among the patients treated with oral bronchodilators during the run-in period ($n=8$) and the remaining patients ($n=13$), no differences in increases in PEF, asthma symptoms, or number of extra doses of aerosol could be seen.

Possible adverse reactions were reported spontaneously by the patients. In Table 2, the mean score for the adverse reactions reported during the last 2 weeks in each period is shown. The adverse reactions included tremor, palpitations, dry mouth, and throat problems. When present, the adverse reactions were experienced as mild to moderate.

The use of extra aerosol during the night was virtually the same in all three treatment periods. Pa-

Table 2. Asthma symptom score (0–3) and adverse reactions score (0–3) during day and night during days 8–21 in each treatment period (mean $\pm$ SD, $n=21$)

	Run-in	Terbutaline CR 10 mg $\times$ 2	Ipratropium 40 μ g $\times$ 4	Combination
Asthma symptoms night	0.99 $\pm$ 0.59	0.42 $\pm$ 0.46	0.55 $\pm$ 0.52	0.43 $\pm$ 0.51
day	0.85 $\pm$ 0.70	0.48 $\pm$ 0.56	0.56 $\pm$ 0.53	0.59 $\pm$ 0.61
Adverse reactions night		0.06 $\pm$ 0.23 (8)	0.08 $\pm$ 0.31 (6)	0.11 $\pm$ 0.30 (7)
day		0.26 $\pm$ 0.52	0.19 $\pm$ 0.39	0.20 $\pm$ 0.41

The figures within parentheses are the number of patients reporting any adverse reaction with score.

tients used their aerosols only during approximately 30% of the nights in each period. In the run-in week, the corresponding figure was almost 50%.

At the last visit to the clinic (after 9 weeks' treatment), patients were asked which treatment period they preferred in respect of both effect and adverse reactions. Four patients preferred the terbutaline CR period, nine patients the ipratropium period, and six patients the period with the combination of the two drugs. Two patients could not differentiate between the period with terbutaline CR alone and the period with the combination. There was no difference in preference of period with respect to severe asthma symptoms during the night. Four of the patients reporting adverse reactions experienced them as most severe during the night in the period with the combination therapy.

Discussion

Nocturnal asthma is a very common problem among asthmatic patients (10). Many possible mechanisms for this symptom have been proposed, including exposure to allergens, gastric reflux, mucus plugging, and airway cooling (7). Even though these factors may contribute to nocturnal asthma in individual patients, they do not provide a universal explanation for the deterioration of asthma at night. Another explanation for the early-morning dyspnea may be the circadian variation in various biological functions related to the airways, such as airway caliber (9).

Catecholamine excretion is decreased and cholinergic stimulation is probably increased during the night in asthmatic patients. Therefore, β -agonists, as well as anticholinergic drugs, may be useful in the treatment of nocturnal asthma symptoms.

In asthmatic patients, CR tablets of terbutaline have been shown to reduce significantly, or even prevent, the nocturnal decline in lung function when doses from 10 to 15 mg were given in the evening (3–6). These studies included a placebo period and were able to show a reduction in nocturnal decline

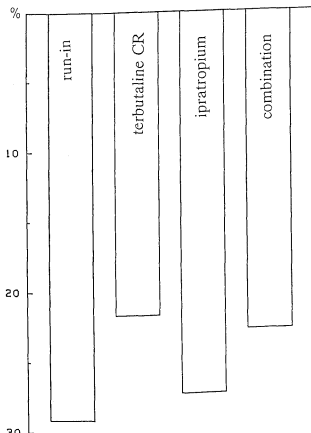


Fig. 1. Nocturnal decline in peak flow (%): mean values for the run-in week and the last 2 weeks in each treatment period.

of more than 20% during the terbutaline CR period, as compared with the placebo period. In the present study, no placebo period was included but the mean nocturnal decline was reduced from 29% in the run-in period (on ordinary medication) to 22% in the period with terbutaline CR alone. The combination therapy was almost as effective (Fig. 1).

A study with ipratropium has shown a significant reduction in the decline in lung function overnight (2). The results were the same with another anticholinergic drug, oxitropium (1). However, in those studies, the anticholinergic drugs were given in a rather high dose at bedtime. In the present study, the dosage regimen used was the one recommended, two inhalations four times daily. Perhaps the dosage of ipratropium in the present study was too low to be fully effective in nocturnal asthma. This may also explain why the reduction in nocturnal decline was not as pronounced in this study.

In the present study, both terbutaline CR (2 × 5 mg twice daily) alone and the combination with ipratropium were effective in the treatment of patients with nocturnal asthma. The subjectively scored nocturnal asthma symptoms decreased, and the night and morning PEFR increased during both treatment periods. Treatment with ipratropium alone did not increase the PEFR values as much as did the other two treatments. There was also a somewhat higher mean score for nocturnal asthma symptoms during this period.

The small differences in nocturnal decline between the treatments also corresponded to patients' preferences, as 12 patients preferred terbutaline CR or the combination with ipratropium and 9 patients preferred ipratropium alone.

In conclusion, all three treatments reduced the

nocturnal decline in PEFR, as compared with the run-in week. In addition, treatment with terbutaline CR alone and the combination significantly improved the evening and night lung function, as compared with treatment with ipratropium alone. There was no difference in preference between treatment with terbutaline CR alone or the combination and the treatment with ipratropium alone.

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