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# Nocturnal asthma: effects of slow-release terbutaline on spirometry and arterial blood-gases

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*Nocturnal asthma: effects of slow-release terbutaline on spirometry and arterial blood-gases. L. Eriksson, B. Jonson, G. Eklundh, G. Persson.*
**ABSTRACT: The effect of terbutaline, in a slow-release preparation, on spirometry and arterial blood-gases, was studied in fourteen patients with nocturnal asthma. The patients were treated with either 15 mg of slow-release terbutaline or placebo given as a single dose at 10 pm for eight days in a double-blind crossover trial. The patients were studied in the hospital for one night at the end of each treatment period. During active treatment the patients had a significantly higher $FEV_1$ and $PaO_2$ compared with placebo. Tolerance to the high single dose was good and none of the patients discontinued treatment because of side-effects. In patients with nocturnal asthma treatment with a high dose of slow-release terbutaline given as a single dose in the evening appears to be effective.**
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Early morning wheezing is a common symptom in asthma [1]. The patients can be relatively free of symptoms during the day and their pulmonary function tests and chest auscultation may be normal or close to normal. However, during the night they may have severe airflow limitation leading to disturbed sleep. Large diurnal variations in bronchomotor tone also seem to be related to an increased risk of sudden death in asthma [2, 3].

Treatment of these patients has proven difficult, partly because of lack of drugs with sufficiently long duration to cover the early morning hours when the symptoms are often most severe. In recent years, slow-release preparations of both theophylline [4] and beta-2-receptor stimulants, such as salbutamol [5] and terbutaline [6], have been introduced in the treatment of nocturnal asthma.

The aims of the present investigation were to study the effect on spirometry and arterial blood-gases of a single dose of slow-release terbutaline ($2 \times 7.5$ mg Bricanyl-Depot$^R$, Draco, Sweden) given at night, and to study the plasma concentrations of terbutaline using this dose.

## Patients and Methods

Fourteen patients, nine women and five men, with a mean age of 50 (range 30–63) yrs were investigated. The patients all had a history of nocturnal asthma that gave disturbed sleep and early awakening, with wheezing which required treatment with bronchodilating aerosol. Apart from the history of nocturnal asthma the patients met the following inclusion criteria: a) no cardiopulmonary disease other than asthma; b) no airway infection for at least one month; c) an increase in peak expiratory flow >15% after two doses of terbutaline spray.

The study was designed as a double-blind, placebo-controlled, cross-over study divided into three 8-day periods, a run-in period followed by two study periods. During the run-in period the patients recorded their peak expiratory flow (PEF), measured with a mini-Wright peak-flow meter, in the evening and in the morning. During this period they were kept on their ordinary medication, which did not include slow-release terbutaline. All were on 'plain' oral beta-2-agonists given three times daily and slow-release theophylline (Theo-Dur$^R$, Draco, Sweden) given twice daily. Four of the fourteen were on oral steroids and ten were on inhaled steroids. All were on inhaled beta-2-agonists and two were also on inhaled anticholinergics.

During the two study periods their ordinary oral beta-2-stimulants were substituted with either placebo or active treatment with slow-release terbutaline. Active treatment was given as $1 \times 7.5$ mg terbutaline (Bricanyl Depot$^R$, Draco, Sweden) for three days which was then increased to $2 \times 7.5$ mg terbutaline for the rest of the period. The tablets were given at 22.00 h. All the patients tolerated the high single dose well. The patients were allowed to keep their bronchodilating aerosols and use them when needed. They were told, however, to avoid using them for 5 h before each PEF or forced expiratory volume in one second ($FEV_1$) measurement, if possible. During the run-in week the patients used their ordinary bronchodilating aerosols. During the nights in the hospital rimiterol was given because it has a slightly shorter duration compared with other beta-2-agonists and because it would not interfere with the terbutaline analysis. No other change in medication was made.

At the end of each of the two study periods the patients came to the Department of Clinical Physiology at 16.00 h. Static lung volumes were measured with a body plethysmograph and spirometry was performed with a dry spirometer (Vitalograph). Normal values for lung volumes are from BERGLUND *et al.* [7] and from GRIMBY *et al.* [8].

A radial artery catheter was inserted (Venflon, Viggo) and samples for arterial blood-gases, S-theophylline and S-terbutaline were drawn. Arterial blood-gases were analysed in an automatic blood-gas analyser (IL 413, Instrumentation Laboratories). The patients then went to one of the medical wards where they were ambulant until 22.00 h when they went to bed. They remained in bed until 07.00 h. Spirometry was performed and S-theophylline was analysed at 22.00, 01.00, 0.40 and 07.00 h. Arterial blood-gases and P-terbutaline were analysed once every hour from 22.00 to 07.00 h. Heart rate and arterial blood pressure were also measured hourly. P-terbutaline was analysed with gas chromatography mass-spectrometry [9].

Figures in the text are mean $\pm 1$ standard deviation. Student's paired t-test was used for the statistical analysis.

## Results

None of the patients was heavily overweight. They had normal total lung capacity (TLC), $99 \pm 8.7\%$ predicted and increased residual volume (RV), $133 \pm 28.7\%$ predicted. Vital capacity (VC) and forced expiratory volume in one second ($FEV_1$) were slightly reduced, $83 \pm 12\%$ and $72 \pm 19\%$ predicted respectively.

Despite being on ordinary medication during the run-in period, eleven patients showed a fall in PEF of more than 20% overnight during three nights or more.

Serum theophylline levels were maximal at 16.00 h during both study nights and were $43 \pm 20$ µmol/*l* ($7.8 \pm 3.6$ mg/*l*) during active treatment and $45 \pm 18$ µmol/*l* ($8.2 \pm 3.2$ mg/*l*) during placebo. The lowest levels were seen at 07.00 h and were $34 \pm 24$ µmol/*l* ($6.2 \pm 4.4$ mg/*l*) during treatment and $39 \pm 20$ µmol/*l* ($7.1 \pm 3.6$ mg/*l*) during placebo.

Plasma terbutaline measurements during active treatment, (fig. 1), showed serum levels of about 10 nmol/*l* in the early evening as a result of the dose given the previous evening. After drug intake at 22.00 h the plasma terbutaline rose to a peak of about 26 nmol/*l* at around 06.00 h. Four of the fourteen patients had low, but detectable, levels of terbutaline during the placebo night.

There was no difference in $FEV_1$ between the placebo and terbutaline periods at 16.00 and 22.00 h, (fig. 2). After tablet intake $FEV_1$ increased during the night after active drug, and decreased after placebo. The differences between drug and placebo are highly significant. The mean overnight change in $FEV_1$ calculated from 22.00 to 07.00 h was an increase of

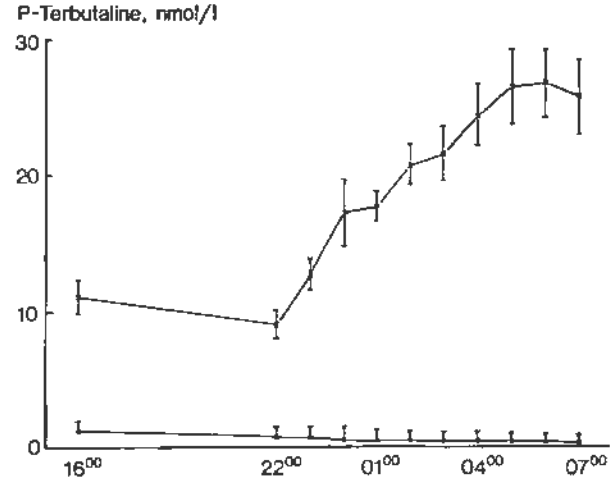


Fig. 1. Serum-terbutaline (mean ± SEM) during active treatment (-x-) and during placebo (-o-).

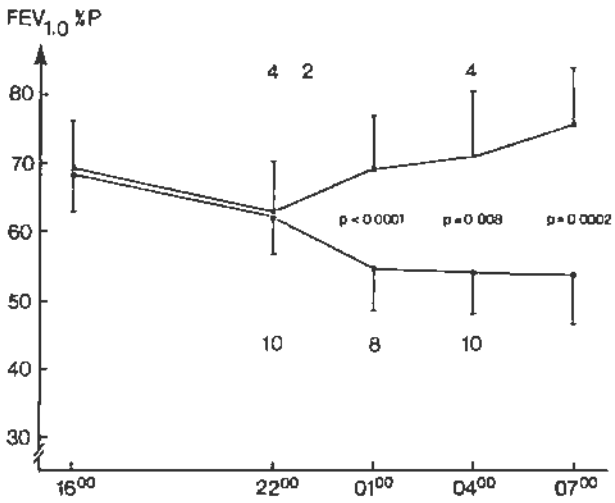


Fig. 2. $FEV_1$ in % of predicted value (mean ± SEM) during active treatment (-x-) and during placebo (-o-). The numbers above and below the curves indicate the number of extra doses of bronchodilating spray the patients were given.

$27 \pm 30\%$ during active treatment and a decrease of $14 \pm 19\%$ during placebo. The largest decrease during active treatment in a single patient was 11%. Eleven patients had a higher $FEV_1$ in the morning than at bedtime. During placebo, five patients had reductions of more than 20% in $FEV_1$, the largest decrease being 44%. On request the patients were given extra doses of rimiterol aerosol. The numbers in the figure indicate the number of extra aerosol doses that were given. During the placebo night 28 extra doses were administered and during the terbutaline night 10 ($p < 0.01$).

$Pa_{O_2}$ was higher throughout the terbutaline night compared with placebo (fig. 3). The mean difference was about 0.7 kPa. At any single time during the night the difference was not significant. However, when comparing the mean value calculated for each patient during the study nights, $Pa_{O_2}$ was significantly higher

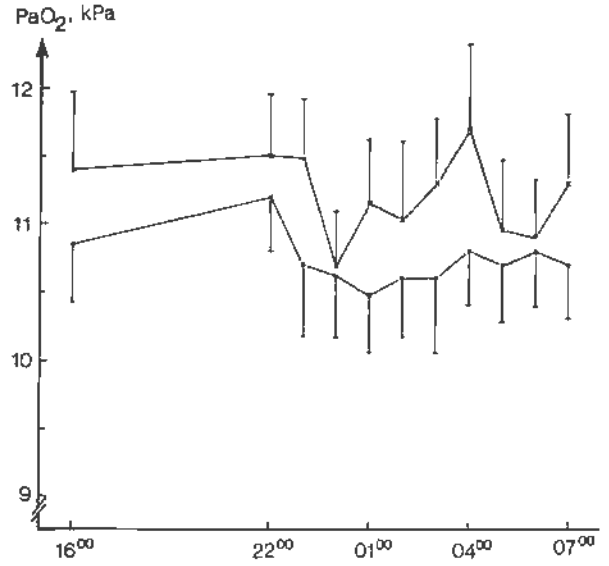


Fig. 3. $Pao_2$ (mean±SEM) during active treatment (-x-) and during placebo (-o-).

during terbutaline treatment than during placebo ($p<0.05$). The calculated alveolar-arterial $O_2$-gradient was lower during treatment than during placebo. The difference increased during the night and was significant at 04.00 h ($p=0.005$) and 07.00 h ($p=0.036$). The lowest recorded $Pao_2$ during a placebo night was 7.3 kPa, the lowest during terbutaline was 8.2 kPa. A slight increase in arterial carbon dioxide tension ($Paco_2$), which is also seen in normals, occurred during the night [10]. There was no difference between placebo and terbutaline. The highest recorded $Paco_2$ was 6.4 kPa.

The mean pulse frequency during the treatment night was 77±8 beats/min and during placebo 69±7 beats/min ($p<0.001$). None of the patients complained of palpitations or other symptoms related to the increased heart rate during treatment.

There were no differences in mean systolic blood pressure during the study periods, 126±12 mmHg during active treatment and 128±16 mmHg during placebo. Mean diastolic blood pressure was significantly lower during active treatment, 80±6 mmHg compared with placebo, 84±6 mmHg.

## Discussion

The patients selected for the study had nocturnal asthma with symptoms in spite of intensive treatment. Their daytime obstruction was slight to moderate. However, they all had symptoms of bronchoconstriction in the early morning hours. During the run-in period, when the patients were kept on their ordinary medication, eleven of the fourteen patients showed a fall in PEF of more than 20% during three nights or more, and in four of these patients PEF fell more than 20% on all of the nights. The normal TLC indicates that no patient had a severe emphysema. Patient compliance with the study protocol was very good. Low, but detectable, plasma levels of terbutaline were seen in only four patients at the beginning of the placebo night, probably because they had used their terbutaline aerosols. The tolerance to the high once a day dose, 15 mg, was surprisingly good and none of the patients discontinued treatment because of unwanted side effects. Objective registration of side effects was not performed. After each study night the patients were questioned about symptoms such as tremor and tachycardia. Only one patient voiced complaints and that was during a placebo night. The subjective benefits of the treatment were clear. One objective measurement of this is the reduced number of extra aerosol doses that the patients were given on demand during the two study nights, 10 during active treatment compared to 28 during placebo. After the study was completed all the patients were put on slow-release terbutaline as a regular medication.

There is no well defined therapeutic range for plasma terbutaline. BILLING *et al.* [11] showed that a plasma level of 4–9 nmol/*l* (1–2 ng/ml) was needed to see a clinical effect on $FEV_1$ (monotherapy). They also showed a dose-dependant increase in $FEV_1$ up to a mean plasma concentration of 28 nmol/*l* (6.3 ng/ml). At this level about 50% of the patients had reached maximum response. Similar results have been obtained by others [12]. The mean plasma level in our patients was 9 nmol/*l*, *i.e.* at the lower end of the therapeutic range, 24 h after the previous dose. After tablet intake (22.00 h) the plasma concentration rises to a maximum of about 27 nmol/*l*, thus covering the same plasma concentrations as in the study by BILLING *et al.* [11]. The plasma concentration curve reaches its maximum after about 8 h (06.00 h) clearly showing that slow-release terbutaline also covers the early morning hours when symptoms are often most severe. Pharmacokinetic studies of 'plain' terbutaline tablets show a maximum after 3–4 h [13].

In our material all patients except one were on regular steroid medication, and all were on slow-release theophylline. With this perspective the effect of slow-release terbutaline on $FEV_1$ was remarkably clear. Eleven patients actually had a higher $FEV_1$ at 07.00 h than at 22.00 h. The increase in $FEV_1$ during the terbutaline night shows a pattern similar to the plasma concentration curve for terbutaline. The $FEV_1$ in the evening before going to bed did not differ between the two study nights. At this time P-terbutaline was in the lower therapeutic range during treatment. This finding is also consistent with the diurnal pattern in $FEV_1$ seen in these patients. They may have a normal or close to normal spirometry in the late afternoon and early evening even without treatment.

The finding that the mean $Pao_2$ is higher with terbutaline than placebo is interesting. In the literature studies are often cited which show the opposite effect of beta-agonists [14]. These studies refer, however, to the acute effect of inhaled beta-agonists, mainly isoprenaline but also of the more selective beta-2-agonists. These results are probably

not relevant to beta-2-agonists given orally. As far as we know only one study with data on arterial blood-gases during treatment with slow release terbutaline has been published [15] and that also shows an increase in $Pa_{O_2}$.

The higher $Pa_{O_2}$ and the lower alveolar-arterial oxygen tension gradient during active treatment can be explained by better ventilation-perfusion matching and/or reduced right-left shunting as a result of bronchodilation. It can also be due to a higher cardiac output, leading to an increased mixed venous oxygen tension. Terbutaline has been shown to increase heart rate and stroke volume and to reduce peripheral resistance [16]. The higher heart rate and lower diastolic blood-pressure recorded in this study during active treatment are consistent with these observations.

We conclude that in patients with nocturnal asthma slow-release terbutaline given as a high dose in the evening gives a significant improvement of lung function (measured as $FEV_1$) and $Pa_{O_2}$ compared to placebo. In patients with mainly nocturnal asthma, treatment with a high once a day dose of slow-release terbutaline in the evening should be considered.

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RÉSUMÉ: Nous avons étudié, chez 14 patients atteints d'asthme nocturne, l'effet de la terbutaline à libération lente sur la spirométrie et les gaz du sang artériel. Les patients ont reçu, soit 15 mg de terbutaline à libération lente, soit du placebo, donnés en une dose unique à 10 h, du matin pendant 8 jours, dans un essai en double aveugle avec permutation croisée. Les patients ont été étudiés à l'hôpital pendant une nuit à la fin de chaque période de traitement. Au cours du traitement actif, le VEMS et la $Pa_{O_2}$ des patients s'avèrent significativement plus élevés qu'avec placebo. La tolérance à la dose unique élevée fut bonne, et aucun des patients n'a interrompu le traitement en raison d'effets collatéraux. Chez les patients atteints d'asthme nocturne, le traitement au moyen d'une dose élevée de terbutaline à libération lente donnée en une prise unique respérale apparaît donc efficace.