

## Sustained-Release Terbutaline in Nocturnal Asthma

C. J. J. WESTERMANN<sup>1</sup>, B. M. VAN WEELDEN<sup>2</sup> and C. D. LAROS<sup>1</sup>

<sup>1</sup>Dept. of Pulmonary Diseases, St. Antonius Hospital, Nieuwegein, and <sup>2</sup>Dept. of Pulmonary Diseases, Bleuland Hospital, Gouda, The Netherlands

Fifteen adult patients with nocturnal asthma entered a double blind study. They received a single evening dose of one sustained-release (SR) terbutaline tablet à 7.5 mg or an identical placebo tablet for 1 week, each in a randomised cross-over fashion in addition to their usual medication. In the 12 evaluated patients there was no change in evening PEF but a significant improvement in morning PEF ( $P < 0.05$ ) and in overnight fall of PEF ( $P < 0.01$ ) on active treatment. Symptoms were improved by both placebo and active medication. Three patients experienced tremor as a side effect. A single evening dose of SR-terbutaline can be of help in nocturnal asthma.

*Key words:* nocturnal asthma; sustained-release terbutaline.

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Sustained-release (SR) terbutaline was first introduced in 1981 (7). The main advantage over ordinary tablets seemed to be improved patient compliance and morning PEF.

Many asthmatic patients complain of nocturnal symptoms, but there is a subgroup in which this symptom persists despite adequate daytime therapy.

A single evening dose of 16 mg SR salbutamol has been reported not to abolish the overnight fall in PEF (3) though to increase morning PEF. In another study, a twice daily administration of 8 mg salbutamol as SR tablets did significantly improve both morning and evening PEF; although the "morning dip" decreased from 41 to 29 l/min, this difference was not statistically significant (5).

The present study was undertaken to evaluate the effect of a single evening dose of terbutaline given as one 7.5 mg SR tablet in patients with persistent complaints of nocturnal asthma.

### MATERIAL AND METHODS

Fifteen adult out-patients with moderately severe asthma and daytime basal forced expira-

tory volume in 1 s ( $FEV_1$ ) above 60 % of predicted normal and a reversibility of more than 15 % were studied. The selection criterion was sleep disturbance due to dyspnoea, and the patients had been awakened during at least three nights in the week prior to the trial. During the study, in addition to their usual medication which was kept constant, they received a single evening (22.00 h) dose of either one 7.5 mg SR terbutaline tablet (Bricanyl® Retard, Astra Pharmaceutica, Rijswijk, The Netherlands) or an identical placebo tablet. Each medication was given for 1 week in a randomised, cross-over fashion. The patients kept daily records of morning and evening PEF, quality of sleep, number of awakenings due to dyspnoea, comedication used, and side effects. Quality of sleep was scored as: 4 = good, 3 = reasonable, 2 = moderately bad, 1 = very bad.

PEF was determined with a Mini-Wright peak-flow meter, and the best of three values was used in the statistical analysis; a PEF recorded within 3 h of using inhaled bronchodilators was not included. Student's *t* test for paired obser-

vations was used in the statistical analysis. All patients were informed about the aim and nature of the trial and participated voluntarily.

## RESULTS

Three patients were not evaluated: two were hospitalised because their asthma worsened on the 2nd day of the trial (both started with active medication) and one failed to keep records. Thus, 12 patients were evaluated (5 men and 7 women; mean age  $\pm$  SD was  $40 \pm 17$  years, range 21–75). Basal FEV<sub>1</sub> was  $2.81 \pm 0.94$  (1.45–4.29) l being  $82.8 \pm 11.9$  (62–97) % of predicted normal.

Seven patients received steroids (3 beclomethasone dipropionate inhalation, 1 oral prednisone, and 3 a combination of both). Nine patients were on maintenance oral theophylline, three on oral sympathomimetics and eight on inhaled bronchodilators. As detailed analysis showed no run-in effect, the values of all 7 days were used to calculate the mean data.

The results obtained during the two study periods are shown in the table. In one patient all evening PEF and in another patient all morning PEF were obtained after inhalation of a sympathomimetic. The overnight fall is the mean of the daily nocturnal variations of the remaining 10 patients. Mean morning PEF was significantly improved and the mean overnight fall in PEF was almost abolished by the SR terbutaline medication. Only one patient had a

greater overnight fall in PEF on active medication, compared with placebo.

The sleep parameters, however, were not significantly different in the two periods, but were much better than before the trial, when sleep quality was averagely scored as 2.3, with 1.3 awakenings and 2.0 times extra medication per night. Three patients experienced a bothersome tremor during active treatment, six other patients had minor complaints during both active and placebo treatment. Six patients preferred the period with active treatment, four the placebo period (2 experienced tremor), and the remaining two patients had no preference.

## DISCUSSION

The present study has shown a significant reduction of overnight fall in PEF with a single evening dose of SR terbutaline compared with placebo. Other studies have also shown a superior effect on morning PEF using SR terbutaline rather than ordinary terbutaline or salbutamol (1, 2). The advantages of SR medication are improved patient compliance and coverage of a longer dosing interval during the night.

In the present study no plasma terbutaline concentrations were measured. Taudorf (7) found no difference in plasma concentrations 6 h after oral SR or ordinary terbutaline. He also found no difference in morning PEF between the two types of medication. However, his measurements of terbutaline plasma concentrations did not extend beyond 6 h and his population was not selected on nocturnal symptoms. In another study of patients with a diurnal variation of PEF  $> 20\%$ , nocturnal and early morning plasma concentrations were above the minimum therapeutic level of 2 ng/ml with SR terbutaline: 5 mg at 08.00 h and 10 mg at 20.00 h (4).

The objective improvement of the overnight fall in PEF in the present study is not reflected by the subjective experience, although extra nocturnal medication was less than on active medication. There is no obvious explanation for this discrepancy, which was also present in the studies of Erikson (2) and Beskow (1), but not in those of Koeter (4) and Stewart (6). Presum-

Table 1

Results during single evening dose therapy (mean  $\pm$  s.e.m.)

|                                     | SR-terbutaline<br>7.5 mg | Placebo           | n  |
|-------------------------------------|--------------------------|-------------------|----|
| Evening PEF<br>(1/min)              | 386.0 $\pm$ 40.0         | 395.4 $\pm$ 40.0  | 11 |
| Morning PEF<br>(1/min)              | 367.5 $\pm$ 33.0         | 340.8 $\pm$ 34.0* | 11 |
| PEF fall<br>overnight (1/min)       | 15.1 $\pm$ 15.2          | 71.8 $\pm$ 16.3** | 10 |
| Quality of sleep                    | 3.1 $\pm$ 0.2            | 3.1 $\pm$ 0.2     | 12 |
| No. awakenings/<br>night            | 0.64 $\pm$ 0.19          | 0.64 $\pm$ 0.13   | 12 |
| Extra nocturnal<br>medication/night | 0.44 $\pm$ 0.13          | 0.60 $\pm$ 0.12   | 12 |

\*  $P < 0.05$  \*\* $P < 0.01$

ably, subjective symptom scores are less sensitive parameters than PEF recordings.

Treatment of nocturnal asthma with SR theophylline is well accepted. Comparison between a single evening dose of SR theophylline and SR salbutamol in a group of patients with nocturnal asthma showed equal effectiveness of both drugs (3, 5). However, there were individual differences; some responded only to SR theophylline, some only to SR salbutamol and others to both drugs (3). To our knowledge, a comparison between SR theophylline and SR terbutaline has not been published, but from our study 7.5 mg SR terbutaline appears to be at least as effective, particularly in reducing the overnight fall in PEF. Moreover, nine of the 12 evaluated patients already used SR theophylline b.i.d.

Side effects are rather common with SR theophylline and SR sympathomimetics. Because of the individual susceptibility to side effects and the individual response regarding nocturnal symptoms, both drugs seem to have a place in the treatment of nocturnal asthma. The six patients who preferred SR terbutaline over placebo have successfully continued to take this medication at night.

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Address

C. J. J. Westermann, M.D.  
St. Antonius Hospital  
P.B. 2500  
3430 EM Nieuwegein  
The Netherlands

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