Oral terbutaline alone and in combination with theophylline: dose, plasma concentration, and effect in long-term treatment of bronchial asthma

G. Stålenheim, B. Lindström, G. Lönnerholm


ABSTRACT: Oral terbutaline, in gradually increasing doses from 2.5 to 10 mg three times daily (t.i.d.) was administered to 12 patients with chronic bronchial asthma. There was a linear relationship between dose and steady-state plasma concentrations in individual patients, but the plasma levels varied fourfold between patients taking similar doses. The need for other medication tended to decrease, and the symptom score, peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV$_1$) improved significantly during the treatment, with a roughly linear dose-effect relationship for the doses 2.5, 5 and 7.5 mg t.i.d. An increase in the dose from 7.5 to 10 mg did not improve PEFR and FEV$_1$, any further. Side-effects were generally few and mild. Oral theophylline 200 mg t.i.d. added to terbutaline 10 mg t.i.d. brought about a further improvement in pulmonary function without adding any troublesome side-effects. Our data indicate that there is little to gain by prescribing terbutaline doses higher than 7.5 mg t.i.d. Instead, theophylline might be added, since this combination seems to have a favourable therapeutic index.

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Beta$_2$-adrenoceptor stimulating agents, such as terbutaline, hold a central place in the treatment of reversible bronchoconstriction. The current tendency is to use inhaled beta$_2$-agonists both for acute symptoms and as regular long-term treatment [1], but there are still situations when oral bronchodilators are desirable.

Terbutaline has been used extensively in the treatment of obstructive airway disease for more than a decade [2–4], but there is still some controversy regarding the proper therapeutic dosage [5–7]. It is also unclear whether addition of theophylline to optimal, individually titrated doses of oral theophylline adds any further to the bronchodilating effect of this drug.

The aim of the present investigation was to study the relationship between the dose, plasma concentration, and effect of oral theophylline administered for maintenance therapy in adults with chronic bronchial asthma. After individual titration of the terbutaline dose, a standard dose of theophylline was added to study the further effects of this combined regimen.

Patients and methods

Patients

Twelve patients were selected for the study. The inclusion criteria were: 1) moderate to severe chronic bronchial asthma in a stable state; and 2) reversibility of bronchial obstruction as shown by a 20% or more improvement in the forced expiratory flow volume during the first second (FEV$_1$) after inhalation of nebulized salbutamol in a dose of 0.05 mg·kg$^{-1}$. Exclusion criteria were age above 70 yrs, pregnancy, and other chronic diseases such as cardiovascular, hepatic or renal disease, diabetes mellitus, and chronic bronchitis.

Some characteristics of the patients are shown in table 1. There were seven women and five men. Their mean age was 56 yrs (range 44–68 yrs). Before entering the trial, ten of the patients had been treated regularly with oral terbutaline in doses of 7.5–15 mg daily or salbutamol 6 mg daily for at least several months. Four of the
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Asthma duration (yrs)</th>
<th>Smoking habits</th>
<th>Beta₂-agonist and theophylline at start of study</th>
<th>Other medication at start of study</th>
<th>Allergy of importance</th>
<th>PEFR variation* (%)</th>
<th>Pred</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>65</td>
<td>48</td>
<td>ExS</td>
<td>Oral terbutaline</td>
<td>Inhaled beclomethasone, oral bromopheniramine + phenylpropanolamine</td>
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<td>38-90</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>47</td>
<td>20</td>
<td>ExS</td>
<td>Inhaled terbutaline, oral terbutaline, oral theophylline</td>
<td>Inhaled beclomethasone, oral sodium cromoglycate</td>
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<td>57-121</td>
<td></td>
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<tr>
<td>3</td>
<td>M</td>
<td>53</td>
<td>4</td>
<td>ExS</td>
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<td>Inhaled beclomethasone</td>
<td>No</td>
<td>22-62</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>59</td>
<td>29</td>
<td></td>
<td>Inhaled terbutaline, oral terbutaline</td>
<td>Inhaled beclomethasone, oral triamcinolone, oral bromhexin, oral cinnarizine + phenylpropanolamine</td>
<td>No</td>
<td>58-169</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>44</td>
<td>20</td>
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<td>28-96</td>
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<td>6</td>
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<td>49</td>
<td>20</td>
<td>S</td>
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<td>Inhaled beclomethasone</td>
<td>No</td>
<td>42-63</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>61</td>
<td>2</td>
<td>ExS</td>
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<td>Inhaled beclomethasone</td>
<td>No</td>
<td>35-134</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>58</td>
<td>8</td>
<td></td>
<td>Inhaled terbutaline, oral terbutaline, oral theophylline</td>
<td>Inhaled beclomethasone</td>
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<tr>
<td>9</td>
<td>M</td>
<td>68</td>
<td>1</td>
<td>ExS</td>
<td>Inhaled salbutamol</td>
<td>Inhaled beclomethasone, oral acetylcysteine</td>
<td>No</td>
<td>45-89</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>61</td>
<td>7</td>
<td></td>
<td>Inhaled salbutamol, oral salbutamol, oral theophylline</td>
<td>Inhaled beclomethasone</td>
<td>No</td>
<td>49-89</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>57</td>
<td>16</td>
<td></td>
<td>Inhaled terbutaline, oral terbutaline, oral theophylline</td>
<td>Inhaled beclomethasone, oral prednisolone</td>
<td>No</td>
<td>49-101</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>58</td>
<td>10</td>
<td></td>
<td>Inhaled terbutaline, oral theophylline</td>
<td>Inhaled beclomethasone</td>
<td>No</td>
<td>52-139</td>
<td></td>
</tr>
</tbody>
</table>

S: smoker; ExS: ex-smoker; 0: never smoked; PEFR: peak expiratory flow rate; *: PEFR values recorded within a one year period prior to the study (min-max).

Patients had been treated with inhaled beta₂-agonists regularly and seven as required for long periods of time. All of the patients were taking inhaled corticosteroids regularly and two of them low doses of oral corticosteroids. Eight of the patients were being treated regularly with oral theophylline preparations, and one was using inhaled sodium cromoglycate. Theophylline and beta₂-agonists were discontinued the day before the start of the study and the other medications were kept constant during the study period. The baseline FEV₁, with the patients taking their ordinary medicines except for beta₂-agonists and theophylline, was 45% of the expected value (range 20.5-74%). The variability in the peak expiratory flow rate (PEFR) values noted in the patients' records within a one year period prior to the study are shown in Table 1.

Informed consent was obtained from the patients and the study was approved by the local Ethics Committee.
The study was open. This design was chosen to allow dose titration of terbutaline similar to that in clinical practice. During the first week no terbutaline was administered but subsequently terbutaline in tablet form (Bricanyl®, Draco, Lund, Sweden) was given in increasing dose. The initial dose was 2.5 mg three times daily (t.i.d.), followed by doses of 5, 7.5 and 10 mg t.i.d. Each dose was administered for a period of one week. At the end of each week the side-effects of the treatment were evaluated, to see whether the patient would tolerate a further dose increase. The maximum dose administered was 10 mg t.i.d. During the last week of the study oral theophylline in slow-release form (Theo-Dur®, Draco, Lund, Sweden), 200 mg t.i.d., was added to the highest dose of terbutaline tolerated by the patient. The dose intake was at 7 am, 2 pm, and 9 pm, both with terbutaline and theophylline.

The patients kept a daily diary, in which they recorded PEFR at 7 am, 4 pm and 9 pm. They also noted their symptoms, medication and any side-effects (tables 2 and 3). They were particularly questioned concerning tremor and palpitation, which were graded 0–3.

At the end of each week (day 7), the patients visited the out-patient clinic. After a 15 min rest, the pulse rate, blood pressure, tremor, PEFR, and FEV1, were measured, and blood samples were taken for determination of the terbutaline concentration in the plasma. Immediately thereafter, at 2 pm, a terbutaline dose (the same as had been taken during the preceding week) was ingested with about 100 ml of water. The patients were fasting; they had had lunch 2–3 h before dose intake. Two hours after the dose the above procedures were repeated. The patients then inhaled salbutamol, 0.05 mg·kg⁻¹ body weight, administered by a nebulizer, and 20 min later the pulse rate, blood pressure, tremor, PEFR and FEV1 were measured again. PEFR was measured in the same way as at home with a Mini-Wright peak flow meter (Clément Clarke, International Ltd, London, England) and FEV1 was measured with a dry spirometer (Vitalograph). For both FEV1 and PEFR the highest value of three measurements was used. When the values were expressed as percentage of the expected, the standard values of FRIDRIKSSON et al. [8] were used.

Terbutaline concentrations in plasma were determined in duplicate. Blood (10 ml) was collected in heparinized test tubes. After centrifugation, the plasma was separated and frozen until analysed. Two ml samples of plasma were extracted and derivatized according to the method of JACOBSSON et al. [9]. The gas chromatography-mass spectrometry measurements were performed as described by LEFERN and co-workers [10, 11]. The coefficient of variation of the terbutaline assay was 4% (1 ng·ml⁻¹).

Tingler tremor was measured by an optoelectronic displacement transducer [12]. The last 90 s of the 2 min recording period were used for quantitative estimation of the tremor.

The patients were allowed to use extra medication with salbutamol dose aerosol if necessary, but not within 6 h before the visit to the out-patient clinic. Oral theophylline in the form of a rapidly dissolving tablet (Theovent®, Ferrosan, Malmö, Sweden) could be added to the salbutamol inhalations as extra medication, but not within 12 h before the visit to the out-patient clinic. No extra theophylline was allowed during the week when Theo-Dur® was administered. All extra medication had
to be carefully recorded in the daily diary. Beverages containing caffeine were not allowed on the day of the visit to the out-patient clinic.

Values from days 2–6 were used for the calculations. During day 1 the patient was not considered to be in steady-state, and on day 7 the patient visited the out-patient clinic. An analysis of variance was used to detect any influence of the terbutaline dose on the different variables tested. The effect of the combined treatment with theophylline plus terbutaline was compared with that of the corresponding doses of terbutaline alone by a Student's paired t-test (two-tailed). The 5% level was considered significant.

Symptom scores. The sum of the scores for asthmatic symptoms decreased significantly (p<0.05) with increasing doses of terbutaline (table 2). When the scores for the different asthmatic symptoms were analysed separately, only the improvement regarding breathlessness reached statistical significance (p<0.01). The p values for the improvement in physical activity and cough were 0.08 and 0.09, respectively. The addition of theophylline 200 mg t.i.d. tended to improve the symptom scores for breathlessness, impairment of physical activity and cough, but the differences did not reach statistical significance.

With increasing doses of terbutaline, the consumption of salbutamol in aerosol form as extra medication tended to decrease (table 2). The extra intake of oral theophylline was low throughout the trial. It decreased slightly from a mean dose of 115 mg per day during the first week to 47 mg per day during week 5 (table 2).

Results

**Dose tolerance.** Eleven of the 12 patients tolerated terbutaline well enough to be able to test even the highest dose of the drug, i.e. 10 mg t.i.d. One patient (no. 12) reported restlessness, difficulty in sleeping and chest pain when taking 7.5 mg of terbutaline t.i.d., and did not receive the highest dose; when adding oral theophylline to the terbutaline of this patient, the terbutaline dose was 5 mg t.i.d. In the other 11 patients 10 mg of terbutaline plus 200 mg theophylline was administered three times daily during the last week of the trial.

![Fig. 1. - PEFR during days 2-6. The results are expressed as means of expected PEFR values [8]. Bars indicate ±10% treatment with terbutaline 10 mg plus theophylline 200 mg t.i.d. PEFR: peak expiratory flow rate.](image1)

![Fig. 2. - FEV₁ measured on day 7. The results are expressed as means of expected FEV₁ values [9]. Bars indicate ±10% treatment with terbutaline 10 mg plus theophylline 200 mg t.i.d. FEV₁: forced expiratory volume in one second.](image2)
Spirometry. The mean PEFR values during days 2–6 in percentage of the expected values are shown in figure 1. The 7 am and 9 pm values were obtained immediately before dose intake, whilst the 4 pm values were obtained about 2 h after the intake. This might explain why the 4 pm values showed the most clearcut improvement with increasing doses of terbutaline (p=0.001). The 7 am and 9 pm values also showed a significant improvement with increasing doses (p<0.01). However, the increment in the terbutaline dose from 7.5 to 10 mg t.i.d. did not further improve PEFR. The data shown in figure 1 even suggest that the mean PEFR values were lower with 10 mg than with 7.5 mg. This is explained by the fact that one patient with very high PEFR values did not receive the highest dose (see above). If the data are recalculated for the 11 patients receiving all terbutaline doses, the PEFR values obtained with 7.5 mg and 10 mg are similar.

Addition of theophylline increased the FEV₁ to the highest tolerated dose of terbutaline, brought about a further significant improvement in PEFR at 7 am and 4 pm (p<0.01) and also at 9 pm (p<0.05).

The mean FEV₁ values on day 7 are presented in figure 2. The values both before and 2 h after dose intake tended to increase with the terbutaline dose (p=0.07 and 0.06, respectively). With the highest dose of terbutaline, mean FEV₁ 2 h after dose intake was 58% of the expected value, as compared with 45% during the first, terbutaline-free week. Inhalation of salbutamol gave further improvement, which was most marked with no or low terbutaline doses (fig. 2, lower panel), as might be expected. The mean increment was 21% during the first, terbutaline-free week and 3% at the last visit, after one week of treatment with terbutaline plus theophylline.

Addition of theophylline increased the FEV₁ values further. The increase in FEV₁ before the dose was not statistically significant (p=0.1), 2 h after the dose it was of borderline significance (p=0.06) and after inhaled salbutamol it was significant (p<0.01). The PEFR values on day 7 (not shown) were similar to those of FEV₁, except that the PEFR values were consistently 20–30% higher (both variables were calculated as percentage of expected values). Thus, the mean PEFR 2 h after dose intake increased from 70% during the first, terbutaline-free week to 86% after intake of the highest dose of this drug. With terbutaline plus theophylline the mean value was 95%.

Side-effects. The side-effects reported were generally few and mild. Five patients complained of muscle cramps, two patients had difficulty in falling asleep, two patients had chest pain and one patient suffered from restlessness. The mean symptom scores for tremor and palpitation are presented in table 3. There was a gradual increase in the tremor score with increasing terbutaline doses (p<0.05). The score for palpitation was low throughout the study.

The mean pulse rate on day 7 before and 2 h after a dose intake is shown in table 4. The values were similar throughout the trial, and the same was true for systolic and diastolic blood pressures (not shown).

The mean skeletal muscle tremor on day 7 was about twice as great with the lowest dose of terbutaline as the control value obtained during week 1, both before and 2 h after a dose (table 4). Higher doses caused no further increase. Throughout the study there was a wide scatter of the tremor values. This might be one of the explanations for the lack of a statistically significant increase in tremor with increasing doses of terbutaline.

The addition of theophylline did not cause any significant increase in symptom scores (tables 2 and 3), pulse rate or tremor (table 4), nor were there any new spontaneously reported side-effects during the week of combined treatment with terbutaline and theophylline.

Plasma concentrations of terbutaline. Figure 3 shows the plasma concentrations of terbutaline before and 2 h after dose intake on day 7, i.e. in steady-state. There was clearly a linear relationship between dose and plasma concentration in the individual patients, at least up to a dose of 7.5 mg t.i.d. The further increase to 10 mg resulted in a relatively small increase in plasma concentration.

The plasma concentrations varied about fourfold between patients taking similar doses, both before and 2 h after a dose. Low pre-dose levels were generally associated with low 2 h levels and vice versa. The 2 h levels were roughly twice as high as the pre-dose levels.

The addition of theophylline 200 mg t.i.d. to terbutaline 10 mg t.i.d. did not generally cause any marked change in the terbutaline plasma concentrations (fig. 3). The mean pre-dose terbutaline concentration was 6.1 µg·l⁻¹ when terbutaline was given alone and 6.4 µg·l⁻¹ when it was

### Table 4. – Pulse rate and tremor measured on day 7, mean and (so)

<table>
<thead>
<tr>
<th>Week no.</th>
<th>Pulse rate (beats per min)</th>
<th>Tremor (% of first terbutaline-free week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before dose</td>
<td>2 h after dose</td>
</tr>
<tr>
<td>1</td>
<td>80 (7.8)</td>
<td>81 (6.8)</td>
</tr>
<tr>
<td>2</td>
<td>79 (13)</td>
<td>80 (10)</td>
</tr>
<tr>
<td>3</td>
<td>83 (10)</td>
<td>85 (9.2)</td>
</tr>
<tr>
<td>4</td>
<td>81 (11)</td>
<td>80 (11)</td>
</tr>
<tr>
<td>5</td>
<td>80 (8.9)</td>
<td>79 (9.6)</td>
</tr>
<tr>
<td>6</td>
<td>82 (7.2)</td>
<td>78 (8.7)</td>
</tr>
</tbody>
</table>

ORAL TERBUTALINE IN CHRONIC ASTHMA
given together with theophylline. The corresponding figures for the terbutaline concentration 2 h after a dose were 11.7 and 11.4 µg·l⁻¹, respectively.

![Graph](image)

**Fig. 3.** - Individual plasma concentrations of terbutaline on day 7 before (upper panel) and 2 h after dose intake (lower panel). Mean values are indicated by horizontal bars. 10+ is treatment with terbutaline 10 mg plus theophylline 200 mg t.i.d.

**Correlations.** There was no statistically significant correlation for the group as a whole between the plasma concentration of terbutaline and PEFR or FEV₁, either before or 2 h after a dose. When this correlation was studied in the individual patients, only four of them showed a significant correlation between the plasma concentration and the lung function parameters.

No clearcut correlation was found between plasma concentrations and side-effects. It is true that the patient who was unable to take the highest dose of terbutaline because of marked side-effects when taking 7.5 mg terbutaline t.i.d., had the highest pre-dose plasma concentration and the third highest plasma concentration 2 h after a dose. But, on the other hand, several patients with high plasma concentrations reported no or little tremor, palpitations or other side-effects.

**Discussion**

Stepwise increasing doses of oral terbutaline administered during weekly periods tended to reduce the need for other medication. The decreasing use of other medication during the study must have tended to obscure the improvements brought about by the increasing doses of terbutaline. In spite of this an improved pulmonary function (PEFR and FEV₁) was demonstrated. For the doses 2.5, 5 and 7.5 mg terbutaline t.i.d. there was a roughly linear dose-effect relationship. For the individual patients the pattern was difficult to interpret, since the variability in PEFR values was great as a reflection of the variability in the disease itself. The increase in dose from 7.5 to 10 mg did not cause any further improvement, however, which might indicate a ceiling for the bronchodilator effect of the drug. This hypothesis is supported by the results of Billing et al. [13], who also found a ceiling in effect with high plasma concentrations of terbutaline.

The plasma concentrations of terbutaline showed a fourfold interindividual difference in steady-state, both 2 h after dose intake (2 h is the approximate time for the peak plasma concentration after oral intake) and 7 h after intake, i.e. immediately before the next dose. The observed interindividual linear relationship between dose and plasma concentration contraindicates the idea of dose-dependent kinetics of the drug within the tested dose range.

Analysis of variance revealed a statistically significant relationship between the plasma concentration of terbutaline and pulmonary function in only four out of 12 patients. Furthermore, there were large interindividual variations in the degree of bronchodilatation at the same plasma terbutaline level. This is in agreement with the findings of Billing et al. [13] after intravenous administration of terbutaline. At present, therefore, there is no reason for basing the adjustment of terbutaline therapy on the plasma concentration. However, further trials comprising larger numbers of patients are needed to determine whether a therapeutic range of plasma terbutaline concentrations can be defined.

An important observation was that oral theophylline 200 mg t.i.d. added to a high individually titrated dose of terbutaline (10 mg t.i.d. in 11/12 patients) brought about a further improvement in pulmonary function. Several studies have shown that theophylline plus terbutaline gives more bronchodilatation than terbutaline alone [14-18], but in these studies standardized, conventional doses of terbutaline have generally been used (the terbutaline dose recommended by the manufacturer is 5 mg t.i.d.). Our data indicate that theophylline has a bronchodilating effect even when added to high doses of oral terbutaline.

As a rule the plasma concentration of terbutaline did not change markedly when theophylline was added. One
patient was a remarkable exception, with a terbutaline concentration 2 h after dose intake rising from 20.4 to 35.5 μg·L⁻¹ after addition of theophylline. The reason for this is unknown to us. Interestingly, this patient did not report any side-effects spontaneously during the study period, and the symptom scores for the tremor and palpitations were very low.

Our finding of a fourfold interindividual variation in plasma levels of terbutaline during oral maintenance therapy clearly indicates a need for individualized dosing of the drug. At present, determination of plasma terbutaline levels seems to be of limited value in clinical practice, since there are considerable interindividual variations in response at the same plasma level. Instead, the dose should be individualized on the basis of the clinical effect and tolerance. Although many patients might tolerate a higher dose, our data indicate that there is little to gain by administering doses higher than 7.5 mg t.i.d. Instead of raising the dose above this level, we suggest addition of theophylline, since this combination seems to have a favourable therapeutic index [18].

We want to point out that this study did not include the effect of regular inhalations of a beta-stimulant. In our opinion, regular administration of a beta-stimulant by a metered aerosol should generally be tried before oral maintenance treatment with terbutaline or any other beta-stimulant is initiated.

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References


La terbutaline par voie orale, seule et en combinaison avec la theophylline: Dose, concentration plasmatique et action, dans le traitement au long cours de l'asthme bronchique. G. Stålemheim, B. Lindström, G. Lönnerholm.

RÉSUMÉ: Nous avons administré, chez 12 patients atteints d'asthme bronchique chronique, de la terbutaline orale à des doses progressivement croissantes de 2.5 à 10 mg trois fois par jour. L'on a noté une relation linéaire entre la dose et les concentrations plasmatiques en état stable chez les patients pris individuellement, mais les taux plasmatiques variaient de 1 à 4 entre les patients prenant des doses similaires. La nécessité d'une autre médication tend à diminuer, et les scores de symptômes, le débit expiratoire de pointe et le VEMS, s'améliorent significativement pendant le traitement, avec une relation grossièrement linéaire dose-éfficacité pour les doses de 2.5, 5 et 7.5 mg trois fois par jour. Une augmentation de la dose de 7.5 à 10 mg n'améliore pas davantage le débit de pointe et le VEMS. Les effets collatéraux sont généralement peu marqués et peu abondants. La théophylline en dose orale de 200 mg trois fois par jour additionnée à 10 mg de terbutaline trois fois par jour, entraîne une amélioration complémentaire de la fonction pulmonaire, sans augmenter les effets collatéraux. Nos observations indiquent qu'il y a peu à gagner en prescrivant la terbutaline à des doses supérieures à 7.5 mg trois fois par jour. Par contre, la théophylline peut y être adjointe, puisque cette combinaison semble avoir un index thérapeutique favorable.