

Terbutaline Slow-Release Tablets in Children with Bronchial Asthma

Effect and Pharmacokinetics Compared with Plain Terbutaline Tablets.

G. WETTRELL,¹ S. ANEHUS,² G. HATTEVIG,¹ and B. KJELLMAN¹

¹Dept. of Pediatrics, Kärnsjukhuset, Skövde, and ²Dept. of Clinical Research, AB Draco*, Lund, Sweden

The effect of terbutaline sulphate in slow-release (SR) tablets (Bricanyl® Depot), 5 mg twice daily, was compared with that of terbutaline sulphate in ordinary tablets (Bricanyl®), 2.5 mg three times daily, in a double-blind, randomized, cross-over study during 2 consecutive weeks in 10 asthmatic children. Plasma concentrations and urinary excretion of terbutaline were measured at various times during both treatment periods. The SR tablets produced a higher mean plasma concentration in the morning and a smaller peak-trough variation over the day than the ordinary ones. No differences between the two treatments were observed concerning FEV₁ (forced expiratory volume in 1 s). Tremor, measured with an opto-electronic tremorgraph, was about the same for two treatments and not significantly different from tremor seen in healthy children. The reported side effects were less frequent in the SR tablet period.

Key words: childhood asthma; pharmacokinetics; slow-release tablets; terbutaline.

Accepted for publication 25 April 1986

In Sweden, the drug of choice for treatment of asthma in children is a β_2 -receptor agonist. Terbutaline sulphate (Bricanyl®, AB Draco, Sweden) is one of them. A variety of dosage forms of terbutaline sulphate are available to meet different therapeutic requirements.

The slow-release (SR) preparation of terbutaline sulphate (Bricanyl® Depot, AB Draco, Sweden) was developed to allow a twice-daily dosage. This change had already been made for theophylline preparations in order to improve patients compliance and make possible a prolonged effect on asthma symptoms at night. The dosage is of advantage for the treatment of asthma in children (5, 9).

The aim of the present study was to compare the effect on asthma symptoms and the side

effects of terbutaline SR (Bricanyl Depot) tablets (5 mg b.i.d.) with ordinary (Bricanyl) tablets (2.5 mg t.i.d.) during steady state therapy in asthmatic children.

MATERIAL AND METHODS

Ten children (7 boys and 3 girls) with chronic bronchial asthma (duration 3 to 13 years, mean age 7.9 years) and a reversibility in FEV₁ of $\geq 15\%$ participated in the study. Their mean reversibility (after inhalation of 0.25 mg terbutaline/kg b.w. by nebulization) was 40.2%. The children were between 7 and 13 years old (mean 10.7 years) with a mean weight of 35.1 kg (range 21 to 45 kg) and a mean height of 142.2 cm (range 120 to 158 cm).

The study consisted of two consecutive treatments, each lasting for 1 week. During one

* Subsidiary of AB Astra, Sweden.

period the patients were treated with plain Bricanyl tablets 2.5 mg t.i.d. (every 6 h during the day) and during the other with Bricanyl Depot tablets 5 mg b.i.d. (every 12 h). The individual dose of terbutaline sulphate varied for ordinary tablets from 0.056 to 0.119 mg/kg b. weight and for SR tablets from 0.089 to 0.190 mg/kg b. weight. The study was conducted by using a randomized, double blind, cross-over design with a double-dummy technique. The patients who used theophylline and/or sodium cromoglycate (Lomudal®) were allowed to continue this medication provided that the dose was kept constant. No other medicines were used, except a short-acting aerosol, rimeterol (Pulmadil®), used when needed, but not later than 3 h before PEF measurements.

During each treatment period the children or their parents filled in a diary card in the morning and evening before the drug intake. The variables to be recorded were: PEF (morning and evening), asthma symptoms (during day and night), use of extra aerosol (during day and night) and side effects.

The children visited the clinic at the end of each period and stayed there during the 6th night and the following day. At various times (0, 2, 4, 6, 8, 10, and 12 h after the morning dose) during the 7th day, heart rate, blood pressure, PEF, FEV₁ and tremor were recorded. Finger tremor was measured by an opto-electronic tremorograph (10). Blood samples for determination of terbutaline concentrations were taken at 0, 2, 6, 8, and 12 h following the morning dose, and urine was collected at 2-h intervals during the 7th day at the clinic. The blood samples were immediately centrifuged and the plasma removed and frozen. Samples of urine were also frozen. All analyses were performed by a method based on gas chromatography chemical ionization mass spectrometry (4). The children were asked questions about specific side effects, tremor and restlessness/uneasiness, during the preceding week. At the end of the study, they were asked which period they preferred in view of the effects and the side effects.

Objective tremor was also recorded in a control group consisting of 10 healthy children

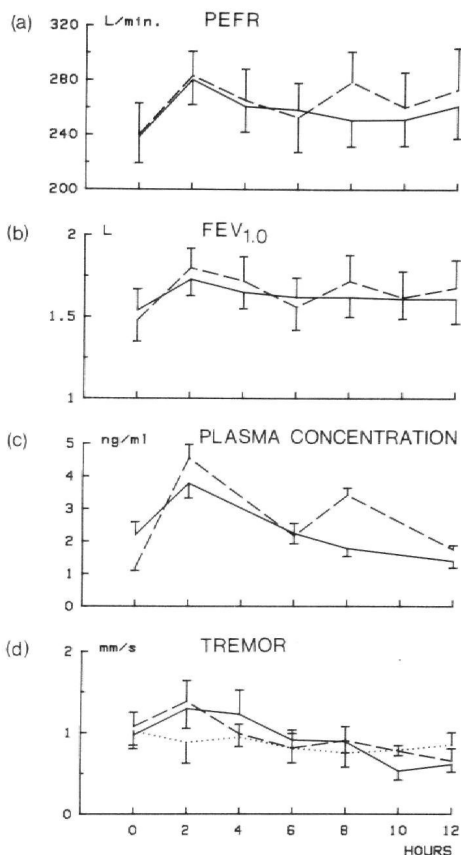


Fig. 1. PEF (a), FEV₁ (b) and plasma concentration (c) recorded during 12 h at the clinic following terbutaline SR tablets, 5 mg b.i.d., (solid line) and terbutaline ordinary tablets, 2.5 mg t.i.d., (interrupted line). Tremor (d) measured with the opto-electronic tremorograph, recorded during 12 h at the clinic. Solid line: terbutaline SR tablets (5 mg b.e.d.). Interrupted line: terbutaline ordinary tablets (2.5 mg t.i.d.). Dotted line: control group. Means and SEM values are given.

(4 boys and 6 girls). These children were between 8 and 12 years old (mean 10.2 years).

The statistical evaluation was performed using the Student's *t* test of paired differences. Calculations concerning the recordings at home

were based on the mean values of the last 4 days in each period (steady state).

The local Ethics Committee agreed to the protocol of the study. All patients and their parents received verbal and written information and gave their informed consent to the participation.

RESULTS

Lung function test

The mean values of PEF recorded at home showed no significant differences between the two treatments. When measured at the clinic, the mean PEF increased significantly during the first 2 h after the morning dose of both ordinary tablets ($P < 0.01$) and SR tablets ($P < 0.05$) (Fig. 1a), and then decreased slowly throughout the day. No significant difference was found between the two treatments. The individual data varied between the patients. However, most of the patients showed the lowest PEF value in the morning.

The mean morning FEV₁ value, before drug intake, was somewhat higher during treatment with SR tablets than with ordinary ones, but the difference was not statistically significant (Fig. 1b).

Terbutaline plasma and urine concentrations

The mean morning plasma concentration of terbutaline obtained before drug intake (reference value) was significantly higher ($P < 0.05$) during treatment with SR tablets than treatment with ordinary ones. The peak values were reached 2 h after drug intake in the morning; 3.8 ng/ml for SR tablets and 4.6 ng/ml for ordinary tablets (Fig. 1c). The average peak/trough ratios were 2.7 for SR tablets and 3.8 for ordinary tablets.

The correlation coefficients between the mean plasma concentration and the mean values of PEF, FEV₁ and tremor for both preparations were found to be 0.74, 0.84, and 0.74 respectively.

The mean urinary excretion of terbutaline was measured at 2-h intervals during steady

state over a period of 12 h after the drug intake. The amount of terbutaline excreted over 12 h was 192.2 µg with ordinary tablets and 146.7 µg with SR tablets. Since the urinary excretion reflects the plasma concentration, the data for the urine indicate that the mean plasma concentration during the day with SR tablets was 76.3 % of the corresponding plasma concentration with ordinary tablets. The renal clearance was 2.5 ml/min./kg b.w. with both preparations and was calculated by using the mean values.

Peripheral effects

The mean systolic blood pressure remained almost constant (115–117 mmHg) at a normal level following the intake of SR tablets. Following the intake of ordinary tablets, the mean systolic blood pressure decreased with the lowest value at 6 h (109.5 mmHg). The diastolic blood pressure showed only small fluctuations.

The heart rate increased significantly ($P < 0.01$) – i.e., a mean increase of 10 beats/min, – within 2 hours of the morning dose of both preparations.

Side effects

Three patients spontaneously noted side effects in their diary cards: one during treatment with SR tablets (headache), one during treatment with ordinary tablets (tremor) and one during both periods (chest pain with SR tablets and uneasiness, restlessness and headache with ordinary tablets). When measured at the clinic, the tremor increased during the first 2 h after the morning dose of both preparations (Fig. 1d), and then decreased slowly. No significant differences in tremor were found between the control group of healthy children and the children on treatment. However, the tremor curve showed smaller fluctuations over the day in the control group. Five of the patients experienced no side effects. Tremor or restlessness were reported by four patients during the period with ordinary tablets and by one patient during both treatments.

DISCUSSION

The mean morning plasma terbutaline concentration was higher with terbutaline SR tablets than with ordinary ones. The mean evening plasma terbutaline concentration was almost identical during the two treatment periods. During the SR tablet period, the mean morning value was higher than the mean evening value. This may have been due to a prolonged absorption of terbutaline during the night (7). With an SR preparation of theophylline higher plasma concentrations of theophylline in the morning have been demonstrated (8).

One might expect that higher morning plasma concentrations would lead to increased morning values of the lung parameters studied (FEV_{10} , PEF). In fact, higher morning PEF values have been found in both adults (2) and children (1) during treatment with SR tablets, but pharmacokinetic data are not reported. However, in the present study, the mean morning values of PEF and FEV_{10} were not increased, despite the higher mean morning plasma level. This lack of improvement in lung functions may be due to the great interindividual variations in the small group of patients studied.

Good correlations between the mean plasma concentrations and the mean values of PEF, FEV_{10} , and tremor for both preparations were demonstrated. Thus, a mean increase in the plasma terbutaline concentration from 0 to 4 ng/ml gave a mean improvement of 20% in the lung function value; the mean tremor relationship between the plasma terbutaline concentration and FEV_{10} and PEF has been demonstrated in asthmatic children by Lönnnerholm et al. (6). They also found great interindividual variations in the degree of bronchodilation at the same plasma level.

The smoother plasma terbutaline profile which was observed during treatment with SR tablets should reduce the frequency and severity of side effects. In the present study, however, the specific side effects – tremor (subjective/objective) and restlessness/uneasiness – were of a minor nature during both treatments.

The weights of children participating in the study ranged from 21 to 45 kg. Since they all

received the same amount of terbutaline sulphate, the individual dose of the drug varied widely – i.e., within an approximately two-fold range – both for ordinary tablets and for SR tablets. However, the side effects were almost identical, whether the children received a higher or a lower dose of terbutaline.

Our study confirms previous reports that children have a slightly higher clearance of terbutaline than adult men (3). Thus, they eliminate terbutaline somewhat faster than the adults. This may mean that some young children require a dose more frequently than every 12 h.

In conclusion, the clinical efficacy of terbutaline in an SR tablet (5 mg b.i.d.) is comparable to that of ordinary tablets (2.5 mg t.i.d.). However, the higher morning plasma concentration and the smoother plasma terbutaline profile with SR tablets may keep the patients on a clinically more stable level. Moreover, the need to take the SR tablets less frequently should benefit the patients.

REFERENCES

1. Croner, S., Gustafsson, M., Kjellman, M. & Säweda, L.: Terbutaline slow-release tablets in children with asthma – a comparison with ordinary maintenance therapy. (accepted for publication in *Allergy*).
2. Eriksson, N. E., Haglund, K. & Ljungholm, K.: A comparison of sustained-release terbutaline and ordinary terbutaline in bronchial asthma. *Br. J. Dis. Chest* 76, 202–204, 1982.
3. Hultquist, C., Lindberg, C., Nyberg, L., Kjellman, B. & Wetterell, G.: Kinetics of terbutaline in asthmatic children. *Eur. J. Respir. Dis.* 65, Suppl. 134, 195–203, 1984.
4. Jacobsson, S. E., Jönsson, S., Lindberg, C. & Svensson L. Å.: Determination of terbutaline in plasma by gas chromatography chemical ionization mass spectrometry. *Biomed. Mass Spectrom.* 7, 265–268, 1980.
5. Lönnnerholm, G., Foucard, T. & Lindström B.: Combined treatment with sustained-release theophylline and beta₂-adrenoceptor-stimulating agents in chronic childhood asthma. *Br. Med. J.* 282, 1029–1031, 1981.
6. Lönnnerholm, G., Foucard, T. & Lindström B.: Dose plasma concentration, and effect of oral terbutaline in long-term treatment of childhood asthma. *J. Allergy Clin. Immunol.* 73, 508–505, 1984.
7. Nyberg, L. & Kennedy, B. M.: Pharmacokinetics of terbutaline given in slow-release tablets. *Eur. J. Respir. Dis.* 65, Suppl. 134, 119–139, 1984.
8. Simons, F. E. R., Luciak, G. H. & Simons, K. J.: Sustained-release theophylline for treatment of asthma in

- preschool children. *Am. J. Dis. Child.* 136, 790-793, 1982.
9. Tabachnik, E., et al.: Sustained-release theophylline: A significant advance in the treatment of childhood asthma. *J. Pediatr.* 100:489-492, 1982.
10. Taudorf, E., Bundgaard, A., Fagerström, P. O., Weeke, E. & Weeke B.: Terbutaline depot tablets in asthma. A clinical evaluation. *Allergy* 36:9, 495-500, 1981.

Address:

Bengt Kjellman, M.D.
Dept. of Pediatrics
Kärnsjukhuset
S-514 85 Skövde
Sweden

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.