

Nocturnal asthma: slow-release terbutaline versus slow-release theophylline therapy

M. Heins*, L. Kurtin*, M. Oellerich*, R. Maes**, G.W. Sybrecht***

Nocturnal asthma: slow-release terbutaline versus slow-release theophylline therapy. M. Heins, L. Kurtin, M. Oellerich, R. Maes, G.W. Sybrecht.

ABSTRACT: In a double-blind cross-over study, the effects of slow release (S-R) terbutaline tablets (b.i.d. 0.25 mg/kg per day) and S-R theophylline (5.31 mg/kg morning and 10.62 mg/kg evening) were compared in eleven patients with nocturnal asthma. On day seven of each treatment period, drug serum concentrations and peak expiratory flow (PEF) were measured every 2h over a 24-h period. During daytime, terbutaline concentrations ranged from 1.6-14.1 (median 4.5) $\mu\text{g/l}$ and during the night from 2.1-18.7 (median 4.9) $\mu\text{g/l}$. Theophylline concentrations ranged from 3.9-24.3 (median 11.5) mg/l during the day and from 3.3-20.9 (median 10.4) mg/l at night. Nocturnal wheezing occurred during theophylline treatment in four patients 7 times and during terbutaline treatment in six patients 22 times. Daytime PEF values were 472 ± 161 l/min during theophylline therapy versus 445 ± 169 l/min during terbutaline therapy ($p < 0.05$). In the night and early morning there was no significant difference between PEF values with the two treatment forms. During theophylline treatment, fewer inhalations of β_2 -sympathomimetics were used, and there were fewer side effects. One patient experienced severe asthmatic attacks during the terbutaline treatment period. The patients preferred theophylline for the treatment of nocturnal asthma.

Eur Respir J. 1988, 1, 306-310.

* Institut für Klinische Chemie, Medizinische Hochschule Hannover, Federal Republic of Germany.

** Centre for Human Toxicology, State University, Utrecht, The Netherlands.

*** Medizinische Universitätsklinik Homburg (Saar), Abteilung Pneumologie, Federal Republic of Germany.

Keywords: Nocturnal asthma; terbutaline; theophylline.

Received: February 10, 1987; accepted after revision: October 29, 1987.

Patients with nocturnal asthma have been successfully treated with slow-release theophylline preparations provided adequate serum theophylline concentrations were achieved during the critical period in the early morning [1-5]. Slow-release terbutaline preparations have been recommended for maintenance therapy of airway obstruction [6] and recently for treatment of nocturnal asthma [7-12]. The purpose of the present study was to compare a non-specifically individualized treatment form of S-R theophylline, administered in unequally divided doses, to that of an oral S-R terbutaline regimen in patients with nocturnal asthma.

Patients and methods

Patients

Eleven patients with nocturnal asthma (*i.e.* reversible airflow obstruction) aged 18-58 yrs (mean 39 yr) gave informed consent to voluntary participation in the study (table 1). Patient selection and physiological evaluation of functional status were based on routine lung function studies, including static and dynamic lung volumes. Most patients had been on long-term theophylline treatment for at least eight months before entering the study. During the study patients were allowed to use their standard medication, which included inhaled and/or oral steroids, as well as additional inhalations of β_2 -sympathomimetics.

Characteristics of the patient's lung function are included in table 1.

Study design

The study was performed as a double-blind, randomized cross-over trial during two consecutive weeks. Combinations of active and matched placebo were used so that the patients took the same type and number of tablets after breakfast (6.00-9.00 a.m.) and at 9.00 p.m.. This timing was chosen to mimic the general practice of drug intake in ambulant patients. During the run-in period patients stayed on their previous drug regimen. The treatment weeks consisted of:

1) The administered doses ranged from 386-900 mg theophylline per day (Euphyllin CR (c) capsules, Byk Gulden, F.R.G., 150, 250, 350 mg aminophylline = 129, 214, 300 mg anhydrous theophylline per tablet) administered in unequally divided doses (1/3 in the morning, 2/3 in the evening). The dosages were selected according to the clinical condition of the patients and in most cases the previous dose regimen could be continued.

2) 15 mg terbutaline (Bricanyl Durites (c) Astra, Sweden, 7.5 mg per tablet) twice daily as recommended by the manufacturer. During the whole test period patients were asked to measure peak expiratory flow (PEF) with a mini Wright peak-flow meter. At home the PEF recordings were only made during

Table 1. - Anthropometric and clinical data

Patient	Size cm	Sex	Age	Weight kg	Medication	FEV ₁ ¹ %	PEF ² l/min		PEF ³ l/min		Side effects		
							A	B ⁴	P	A	B ⁴	A	B
1	168	F	47	54	OS,IB	74	300	260	317	301	279	-	MD,T
2	153	F	56	56	IS,IB,AH,TQ	53	340	295	357	352	323	-	D,T
3	155	F	49	63	OS,IS,IB	55	169	158	182	182	185	-	D
4	175	M	35	76	OS,IB,IDC	71	599	589	550	569	568	-	D
5	161	F	58	59	IB,OS	38	381	420	435	425	400	N,T	D
6	186	F	41	80	IB	82	738	730	727	736	720	-	T
7*	167	F	24	58	IDC,ML	72	453	445	443	469	409	-	T
8	163	F	18	50	IB	80	509	433	425	491	432	-	H,T,N
9*	179	M	23	60	IB	72	619	617	588	601	613	-	-
10	162	F	22	55	IB,IS	68	421	420	412	436	422	-	-
11*	168	M	51	65	IB	42	(220)	-	(268)	(286)	-	D	AA
\bar{x} :							453	437	444	456	435		
SD:							169	174	151	158	161		

AA: asthmatic attack; AH: oral antihistaminics; D: dyspnoea; H: heart palpitation; IB: inhaled β_2 -mimetics; IDC: inhaled disodium cromoglycate; IS: inhaled steroids; MD: morning dyspnoea; ML: mucolytics; N: nausea; OS: oral steroids; SD: standard deviation; T: tremor; TQ: tranquillizer. 1) values taken from patients documents; 2) mean values of hospital recordings over a period of 24 h; 3) mean values of home recordings during the day; 4) treatment periods; A: theophylline; B: terbutaline; P: prephase; s: smoker; *: drop out, results excluded.

the daytime every 4h from 8 a.m.–8 p.m. (best of 3 blows). Additional inhaled β_2 -sympathomimetics, symptoms and side-effects were documented in a diary throughout the study period. Patients were told to continue their usual diet and activity.

On the seventh day of each week the patients stayed in hospital for 24 hs. Regular hospital meals were given at 8 a.m., 12 a.m., 2.30 p.m. and 6 p.m. The last dose of either theophylline or terbutaline was taken by the patients at 9 p.m. Between 10 p.m. and 8 a.m. the lights were switched off and the patients stayed in bed. Blood samples were obtained from an indwelling venous catheter or by venous puncture at 8 a.m. and every 2 h over a 24-h period. Peak-flow rates were measured immediately after each blood sampling with the best of three readings recorded. During the night (10 p.m.–5 a.m.) and in the early morning (5 a.m.–8 a.m.) samples were taken, disturbing sleep as little as possible. The patients were then woken and sat up for measurement of PEF. According to the evidence presented by HETZEL and CLARK [13] any relevant influence of our experimental conditions on nocturnal asthma is unlikely.

Determination of drugs

Serum was stored for terbutaline determination at -30°C and for theophylline determination at $+4^\circ\text{C}$. Serum theophylline concentrations were measured within ten days by fluorescence polarisation immunoassay (theophylline reagent pack 2, Abbott Laboratories, North Chicago, USA). Terbutaline serum concentrations were measured using gas chromatography-mass spectrometry according to LEFERINK *et al.* [14].

Statistical analysis

Results are expressed as means \pm standard deviation (SD). The paired t-test was used to compare mean levels of PEF time curves. To reveal possible differences in PEF time courses due to treatment effects, a multivariate analysis of variance (MANOVA) for a repeated measure design with two within factors was used [15]. If the whole 24-h test period was analysed with this programme, only every second PEF value of each course was used. A single-sided Wilcoxon test (Matched-pairs-signed-ranks-test) was used to compare the incidence of asthmatic attacks.

Results

Serum drug concentrations

The time course of theophylline and terbutaline serum concentrations, during steady state conditions recorded in hospital, is shown in figures 1 and 2. Peak theophylline serum concentrations ranged from 5.6–24.3 mg/l in the daytime (8 a.m.–8 p.m.), from 7.6–20.9 mg/l at night (10 p.m.–5 a.m.) and from 7.3–20.0 mg/l in the early morning (5 a.m.–8 a.m.). Trough theophylline serum concentrations were between 3.9–11.7 mg/l during daytime, between 3.3–11.0 mg/l at night and between 7.2–18.2 mg/l in the early morning. Patient 4 took the evening dose delayed at 12.00 p.m. The expected increase of theophylline serum concentration was not observed however. In patient 3 high theophylline serum concentrations of 24.3 mg/l at 8 a.m. and of 20.9 mg/l at 2 a.m. were not associated with any subjective side effects.

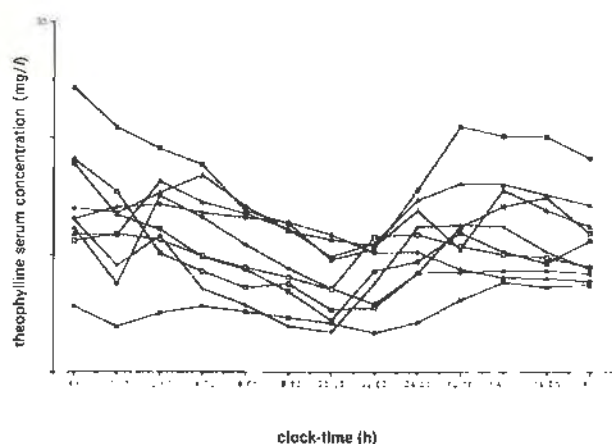


Fig. 1. Serum theophylline concentrations (mg/l) for an unequally divided, twice-daily theophylline regimen in ten patients over a 24-h period. Patient 1 (-□-), 2(-●-), 3(-■-), 4(-○-), 5(-■-), 6(-□-), 7(-▲-), 8(-△-), 9(-▶-◀-), 10(+).

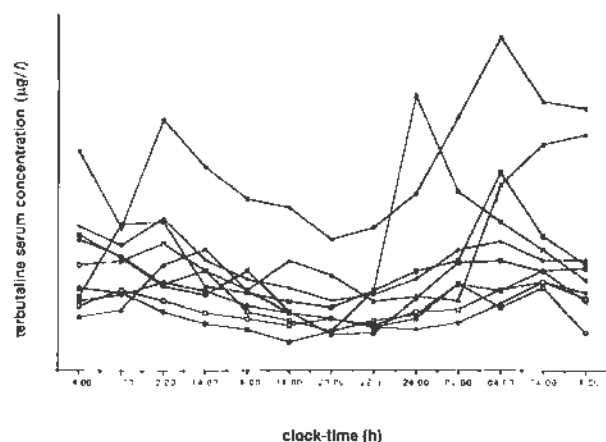


Fig. 2. Serum terbutaline concentrations (µg/l) for a twice-daily terbutaline regimen in ten patients over a 24-h period. Patient 1 (-□-), 2(-●-), 3(-■-), 4(-○-), 5(-■-), 6(-□-), 7(-▲-), 8(-△-), 9(-▶-◀-), 10(+).

Serum theophylline concentrations of patient 9 were below the recommended therapeutic range of 8–20 mg/l [16, 17] during the whole test period. In all of the other patients theophylline serum concentrations were mainly within the therapeutic range during the night.

Peak terbutaline serum concentrations ranged from 4.5–14.1 µg/l in the daytime, from 4.5–18.7 µg/l during the night and between 4.6–15.1 µg/l in the early morning. Trough terbutaline serum concentrations were between 1.6–7.3 µg/l during daytime, between 2.1–8.0 µg/l at night and from 2.1–14.7 µg/l in the early morning. Patients 8 and 9 took the evening dose delayed at 10.05 p.m.

Pulmonary function

Mean values of averaged daytime PEF obtained from ten patients during theophylline treatment showed somewhat higher values than during terbutaline treatment (472 ± 161 l/min versus 445 ± 169 l/min,

$p < 0.05$). Although statistically significant, clinically this difference seems not to be relevant. Mean values of averaged night-time and early morning PEF showed no significant differences between both treatment periods (night-time: 435 ± 181 l/min (theophylline), 424 ± 58 l/min (terbutaline), $p > 0.05$; early morning: 434 ± 175 l/min (theophylline), 437 ± 187 l/min (terbutaline), $p > 0.05$). During the whole 24-h test period mean values of averaged PEF (435 ± 169 l/min versus 437 ± 174 l/min, $p > 0.05$) were not statistically different between both treatment forms (table 1). In addition a multivariate analysis of variance was performed with these data. No significant differences could be detected between the terbutaline and theophylline treatment period during day, night, early morning and the whole 24-h test period (fig. 3). Mean PEF values obtained during home recording periods, which did not include the night-time, are shown in table 1. There was no significant difference between the PEF values during the two treatment periods and the pretreatment period.

A difference was found in the additional use of β_2 -sympathomimetics. During the seven days of terbutaline treatment eight patients used β_2 -sympathomimetics 79 times by inhalation (fig. 4) because of symptoms, whereas five patients used β_2 -sympathomimetics 27 times during the theophylline treatment period ($p > 0.05$). Daytime wheezing occurred 37 times in seven patients under terbutaline therapy and 18 times in four patients under theophylline treatment ($p > 0.05$). Nocturnal wheezing (10 p.m. to 5 a.m.) was found 22 times in six patients under terbutaline treatment and 7 times in four patients under theophylline therapy. Early morning dyspnoea (5 a.m.–8 a.m.) occurred 20 times in six patients during the terbutaline treatment period but only 4 times in three patients under theophylline therapy ($p < 0.05$).

During the hospital stay under terbutaline treatment, six patients used inhaled β_2 -sympathomimet-

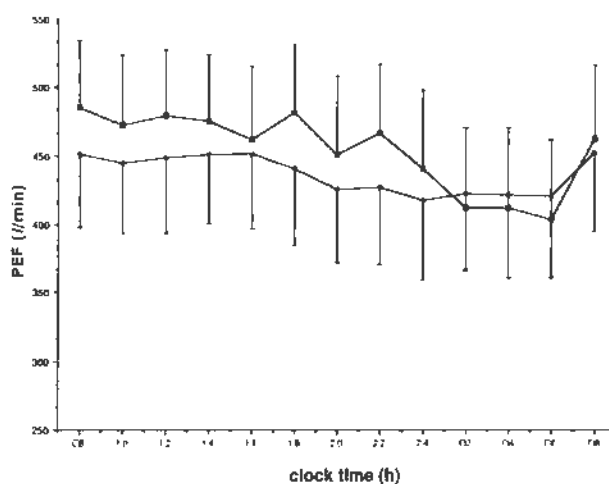


Fig. 3. Averaged peak expiratory flow rates (l/min) for a terbutaline (●-●-) and an unequally-divided, twice-daily theophylline (□-□-) regimen in ten patients over a 24-h period.

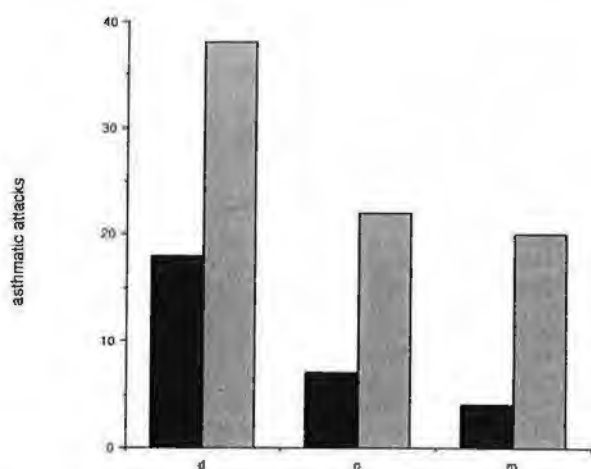


Fig. 4. Use of aerosol β_2 -mimetics because of asthmatic attacks during terbutaline (light shaded bars) and an unequally-divided theophylline (dark shaded bars) regimen in ten patients with nocturnal asthma. Daytime (d): 8.00–22.00 h; night (n): 22.00–5.00 h; early-morning (m): 5.00–8.00 h.

ics 18 times, whereas only four patients complained of nine asthmatic attacks during the corresponding theophylline treatment period ($p > 0.05$). Daytime wheezing occurred 8 times in five patients under terbutaline therapy and 16 times in three patients under theophylline treatment ($p > 0.05$). Nocturnal wheezing (10 p.m.–5 a.m.) was found 6 times in three patients under terbutaline treatment and 2 times in one patient under theophylline therapy ($p > 0.05$). Early morning dyspnoea (5 a.m.–8 a.m.) occurred 4 times in three patients during the terbutaline treatment period but only once in one patient under theophylline therapy ($p > 0.05$).

During the week of terbutaline treatment eight patients self-administered 61 additional inhalations of β_2 -sympathomimetics at home. During the theophylline treatment week four patients inhaled 20 times at home ($p > 0.05$) (fig. 4). Daytime wheezing occurred 29 times in six patients under terbutaline therapy and 12 times in two patients under theophylline treatment ($p > 0.05$). A significant difference was found with the home recorded data at night (10 p.m.–5 a.m.). Six patients used inhaled β_2 -sympathomimetics 16 times, whereas only three patients complained of five asthmatic attacks during the corresponding theophylline treatment period ($p < 0.05$). Early morning dyspnoea (5 a.m.–8 a.m.) occurred 5 times in sixteen patients during the terbutaline treatment period but only 3 times in three patients under theophylline therapy ($p > 0.05$).

In the tested group of patients during the theophylline treatment period, β_2 -sympathomimetics were used 3 times per day at home and 9 times per day in the hospital. With terbutaline, however, β_2 -sympathomimetics were used 10 times at home and in the hospital 18 times per day. The difference in the frequency of β_2 -sympathomimetics use was not statistically significant ($p > 0.05$) between the two treatment periods with theophylline and terbutaline.

Side-effects

During the terbutaline treatment five patients complained of tremor of the hands and two patients had palpitations, which were not so intense during the time of sleep. Theophylline therapy caused nausea in one patient and in another patient a tendency for diaphoresis.

At the end of both treatment periods seven patients preferred theophylline therapy, due to superiority in preventing night-time wheezing (fig. 4). Patients 9 and 10 could not differentiate between the two treatment forms. Patient 5 preferred terbutaline as he experienced nausea during the theophylline treatment period. One patient (No. 11) dropped out of the study as he developed severe asthmatic attacks during the first days of terbutaline treatment.

Discussion

Nocturnal asthma is common in patients with marked bronchial hyperreactivity. Subjective perception of this phenomenon, which has been ascribed to an increased amplitude of circadian PEF [2, 18–20], is very different interindividually. Some patients have only very limited ability to assess their own airway function and, therefore, using only subjective complaints the need for therapy is often underestimated. In the present study we evaluated the therapeutic efficacy not only by asking patients about symptoms, but also by measuring PEF rates during the treatment periods.

With regard to asthmatic symptoms the efficacy of suppressing nocturnal attacks was greater during the theophylline treatment period (fig. 4).

In patients 1, 2, 4, 5, 7 and 10 theophylline serum concentrations were in the middle and/or lower part of the 'therapeutic range' (8–20 mg/l) [16] (fig. 1). In these patients a further increase of PEF values during the night and early morning might be possible by administration of higher evening doses.

In patient 3 theophylline serum concentrations were in the upper part of the therapeutic range and above. In patients 6, 8 and 9 the medication provided seemed to be appropriate, since these patients reached the predicted PEF values of healthy people [21]. At home, however, one of these patients (No. 9) experienced a single asthmatic attack.

Because of occasional observations of a variety of side-effects, including palpitations [11, 22, 23], headache [11, 22, 24], restlessness [23], tremor [10], sweating [11], dizziness and tiredness [22] a therapeutic range for terbutaline is difficult to establish. In patients 2, 5, 7 and 9 serum terbutaline concentrations in excess of 11 $\mu\text{g/l}$ were determined (fig. 2). These values are higher than those reported by KOETER *et al.* [10] with a comparable daily dosage and the incidence of side-effects may well be related to this finding. It indicates that a further increase of oral terbutaline dosage is not possible. Because of the observed decrease in PEF during daytime, a reduced terbutaline morning dose would not have been

suitable. With respect to the high incidence of side effects in the presence of terbutaline it has to be considered, however, that this drug had to be given in a relatively higher dosage during the daytime compared to theophylline.

We conclude that oral terbutaline was less effective than the chosen S-R theophylline regimen. Appropriate timing of administration and appropriate dosage of theophylline, which both need careful individual adjustment, are necessary to yield acceptable results. Further progress in the treatment of nocturnal asthma, both in terms of comfort for the patient as well as the ease and safety of application might be expected from the development of longer-acting inhaled β_2 -sympathomimetics.

Acknowledgement: We wish to thank Dr. U. Ranft Zentrum für Biometrie, Medizinische Informatik und Medizintechnik der Medizinischen Hochschule Hannover for affiliation in statistical analysis of the data.

References

- Barnes PJ, Greening AP, Neville L, Timmers J. - Single-dose slow-release aminophylline at night prevents nocturnal asthma. *Lancet*, 1982, 1, 299-301.
- Neuenkirchen H, Wilkens JH, Oellerich M, Sybrecht GW. - Nocturnal asthma: Effect of a once per evening dose of sustained release theophylline. *Eur J Respir Dis*, 1985, 66, 196-204.
- Turner-Warwick M. - On observing patterns of airflow obstruction in chronic asthma. *Br J Dis Chest*, 1977, 71, 73-86.
- Welsh, Patrick W. - Timing of once-a-day theophylline dose to match peak blood level with diurnal variation in severity of asthma. *Am J Med*, 1986, 80, 1098-1102.
- Wettengel R. - Klinische Aspekte des Asthma und einige Probleme bei der Behandlung mit Theophyllin. In: Theophyllin, Optimierung der Therapie in Klinik und Praxis. M. Oellerich, G.W. Sybrecht, R. Wettengel, eds, I.M.P. Kommunikationsgesellschaft mbH, 1983, 115-126.
- Vandewalker ML, Kray KT, Weber RW, Nelson HS. - Addition of terbutaline to optimal theophylline therapy. *Chest*, 1986, 90/2, 198-203.
- Bengtsson B. - Plasma concentration and side-effects of terbutaline. *Eur J Respir Dis*, 1984, 65(suppl. 134), 231-235.
- Berg VDW, Lefterink JG, Maes RAA, Fokkens JK, Kreukniet J, Bruynzeel PLB. - The effects of oral and subcutaneous administration of terbutaline in asthmatic patients. *Eur J Respir Dis*, 1984, 65(suppl. 134), 181-193.
- Billing B, Dahlqvist R, Garle M, Hörnblad Y, Ripe E. - Separate and combined use of terbutaline and theophylline in asthmatics. *Eur J Respir Dis*, 1982, 63, 399-409.
- Koeter GH, Postma DS, Meurs H. - Effect of oral slow-release terbutaline on early morning dyspnoea. *Eur J Pharmacol*, 1985, 28, 159-162.
- Legge JS, Gaddie J, Palmer KNV. - Comparison of two oral selective β_2 -adrenergic stimulant drugs in bronchial asthma. *Brit Med J*, 1971, 1, 637-639.
- Ripe E, Hörnblad Y, Tegner K. - Oral administration of terbutaline in asthmatic patients. *Eur J Respir Dis*, 1984, 65(suppl. 134), 171-179.
- Hetzel MR, Clark TJH. - Does sleep cause nocturnal asthma? *Thorax*, 1979, 34, 749-754.
- Lefterink JG, Wagemaker-Engels I, Maes RAA. - Quantitative analysis of terbutaline in serum and urine at therapeutic levels using gas chromatography-mass spectrometry. *J Chromatog*, 1977, 143, 299-305.
- SPSSX users guide. 2nd edition, 1986, Mc-Graw, New York, Program version 2.1.
- Jusko WJ, Gardener MJ. - Factors affecting theophylline clearances: Age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates and ethanol. *J Pharm Sci*, 1979, 68, 1358-1366.
- Sybrecht GW, Oellerich M. - Therapie mit Theophyllin: Charakteristik verschiedener Theophyllin-Präparate, Indikation und individuelle Dosierung. In: Theophyllin, Optimierung der Therapie in Klinik und Praxis. M. Oellerich, G.W. Sybrecht, R. Wettengel, eds, I.M.P. Kommunikationsgesellschaft mbH, 1983, 127-139.
- Hetzel MR, Clark TJH. - Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. *Thorax*, 1980, 35, 732-738.
- Hetzel MR. - The pulmonary clock. *Thorax*, 1981, 36, 431-436.
- Rubinfeld AR, Paine MCF. - Perception of asthma. *Lancet*, 1976, 1, 882-884.
- Gregg I, Nunn AI. - Peak expiratory flow in normal subjects. *Brit Med J*, 1973, 3, 282.
- Fagerberg E, Tegner B. - Effects of oral terbutaline in asthmatic patients. A dose response study. *Scand J Respir Dis*, 1972, 53, 3-9.
- Thiede D. - Untersuchungen zur broncholytischen Wirkung von Terbutaline (Bricanyl (c)) unter Berücksichtigung der Kreislaufreaktion. *Med Klin*, 1973, 68, 16-20.
- Sly RM, Badiei B, Faciame J. - Comparison of subcutaneous terbutaline with epinephrine in the treatment of asthmatic children. *J Allergy Clin Immunol*, 1977, 59, 128-135.

RÉSUMÉ: Nous avons comparé, chez 11 patients atteints d'asthme nocturne, au cours d'un essai en double aveugle avec permutation croisée, les effets des comprimés de terbutaline à libération lente (2 fois par jour, 25 mg par kilo et par jour) et ceux de la théophylline à libération lente (dose matinale de 5.31 mg par kilo et dose vespérale de 10.62 mg par kilo). Au jour 7 de chaque période de traitement, les concentrations sériques des médicaments et le débit de pointe ont été mesurés toutes les 2 heures pendant 24h. Les concentrations de terbutaline atteignaient, pendant la journée de 1.6 à 14.1 (valeur médiane 4.5) $\mu\text{g/l}$, et nuit de 2.1 à 18.7 (valeur médiane 4.9) $\mu\text{g/l}$. Les concentrations de théophylline s'élevaient entre 3.9 et 24.3 (valeur médiane 11.5) mg/l pendant le jour, et de 3.3 à 20.9 (valeur médiane 10.4) mg/l pendant la nuit. Des sifflements nocturnes ont existé au cours du traitement à la théophylline chez 4 patients à 7 reprises, et au cours du traitement à la terbutaline chez 6 patients à 22 reprises. Les valeurs du débit de pointe le jour étaient de 472 ± 161 l/minute au cours du traitement à la théophylline, contre 445 ± 169 l/minute au cours du traitement à la terbutaline. On n'a pas noté de différence significative la nuit et au petit matin entre les valeurs de débit de pointe obtenues avec les deux modalités thérapeutiques. Au cours du traitement à la théophylline, on a utilisé moins d'inhalations de bêta 2 sympathicomimétiques, et les effets collatéraux ont été moins nombreux. Un patient a eu des crises asthmatiques sévères au cours de la période de traitement à la terbutaline. La préférence des patients est allée à la théophylline pour le traitement de l'asthme nocturne.