

Comparison of a Sustained-Release Preparation (Theo-Dur®) with a Conventional Preparation (Nuelin®) in the Treatment of Chronic Asthma

TARI HAAHTELA, VESA VILKKA and SØREN KULSTAD

Tiuru Hospital, Dept. of Pulmonary Diseases, Tiuruniemi, Finland, and Medical Department, AB Draco*, Lund, Sweden

In a double-blind, cross-over trial comprising 19 adult asthmatic patients a sustained-release preparation of theophylline (Theo-Dur®), given twice daily, was compared with a conventional fast-release preparation (Nuelin®), given three times daily. The theophylline doses were individually titrated to give plasma concentrations in the lower region of the therapeutic interval. The sustained-release preparation gave higher morning theophylline concentrations than the fast-release preparation (9.2 vs 5.9 mg/l). This resulted in somewhat higher morning peak flow values during Theo-Dur treatment. However, the difference in asthma symptoms was not significant and the patients showed no preference for either preparation. We conclude that the advantage of a sustained-release preparation over a conventional fast-release theophylline preparation is the lower dosing frequency rather than the better clinical effect in patients who suffer from chronic asthma, but whose disease is in a relatively stable phase.

Key words: asthma; drug therapy, combination; sustained-release preparation; theophylline.

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The combination of theophylline and β -adrenoceptor agonists is widely used in maintenance treatment of patients with chronic airway obstruction. A good effect has been achieved by adding sustained-release theophylline to β -adrenoceptor therapy (2).

It has been demonstrated that patient compliance is less than optimal when a drug has to be given several times a day, and better compliance has been reported with 12-h dosing intervals (4). This dosing schedule seems to be preferred at least by pediatric patients (3).

The present study investigates if there also are differences in clinical effect between a

properly designed (1) sustained-release tablet (Theo-Dur®), given twice daily, and fast-release microcrystalline theophylline (Nuelin®), given three times daily, in combination with inhaled β -adrenoceptor agonists, when the theophylline doses are individually titrated.

MATERIAL AND METHODS

Ten women and nine men with a mean age of 42 years (range 31-72) completed the trial. A further two patients entered the trial but later left it because of a deterioration in their asthma, one during the first few days (Theo-

* Subsidiary to AB Astra, Sweden.

Dur period) and the other after the first 2 weeks of treatment (Nuelin period). All patients had moderate to severe chronic bronchial asthma, with a mean duration of 8 years (range 1–36). Only patients who had a strong tendency to early morning obstruction, but whose disease was in a rather stable phase, were included.

All patients used salbutamol aerosol, except one who used nebulized fenoterol. Fifteen patients used beclomethasone aerosol, and six of them were also on oral steroids, mostly on alternate days. All but one had previously taken theophylline preparations, but these were discontinued 2 days before entry in the trial.

The study was designed as a double-blind, cross-over trial comprising two fortnightly periods. Treatment periods were randomized and each patient received either placebo sustained-release tablets with active plain tablets or active sustained-release tablets with placebo plain tablet (double-dummy technique). During a run-in period of 4 days before the first treatment period, the dose of sustained-release theophylline was titrated to give a plasma theophylline concentration at steady state of 10–15 mg/l 3–5 h after the morning dose of the sustained-release preparation. The fast-release tablets were administered three times daily at 8 a.m., 2 p.m. and 8 p.m., and the sustained-release tablets twice daily at 8 a.m. and 8 p.m., with placebo administration at 2 p.m.

During the study the patients recorded symptoms (dyspnoea/wheezing, sputum, and cough) on a scale ranging from 0 to 5, number of inhalations of β -adrenoceptor agonists, peak ex-

piratory flow in the morning and evening before the theophylline dose, and side effects. PEF was measured with a Mini-Wright peak flow meter and the highest values of three measurements was used.

At the end of each treatment period (day 14), blood samples were obtained at 8 a.m. (before tablet intake), 10 a.m. and 2 p.m. (before tablet intake). Plasma concentrations of theophylline were determined by enzyme immunoassay technique (EMIT®).

Standard computer programs were used for statistical calculations, and the Student's two-sided paired *t* test was used for testing significance. Only results from days 4–13 in each period were used, as the patients were not considered to be in a steady state until day 4. Computer-simulated plasma concentration curves were obtained and based on the assumption of a first-order absorption of 0.18 h⁻¹ for the sustained-release and 1.4 h⁻¹ for the fast-release tablet (1), patient's weight 72 kg, distribution volume 0.5 l/kg, half-life 8.7 h, and complete bioavailability.

RESULTS

The mean daily dose of theophylline was 726 mg for Theo-Dur and 681 for Nuelin. Nine patients required Theo-Dur 300 mg twice daily (Nuelin 187.5 mg three times daily), nine patients Theo-Dur 400 mg twice daily (Nuelin 250 mg three times daily) and one patient Theo-Dur 600 mg twice daily (Nuelin 375 mg three times daily). This resulted in the mean plasma concentrations shown in Table 1, which

Table 1
Mean plasma theophylline concentrations (mg/l) on day 14 in each period

	Theo-Dur (SD)	Nuelin (SD)	Intra-individual difference (SEM)	<i>P</i>
At 8 a.m. (before tablet intake)	9.2 (2.6)	5.9 (3.8)	3.33 (0.83)	<i>P</i> < 0.001
At 10 a.m.	10.0 (3.1)	10.3 (3.4)	-0.26 (0.54)	NS ¹
At 2 p.m. (before tablet intake)	11.8 (2.4)	8.1 (2.6)	3.77 (0.73)	<i>P</i> < 0.001

¹ NS = not significant (*P* > 0.05).

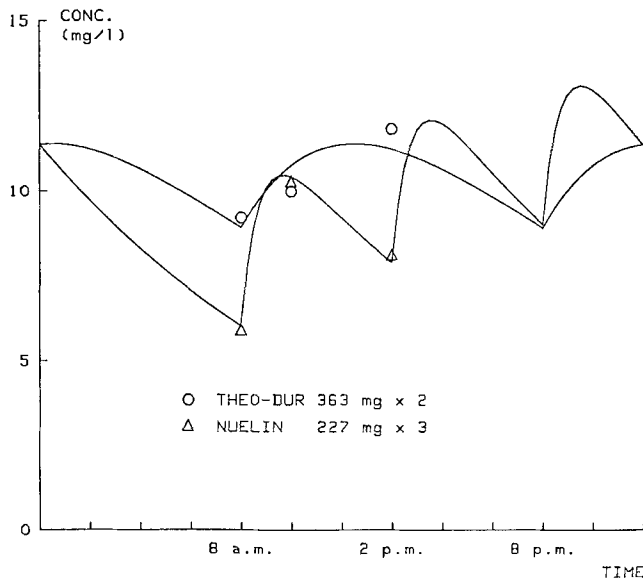


Fig. 1. Computer-simulated plasma theophylline concentration curves and observed values on day 14 in each period.

shows that significantly higher concentrations were obtained immediately before intake of the sustained-release preparation at both 8 a.m. and 2 p.m. The simulated curves in Fig. 1 correspond to a mean steady state concentration of 10.5 mg/l for the sustained-release pre-

paration and 9.9 mg/l for the fast-release preparation.

Table 2 shows the mean peak expiratory flow and symptoms during days 4–13. The PEF was somewhat higher in the morning during treatment with the sustained-release preparation

Table 2
Mean lung function and symptoms during days 4–13 in each period

	Theo-dur (SD)	Nuelin (SD)	Intra-individual difference (SEM)	<i>P</i>
PEF (l/min)				
at 8 a.m. (before tablet intake)	410 (92)	390 (91)	20.1 (8.5)	$P < 0.05$
at 8 p.m. (before tablet intake)	467 (97)	474 (100)	-5.7 (4.8)	NS ¹
Symptom score ²				
dyspnoea/wheezing	1.1 (0.9)	1.3 (0.9)	-0.25 (0.15)	NS
Sputum	0.7 (0.6)	0.8 (0.9)	-0.06 (0.10)	NS
Cough	0.8 (0.7)	0.8 (0.8)	-0.01 (0.07)	NS

¹ NS = not significant.

² 0 = No symptoms, 1 = Very few symptoms, 2 = Few symptoms, 3 = Moderate symptoms, 4 = Severe symptoms, 5 = Very severe symptoms.

($P < 0.05$), but not in the evening. The difference in dyspnoea/wheezing was not significant ($P < 0.10$), although the patients who started on Theo-Dur showed significantly higher symptom scores when they shifted to Nuelin (0.90 vs 1.39, $P < 0.05$). Those who started on Nuelin did not change when they shifted to Theo-Dur (1.28 vs 1.29).

Seven patients preferred the sustained-release treatment, five patients the fast-release treatment while seven patients showed no preference.

Only a few side effects were reported during the study. Twelve patients said that they had not experienced any side effects.

DISCUSSION

In this study, sustained-release theophylline, administered in the morning and the evening, had a slightly better clinical effect on chronic asthma than fast-release theophylline, given three times daily. The sustained-release preparation gave higher plasma theophylline concentrations in the morning, and the higher PEF probably resulted from this. Less dyspnoea/wheezing was noted during the sustained-release period, but the difference was not significant. However, those patients who started on the sustained-release preparation experienced significantly more symptoms when they shifted to the fast-release preparation.

Fagerström et al. (1) showed that it is possible to simulate plasma concentration curves from theophylline determinations, a finding that was confirmed here by the good agreement between the observed and simulated values (Fig. 1). The preparations used in this study seem to have equally good bioavailability. The slight difference in the daily dose between the preparations (6%) affects the concentrations only to a minor extent.

The symptom scores in Table 2 illustrate problems in clinical trials of asthma. Despite the fact that the patients needed regular medical treatment, the majority reported few symptoms. It seems probable that most asthma patients are used to their symptoms and do not record them unless they become moderately severe. This

leaves little room for assessing an improvement with therapy, although it is possible to detect a deterioration. This was also true of our study, in which only the group that changed from sustained-release to fast-release theophylline showed a statistically significant change in the scores for dyspnoea/wheezing.

The patients showed no preference for either preparation. Possibly the difference in the clinical effect was too small with this combination treatment to be expressed by such a preference. However, due to the use of double-dummy technique in the study, it was not possible to assess the benefit of the twice daily dosing of the sustained-release preparation.

In conclusion: in the treatment of chronic but stable asthma the sustained-release preparation gave only slightly better effect than the fast-release preparation, when the theophylline doses were properly titrated and given in combination with inhaled β -adrenoceptor agonists. The advantage of sustained-release theophylline for this group of patients is, therefore, the simpler medication with lower dosing frequency if the formulation, like the preparation in our study, maintains therapeutic plasma levels with 12-h dosing intervals.

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Address:

Tari Haahela, M.D.

Tiuru Hospital, Dept. of Pulmonary Diseases

SF-55330 Tiuruniemi

Finland