

Double-Blind Comparative Trial of Nuelin Depot and TheoDur with Adjusted Dosage in Asthmatic Adults

KJELL ERIK LANGAKER¹, KARIN OSMUNDSEN², JAN ERIK BREDESEN³
and PER KNUT M. LUNDE³

¹Heyerdahlsgt. 1, Oslo, ²Medical Department, Riker Labs, Skjetten, ³Division of Clinical Pharmacology and Toxicology, the Central Laboratory, Ullevål Hospital, Oslo, Norway

Equivalent doses of two sustained release preparations of theophylline, Nuelin Depot and TheoDur, were compared in a double blind, cross-over study. Twenty adult outpatients with COLD were given adjusted doses of the two preparations to reach a peak value of theophylline in steady state within the therapeutic range. The study consisted of two 14-day periods and airway function parameters, plasma concentrations, asthma symptoms, and side effects were recorded the last day in each period. In addition morning PEF, use of beta₂stimulant aerosol and number of nightly attacks were recorded daily. As judged from the peak-trough variation of 24.8 µmol for Nuelin Depot and 26.3 µmol/l for TheoDur as well as the $t_{\max}$ of 4.3 hours for Nuelin and 3.6 hours for TheoDur, both products produced a similar plasma profile. No statistically significant differences were found between the two preparations with respect to airway function parameters, relief of asthma symptoms, need for beta₂-stimulant aerosol or side effects. In conclusion these two sustained release preparations should be considered equivalent for practical use.

Key words: airway function; plasma concentration; sustained-release preparation; theophylline.

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The effectiveness of theophylline for the treatment of asthma is well established. Both efficacy and toxicity are closely correlated with plasma theophylline concentrations. Optimal bronchodilatation with a minimum of toxicity may be expected when the plasma theophylline concentration is maintained in the range 55–110 µmol/l when theophylline is given alone (4, 7). If combined with other antasthmatic drugs such as beta₂-sympatomimetics, the therapeutic effect of theophylline may be enhanced, and a theophylline concentration in the lower part of the therapeutic range may be sufficient in some patients, but not in others (1). The potential risk for an interaction with increasing incidence of side effects, such as tremor, palpitations and arrhythmias should also be considered. In both contexts conventional therapy with theophyl-

line may not be optimal due to the excessive fluctuations in plasma concentration that may occur, especially in patients with rapid elimination.

Sustained release preparations offer the advantage of extended dosing intervals, more stable plasma concentrations and improved patient compliance (6).

The purpose of this study was to compare two of these preparations. Nuelin Depot and TheoDur, during maintenance treatment. Plasma theophylline concentrations, airway function parameters, symptoms and side effects were recorded in patients receiving a dosage adjusted to achieve a peak theophylline concentration in steady state within the therapeutic range.

Table 1
Patient data

No. of patients	20
Females/males	9/11
Mean age	48 (20–73)
Mean reversibility	41.5 % (15–115)
Mean FEV ₁ of predicted	53.6 % (24–88)
smokers	6
Mean daily dose theophylline	10.9 mg/kg bodyweight (7.3 – 15.5)

MATERIAL AND METHODS

Patient selection

Twenty adult outpatients (nine females and 11 males) with a mean age of 48 years (range 20–73 years) were selected for the study (Table 1).

All patients had chronic obstructive lung disease, 16 patients had bronchial asthma, four patients had chronic obstructive bronchitis.

Patients included showed more than 15% increase in FEV₁ over the initial value after inhalation of two puffs of rimiterol. Every patient was previously treated with oral theophylline and the daily dose required to achieve a plasma theophylline concentration in steady state within the therapeutic range was known.

Patients with uncompensated heart insufficiency, hepatic, renal or gastrointestinal disease and pregnant women were excluded as were patients receiving allupurinol, phenobarbital, macrolide antibiotics, cimetidine or high doses of diuretics.

The patients were given verbal and written information about the study and informed about their freedom to withdraw at any time. Verbal patient consent was obtained by the clinical investigator prior to entering the study.

Medication and dosage

Nuelin Depot 250 and 350 mg tablets and TheoDur 200 and 300 mg tablets with matching placebo tablets were provided by Riker Labs. and Draco respectively. Equivalent doses of Nuelin Depot and TheoDur were given. There were three alternative doses (500, 700 or 1000

mg daily), and the dose closest to the adjusted dose required to achieve a concentration within the therapeutic range was chosen for each patient. The tablets were taken at the same time every morning and evening with a 12-hour interval.

Patients were allowed to use their pressurized beta₂-sympathomimetic aerosols when necessary. The number of puffs taken every day were recorded by the patient on a diary card. Established therapy with corticosteroids was maintained throughout the trial.

Systemic intake of other methylxanthine containing drugs or beta₂-sympathomimetics was avoided throughout the study.

Design

The trial was a two-part, cross-over study using a double-blind, double dummy technique. The patients were randomly allocated to receive either Nuelin Depot or TheoDur in the first 14 days and crossed over to receive the alternative treatment in the consecutive 14 days.

Assessment

The patients returned to the clinic on the last day of each 14-day period and the morning tablets were taken at the clinic.

A blood sample was drawn and VC, FEV₁ and PEFR were recorded before the morning dose. In 15 of the patients blood samples were drawn 2, 4 and 6 hours after the morning dose.

Symptoms like dyspnoea, cough, sputum, sleep and physical activity were evaluated on a 10-cm visual analogue scale. The patients were asked if they had experienced any side effects and the side effects were registered in the same way as the symptoms.

PEFR was measured by the patient every morning throughout the study period before tablet intake and recorded on a diary card. Besides the record of their use of beta₂-sympathomimetic aerosol, the number of nightly attacks experienced throughout the trial was noted. In order to avoid a wash-out period only the results from the last 10 days in each test period were used for statistical analysis.

Blood sampling and analysis

Venous blood samples were drawn into heparinized tubes, the plasma separated by centrifugation and stored at -20°C until the theophylline concentrations were measured. All the samples from each patient were analyzed in one set-up. Theophylline concentrations in plasma were assayed quantitatively using a High Pressure Liquid Chromatographic technique (HPLC) with reversed phase column (5). Reproducibility ($n = 20$) of the method is 2.2%.

Airway function

The same Wright Mini Peak Flow Meter was used for measurements of peak expiratory flow rate (PEFR) at the clinic and at home. Three measurements of PEFR were performed each time and the highest result was used for statistical analysis.

Vital Capacity (VC) and Forced Expiratory Volume ($\text{FEV}_{1.0}$) were measured with a Monaghan M 403 spirometer. Three measurements were performed each time and the highest value used for statistical analysis.

Statistical caluculations

A paired t-test was used for statistical significance analysis.

RESULTS

Plasma theophylline assays

The mean morning trough plasma theophylline concentrations in the two periods derived from 20 patients were $44.5\text{ }\mu\text{mol/l}$ in the Nuelin Depot period and $43.1\text{ }\mu\text{mol/l}$ in the TheoDur period. There was no significant difference between these concentrations.

Fairly similar plasma concentration profiles were found for the two preparations (Fig. 1) and no significant difference was found between the pharmacokinetic parameters derived (Table 2).

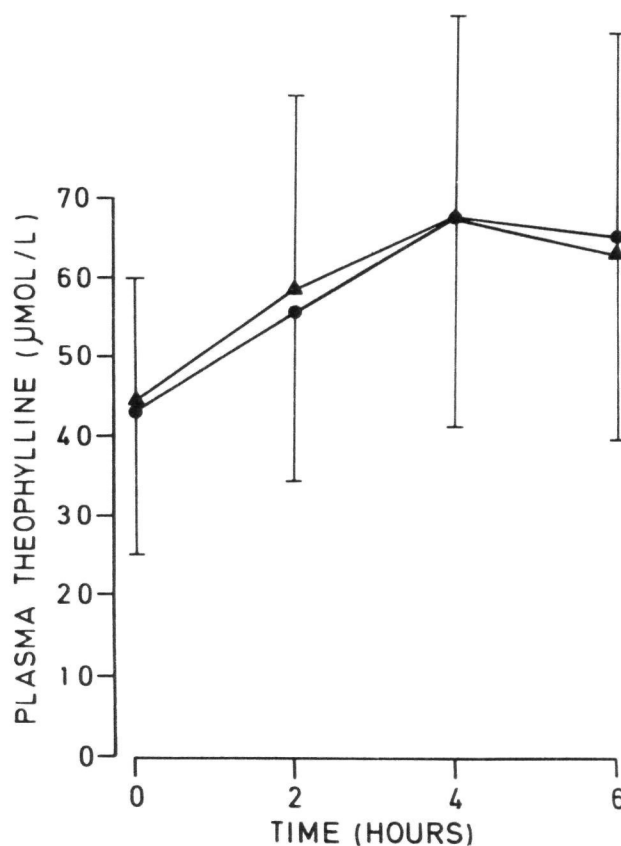


Fig. 1. Plasma theophylline concentration in 15 patients receiving Nuelin Depot ($\blacktriangle$ — $\blacktriangle$) and TheoDur ($\bullet$ — $\bullet$) in adjusted doses. Concentration measurements were performed before and 2, 4 and 6 h after the morning dose on day 14 and day 28. Vertical bars indicate SD.

Table 2

Pharmacokinetic parameters for Nuelin Depot and TheoDur ($n = 15$)

Preparation	$t_{\max}$ (hours)	$C_{\max}$ $\mu\text{mol/l}$	Peak-trough difference $\mu\text{mol/l}$
Nuelin Depot	4.3 SD ± 1.03	69.3 SD ± 24.96	24.8 SD ± 11.74
TheoDur	3.6 SD ± 1.12	70.1 SD ± 26.19	26.3 SD ± 18.26

Airway function

Three patients had to be omitted from statistical analysis of airway function parameters due to infection during the trial period. The airway function parameters are presented in Table 3. No significant differences were found between the values obtained in the Nuelin Depot period and the TheoDur period.

Table 3
Morning airway function values (n = 17)

	Nuelin depot	TheoDur
V C		
Mean	2803 ml	2756 ml
SD	1076 ml	1162 ml
	not significant	
FEV ₁		
Mean	1838 ml	1834 ml
SD	1073 ml	1080 ml
	not significant	
PEFR		
Mean	365 l/min	348 l/min
SD	146 l/min	147 l/min
	not significant	
PEFR at home		
Mean	332 l/min	322 l/min
SD	152 l/min	155 l/min
	not significant	

Table 4
Symptoms experienced by the patients.
Mean symptom-scores in cm (n = 17)

	Nuelin Depot	TheoDur	Mean difference
Dyspnoea	3.3	3.1	0.2
Cough	2.1	2.0	0.1
Sputum	1.7	1.6	0.1
Sleep	4.4	4.3	0.1
Physical activity	4.5	4.5	–
Mean no. of nightly attacks	1.8	2.4	0.6

Symptoms

The mean differences in symptom-scores for dyspnoea, cough, sputum, sleep, physical activity and nightly attacks are presented in Table 4. The difference between the values obtained in the two periods were negligible for all symptoms.

Use of beta₂-stimulant aerosol

Eight patients misunderstood the instruction of recording daily need for beta₂-stimulant aerosol. The mean use of beta₂-stimulant aerosol was 45 puffs in the Nuelin Depot period and 51 puffs in the TheoDur period. There was no convincing difference between the two drugs.

Side effects

Side effects were reported by five patients and consisted of headache, dizziness and gastrointestinal disorders. No side effects exceeded 5 cm.

Two patients experienced side effects in both periods, two patients only in the Nuelin Depot period and one patient only in the TheoDur period.

DISCUSSION

To our knowledge, there exist only two published comparisons of the two sustained release preparations Nuelin Depot and TheoDur (2, 5).

Domson et al. (2) demonstrated a difference in absorption between the two products when given to children. In this study, however, Nuelin Depot tablets had to be broken into fifths and Domson et al. suggest that this caused a more rapid absorption.

In a recent study, Talseth et al. (5) failed to demonstrate any difference in the plasma profile of the two products when equal doses were given to healthy subjects. In the present comparison of equal doses Nuelin Depot and TheoDur in 20 patients with COLD, the results are in agreement with the last mentioned study. Near identical plasma concentrations of theophylline were found after both preparations as judged from plasma concentration measurements performed before and 2, 4 and 6 hours after tablet intake, the peak-trough difference being 24.8 µmol/l in the Nuelin period and 26.3 µmol/l in the TheoDur period.

In contrast to the study of Talseth et al. (5) where t_{max} was 4.0 h for Nuelin Depot and 4.8 h for TheoDur (not significant), we found t_{max} to be 4.3 h for Nuelin Depot and 3.6 h for TheoDur

(not significant). Thus these two sets of results strongly indicate no difference in absorption characteristics between the two drugs.

Since the efficacy of theophylline preparation is closely related to the plasma concentration of theophylline, it was not surprising that no statistically significant differences could be demonstrated with respect to the effect of the two preparations on airway function and asthma symptoms in these patients.

Accordingly, our conclusion is that these two sustained release preparations should be considered equivalent for practical use.

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Address:

Kjell Erik Langaker
H. Heyerdahlsgt. 1
Oslo 1
Norway

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