Efficacy of sustained release theophylline given at three different evening intake times in addition to a baseline medication

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Efficacy of sustained release theophylline given at three different evening intake times in addition to a baseline medication. B. Siebert, G. Kunkel, K. Borner, H.W. Staudinger, V.W. Steinijans.
ABSTRACT: In this randomized crossover study of 26 outpatients with bronchial asthma the efficacy of a new once-daily theophylline formulation given in addition to a baseline medication was investigated; moreover, under steady state conditions, the effect of three evening intake times (6, 8 and 10 p.m.) on 24 h pharmacokinetics and peak-expiratory flow profiles was evaluated. The theophylline dose had been individually titrated. The pharmacodynamic results show a marked improvement of 24 h peak expiratory flow values after adding theophylline to a drug therapy including inhalative β_2-agonists and corticosteroids in nearly all and inhalative anticholinergics in 50% of the treated outpatients. No significant differences between the pharmacokinetic characteristics and the 24 hr averages (mesors) of peak expiratory flow at the three different intake times 6, 8 and 10 p.m. were found; however, intake at 10 p.m. resulted in the highest nocturnal excess of serum theophylline concentrations and the highest peak expiratory flow during the early morning hours between 2 and 6 a.m.
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Appropriate theophylline sustained-release formulations have been shown to be particularly useful in patients with nocturnal asthma [1–8]; the preferred dosage schemes in previous studies have been either a once-daily administration in the evening [2, 4, 6–8] or an unequally divided twice-daily dosage with administration of two thirds of the daily dose in the evening and one third in the morning [1, 3, 5].

The efficacy of theophylline compared to a baseline therapy or to placebo has so far not been investigated over 24 h with regular measurements of lung function parameters every 2 h. The aim of this study with a new theophylline sustained-release formulation was to investigate the efficacy in addition to clinically adjusted baseline therapy, which included inhalative β_2-agonists and corticosteroids in nearly all patients. Also to be investigated was whether different evening intake times had a clinically relevant effect on pharmacokinetic characteristics and 24 h peak expiratory flow profiles.

The test drug was a new theophylline sustained-release pellet formulation with *in vitro* release independent of pH- (imitating gastric acid), rpm- (rotational speed in the dissolution apparatus, imitating gastrointestinal motility) and surfactant (imitating cholic acids) (EUPHYLONG®, Byk-Gulden Pharmaceuticals). It has been designed for once-daily dosing in the evening in normal or slow metabolizers and for unequally divided twice-daily dosing in fast metabolizers. Previous studies have demonstrated low peak trough differences [9] and no clinically relevant food effects [10, 11].

Patients and methods

Patients

Thirty asthmatic patients with at least partially reversible airway obstruction ($\Delta FEV_1 \geq 15\%$, 15 min after two puffs of salbutamol) were included. Three patients dropped out; one dropout was likely due to theophylline related side effects. Another patient was withdrawn because of irregular drug intake prior to steady state. The protocol correct and key point available analysis included 26 patients, 19 males and 7 females, aged (median and range) 48 (22–72) yrs and weighing 74 (57–90) kg. The additional medication remained unchanged throughout the study.

Study design

Initially, a 28 h baseline peak flow profile was performed with measurements every two hours under the additional medication, but without theophylline. The daily

theophylline dose was individually titrated based on the serum theophylline concentration at 8 a.m. in steady state using the formulation-related one-point method [12].

This was followed by three 28 h periods with blood withdrawals for serum theophylline determinations and measurements of peak expiratory flow every two hours. Of the common 28 h periods of measurement, the respective 24 h periods following drug administration were used for pharmacokinetic and pharmacodynamic evaluation. The first treatment period was the reference period with drug intake for all patients at 8 p.m. According to the randomization, patients received the test formulation in the second treatment period either at 6 p.m. or at 10 p.m.; these intake times were crossed over in the third treatment period. The evening meal was always given at 7 p.m. The patients were hospitalized during the 28 h periods of measurements only. The measurements were started in the evening of the seventh day after having changed the evening intake time to ensure steady state conditions.

The final daily theophylline dose ranged from 500 to 1500 mg (median 750 mg). If the total daily dose was lower than 1000 mg, it was given once daily in the evening, if it was 1000 mg or greater, it was administered twice daily, approximately two thirds in the evening and one third in the morning.

Determination of theophylline

The serum theophylline determinations were carried out by EMIT during the dose titration; the pharmacokinetic steady-state characteristics presented here are based on HPLC measurements [13].

Determination of peak expiratory flow

Peak expiratory flow was measured by Mini-Wright peak flow meters immediately before blood sampling in a sitting position. The best of three measurements was recorded. Reference values were calculated according to GREGG and NUNN [14].

Data analysis

From the respective 24 h serum theophylline concentration/time profiles following drug intake at 6, 8 and 10 p.m., the percent peak-trough fluctuation, $\%PTF = 100 \ (C_{max} - C_{min})/C_{av}$, and the nocturnal excess, $100 \ (C_{av \ (0200-0600)} - C_{av})/C_{av}$, were calculated [15]. Relative bioavailability was assessed by distribution-free point estimator and 95% - confidence limits [16], taking the 8 p.m. administration as reference.

Consumption of β_2-agonists during the 4 study periods was compared by the Friedman-test and distribution-free multiple comparisons [17]. Changes of the peak expiratory flow values versus baseline were analysed by the Wilcoxon-Pratt Test (two-sided). The peak expiratory flow values at the end of the respective treatments at 6 and 10 p.m. were analysed by the distribution-free

ANOVA (Analysis of Variance) for a crossover design [18].

Results

Peak expiratory flow, mesor

The 28 h serum theophylline and peak expiratory flow profiles are shown in fig. 1 (once daily, n = 18) and fig. 2 (twice daily, n = 8).

Compared with the baseline therapy, which included inhalative β_2-agonists and corticosteroids in nearly all patients, a significant and marked improvement of the peak flow mesor was achieved after adding theophylline; this holds for all three different intake times. The increase was slightly greater for the unequally divided twice daily administration than for the once daily administration, which corresponded to the 24 h average serum theophylline concentrations. Also, it has to be noted that the baseline PEF-values were different (see table 1).

There was no significant difference between the mesor of the extreme intake times 6 and 10 p.m.

The differences of the peak expiratory flow values between the reference profile and the three theophylline treated periods could not be explained by differences of the additional use of β_2-agonists: the mean number of inhalations ranged between 1.8 and 2.8; although there was a significant difference (p<0.05) between the 4 periods, multiple comparison did not reveal any significant difference between either of the three theophylline periods with the theophylline-free baseline period.

Peak expiratory flow, nocturnal values

The nocturnal peak flow between 2 and 6 a.m. improved also significantly for all three intake times (see table 1). The improvement was significantly better for the intake at 10 p.m. compared with the intake at 6 p.m.

Pharmacokinetic characteristics. The extent of absorption as characterized by the 24 h average concentration in steady state, $C_{av} = AUC/24$, was equivalent for all three times of drug intake; C_{av} was 8.8 ± 0.4, 9.0 ± 0.6 and 9.6 ± 0.5 mg·l^{-1} for drug intake at 6, 8 and 10 p.m., respectively. Separated according to the dosage scheme, C_{av} was 8.2 ± 0.4, 8.0 ± 0.6 and 9.4 ± 0.6 mg·l^{-1} for once-daily administration (median dose 750 mg) and 10.2 ± 0.7, 11.3 ± 0.9 and 10.1 ± 1.1 mg·l^{-1} for twice-daily administration (median dose 1000 mg).

The percent peak trough fluctuation as a steady-state characteristic of the rate of absorption was 72 ± 6, 81 ± 5 and $90\pm4\%$ (once daily) and 71 ± 9, 70 ± 8 and $64\pm7\%$ (twice daily) for evening intake at 6, 8 and 10 p.m., respectively. The percent nocturnal excess was highest for the intake at 10 p.m., lowest for the intake at 6 p.m. (see table 1) and this is reflected in the pharmacodynamic data. The nocturnal excess was 12 ± 2, 24 ± 3 and $29\pm2\%$ for the once daily administration (n=18), and 6 ± 2, 15 ± 4, and 1 ± 6 for the twice daily administration (n=8) with evening intake at 6, 8, and 10 p.m., respectively.
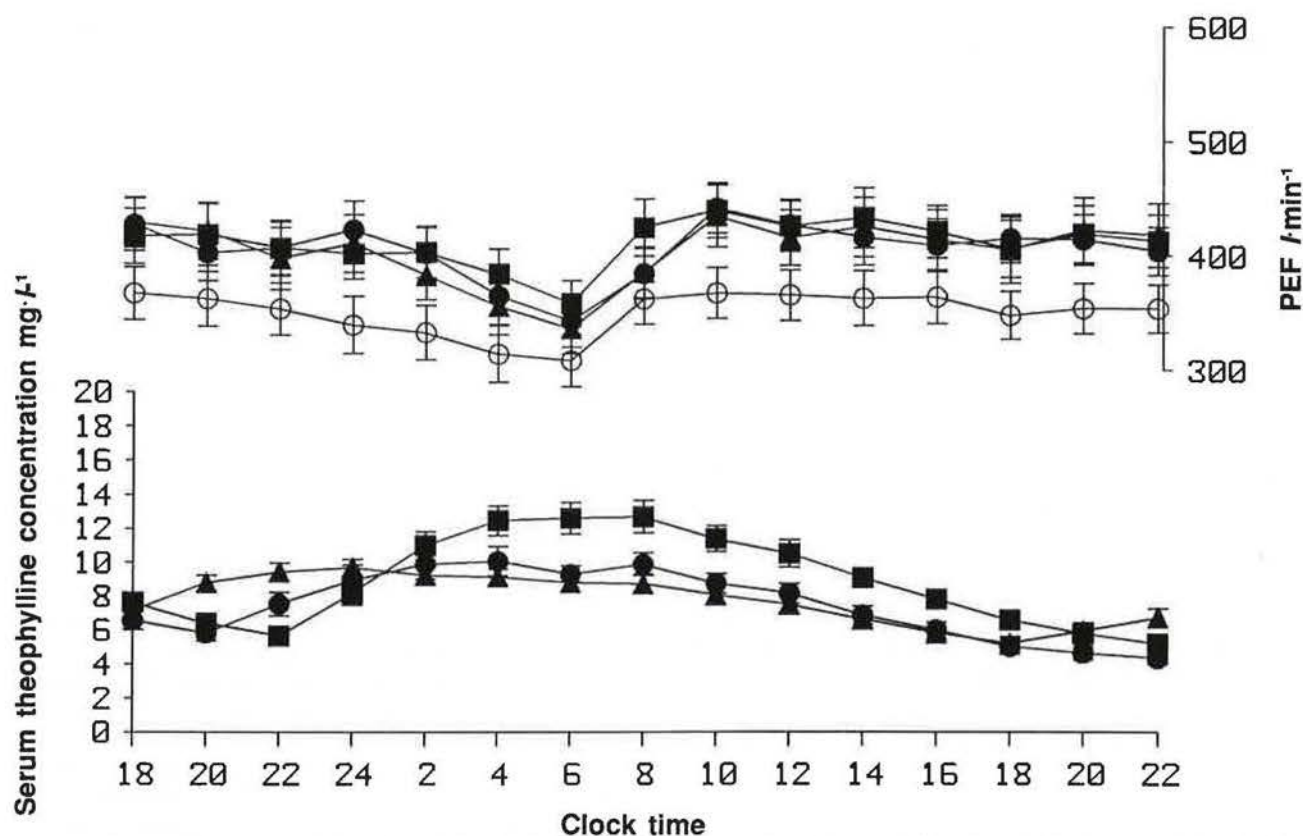
Fig. 1. – Steady-state serum theophylline concentration/time profiles (lower panel) and corresponding PEF-profiles (upper panel) following individualised dosing of theophylline at different evening times (▲ = 6 p.m., ● = 8 p.m., ■ = 10 p.m.) The open circles (○) refer to the baseline PEF-profile without theophylline; n=18 patients with once-daily administration in the evening.
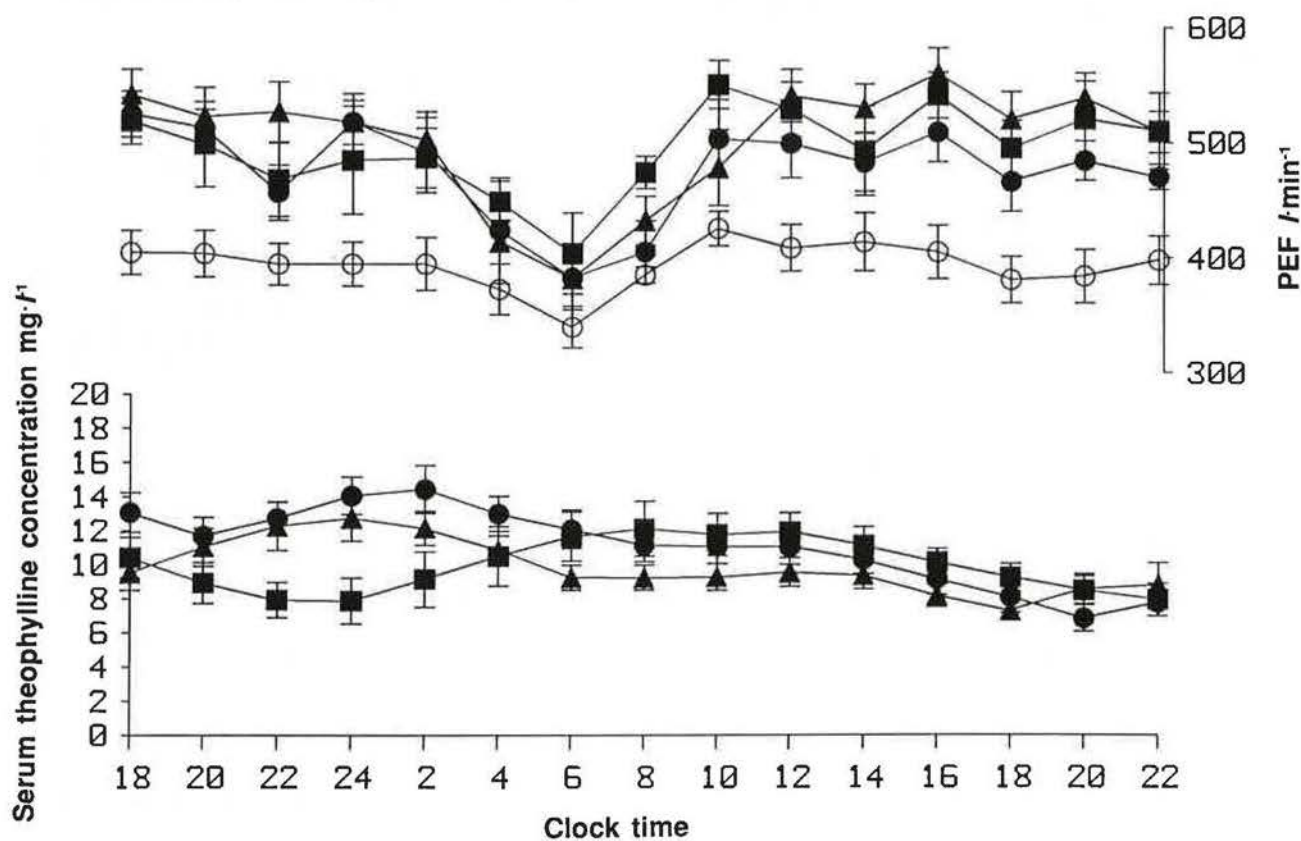

Fig. 2. – As fig. 1; n=8 patients with unequally divided twice-daily administration.

Table 1. — PEF mesor and nocturnal PEF during baseline therapy without theophylline and after evening intake at 6, 8 and 10 p.m. of individually titrated slow-release theophylline

Drug intake			PEF mesor ($l \cdot min^{-1}$)		
dosage scheme	time of administration		baseline	theophylline	%change
once	6 p.m.		350±22	401±22	16±3
daily	8 p.m.		349±22	404±22	18±3
n=18	10 p.m.		348±22	411±21	20±4
twice	8 a.m.	6 p.m.	395±17	495±16	26±5
daily	8 a.m.	8 p.m.	393±16	471±18	20±3
n=8	8 a.m.	10 p.m.	393±16	494±22	28±8

Drug intake			nocturnal PEF ($l \cdot min^{-1}$)		
dosage scheme	time of administration		baseline	theophylline	%change
once	6 p.m.			359±22	15±4
daily	8 p.m.		319±24	370±21	19±5
n=18	10 p.m.			384±21	24±5
twice	8 a.m.	6 p.m.		429±16	18±8
daily	8 a.m.	8 p.m.	371±21	432±36	17±7
n=8	8 a.m.	10 p.m.		448±21	24±11

Mean±SEM.

Side effects

One patient dropped out due to adverse events (nausea, vomiting, sleep disturbances, tremor). In another patient all medications were stopped temporarily for treating a pre-existing tinnitus. One patient dropped out due to nonmedical reasons. 18 patients had side effects, fifteen during the dose titration period only; the side effects were typical and transient despite the ongoing therapy in all but one patient, who suffered from erectile dysfunction. In four patients the dose had to be reduced for reasons of tolerability, in one of them the dosage scheme was changed to twice daily administration despite a dose below 1000 mg.

Discussion

Airway obstruction in bronchial asthma has been shown to exhibit circadian rhythms [19]. The amplitude of the rhythm may vary to a great extent and has been demonstrated to be related to bronchial hyperreactivity [20]. Dyspnoea attacks have been reported to be much more frequent during the night [21, 22]. According to COCHRANE [23], the risk of death from asthma was in excess by 28% during the 8-hour period between midnight and 8 a.m. In this study the highest median peakflow in the reference profile was observed at 6 p.m. (400 $l \cdot min^{-1}$), the lowest at 6 a.m. (305 $l \cdot min^{-1}$), 24% lower than the value 12 h earlier. On this background, a pharmacodynamic evaluation of drugs for the treatment of asthma on a 24 h basis seems to be important. According to HETZEL and CLARK [24], it seems unlikely that the results of the peak flow measurements are influenced to a relevant extent by interruptions of sleep; however, their arguments need confirmation by measurement of resistance during sleep.

The comparison of the 24 hour average peak expiratory flow at baseline, i.e. under the additional medication only (including inhalative β_2-agonists and corticosteroids in nearly all and inhalative anticholinergics in half of the treated outpatients), and after adding theophylline to this drug therapy showed a marked and significant improvement with theophylline (see table 1, figs 1 and 2).

However, the morning dip could not be eliminated; it persisted on a higher level of peak expiratory flow. The most likely explanation for this is slightly different for the once daily and the unequally divided twice daily administration. Although serum theophylline levels were high enough to cause substantial clinical improvement, they were - due to a rather cautious dose titration with the new formulation - too low to abolish the morning dip with the once daily administration (fig. 1). In other studies including one with the same formulation, a complete or nearly complete elimination of the morning dip was observed with higher serum theophylline concentrations of at least 14 $mg \cdot l^{-1}$ during the critical morning hours [4, 6–8, 25]. Correspondingly, in this study the greatest improvement of nocturnal PEF was achieved with the 10 p.m. administration, where higher serum theophylline

concentrations (around 12 mg·l^{-1}) were achieved during the night than with the other intake times. For the twice daily administration, serum theophylline concentrations were somewhat higher over 24 hours. Despite the administration of 2/3 of the total daily dose in the evening and only 1/3 in the morning the nocturnal excess of serum theophylline concentrations was rather small. These results suggest that it may be more appropriate, especially for patients with nocturnal worsening, to administer the total dose in the evening and not to split up the daily dose.

No important differences concerning the pharmacokinetic parameters were found between the three different intake times 6, 8 and 10 p.m.. The mesors of the peak expiratory values did not show any significant difference; however, during the early morning hours between 2 and 6 a.m. intake at 10 p.m. resulted in the highest nocturnal excess of serum theophylline levels and the highest peak expiratory flow. The difference was significant in comparison with the intake at 6 p.m.; therefore, the late intake seems to be the most suitable for patients with pronounced nocturnal worsening of their asthma. For the remaining patients, the evening intake time is not critical and the investigated formulation can be taken within this four hour time span.

The vast majority of side effects occurred during the dose titration only and disappeared despite the ongoing treatment. This suggests that the therapy should be started with lower doses than with the 750 mg administered at the beginning of this study and that the dose should then be increased gradually.

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Efficacité de la Théophylline à libération prolongée, donnée à 3 moments d'administration différents le soir en surplus d'une médication de base. B. Siebert, G. Kunkel, K. Borner, II.W. Staudinger, V.W. Steinijans.

RÉSUMÉ: Nous avons investigué dans cette étude randomisée avec permutation croisée l'efficacité d'une nouvelle formule de Théophylline à administration une fois par jour, donnée en surplus d'une médication basale chez 26 patients ambulants,

atteints d'asthme bronchique. D'autre part, dans des conditions d'état stable, l'effet de 3 moments de prise vespérale (6, 8 et 10 h du soir) a été évalué sur la pharmaco-cinétique de 24 h et sur les profils des débits expiratoires de pointe. La dose de Théophylline a été titrée individuellement. Les résultats pharmacologiques montrent une nette amélioration des valeurs de débit de pointe de 24 h chez presque tous le patients après l'addition de Théophylline à un traitement médicamenteux comportant des bêta 2 agonists et des cortico-stéroïdes en inhalation et chez 50% d'entre ceux qui prenaient un régime d'anti cholinergiques en inhalation. L'on a pas observé de différence significative entre les caractéristiques pharmaco-cinétiques et les moyennes de 24 h (mésors) du débit expiratoire de pointe lors des 3 heures différentes de prise du médicament (6,8 et 10 p.m.). Toutefois la prise à 10 h du soir entraîne le surcroît le plus élevé des concentrations nocturnes de Théophylline ainsi que le débit de pointe maximal pendant les heures du petit matin (entre 2 et 6 h).