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Sleep Disturbances in Asthma: Theophylline Versus Enprofylline

Christer Janson,[1] Thorarinn Gislason,[1] Lena Laxmyr,[2] Gunnar Boman[1] and Carl Persson[3]

[1]*Department of Lung Medicine, Uppsala University, Akademiska sjukhuset, Uppsala,* [2]*AB Draco, Lund and* [3]*Department of Clinical Pharmacology, University Hospital of Lund*

ABSTRACT

A double-blind cross-over study was performed on 22 asthmatic patients receiving maintenance treatment with theophylline who, in a previous study, had reported sleep problems. In one of two three-week periods the theophylline medication was replaced by an equipotent dose of slow-release enprofylline. Analysis of sleep questionnaires answered after each treatment period, and sleep diaries filled in throughout the study, showed no significant differences in the quality of sleep between the treatments. Peak expiratory flow (PEF) in the morning did not differ between the treatment periods, but mean PEF in the evening was slightly higher (20 l/min) during theophylline treatment. It was concluded that replacement of theophylline by enprofylline did not improve the quality of sleep subjectively in this group of theophylline treated asthmatics. The results suggest that adenosine receptor antagonism may not be a significant cause of sleep disturbances in asthmatic patients who are receiving theophylline as maintenance treatment.

INTRODUCTION

It is well established that in patients with asthma and chronic obstructive pulmonary disease the quality of sleep is impaired (7,9,10,11). Many such patients with sleep disturbances are being treated with theophylline, but it is not known to what extent theophylline contributes to the sleep impairment. Theophylline has been reported to cause disturbance of sleep in patients unaccustomed to this drug (8,16). However, in patients with nocturnal asthma this condition is improved by theophylline and for that reason they may sleep better during treatment with this drug than without it.

Since theophylline is very commonly used in asthma, it is important to know whether or not its CNS-stimulant actions contribute to sleeping problems in patients with this disease. The introduction of enprofylline has provided an opportunity to address this question. Enprofylline is a xanthine derivative which shares with theophylline both the anti-asthmatic properties and some adverse effects such as nausea and headache, but it lacks a number of CNS-stimulant actions. No stimulant effects on behaviour or any seizure-inducing effects have been observed on administration of unlimited doses of enprofylline in different animal species (14). In man theophylline, but not

enprofylline, produces tremor (12) and causes awakening of diazepam-sedated subjects (19). Even very high plasma levels of enprofylline in asthmatic patients have not been associated with any theophylline-like excitatory effects (18). The different profiles are probably due to the fact that theophylline antagonizes inhibitory actions of endogenous adenosine, whereas enprofylline does not (13). This property makes enprofylline together with the adenosine antagonist theophylline a useful tool in attempts to determine the physiological roles of adenosine, in particular in man (13).

In the present study the effects of theophylline and enprofylline were compared in selected asthmatic subjects who were receiving theophylline as maintenance therapy and who were suffering from sleep problems. By use of anti-asthmatic doses of the two xanthines, the relationship between sleep disturbances and CNS excitatory adenosine antagonistic effects of theophylline-like xanthines in this category of patients was examined. It was hypothesized that the quality of sleep of these patients will benefit when theophylline treatment is changed to enprofylline.

MATERIAL AND METHODS

In a previous study on sleep disturbances among asthmatics (9), 46 patients with theophylline medication reported moderate or major complaints of at least one of the following: Difficulties in inducing sleep (DIS), difficulties in maintaining sleep (DMS), early morning awakening and daytime sleepiness. Thirty-two of these patients agreed to take part in the present study. The patients had asthma defined as a history of variable dyspnoea and wheezing and a response to β_2-agonists. Reversibility after bronchodilating treatment of at least 15% in peak expiratory flow (PEF) or forced expiratory volume at one second had been recorded previously in all patients. None of the patients were taking any medication for other diseases that are known to affect the quality of sleep, e.g. hypertension, diabetes, depression, rheumatic diseases or chronic pain (7).

The study was designed as a randomized double-blind cross-over study with comparison of enprofylline and theophylline (Fig. 1). Each treatment period lasted 3 weeks, with no wash-out period between the treatments. The daily dose of enprofylline (sustained release tablets: Astra) was gradually increased during one week from 150 mg b.i.d. to 450 mg b.i.d. In order to keep the study blind the theophylline medication (Theo-Dur®) was also gradually increased from 150 mg b.i.d. to 300 or 450 mg b.i.d. (the patient's current dose before entry into the study). The patients visited the outpatient clinic of the department before the study and also after the first week and at the end of each study period. Patient compliance as to medication (pill count) and the accuracy of diary recordings was checked at these visits. Plasma samples (5 ml) were drawn between 3 and 6 hours after the morning dose on the last day of each 3-week treatment period. Plasma theophylline and enprofylline concentrations were assayed by a method of column liquid chromatography (1,5). The patient's regular maintenance anti-asthmatic medication (except theophylline) was allowed to remain unaltered during the study, provided that the dosage was constant.

No sleeping pills or psychotropic drugs were allowed. Any concurrent therapy during the study was recorded. Caffeine-containing beverages were not allowed after 3.30 pm during the study period. Decaffeinated coffee was available through the clinic.

Informed consent was obtained from each patient, and the study was approved by the Ethics Committee of the Medical Faculty of Uppsala University and the Swedish National Board of Health and Welfare.

In a sleep questionnaire, which was filled in by the patients at the start of the study, the patients reported how they had slept during the last months (8,9). The questionnaire was also filled in at the end of each treatment period, when the patients answered how they had slept during the last week of each period (8). The patients answered questions concerning sleep and daytime performance: DIS, DMS, early morning awakenings, daytime sleepiness, nightmares, snoring, symptoms of gastro-oesophageal reflux, involuntarily falling asleep during the daytime, morning tiredness, impairment of concentration and restlessness. A five-point scale was used, where 3 represented moderate complaints and 4 and 5 represented major complaints (7,8,9). In the questionnaire at the start of the study the patients were asked whether they had any sleep problems after drinking coffee in the evening (8).

A sleep diary which was identical to that used previously (8,9) was filled in daily by each patient through out the study period. From this diary calculations were made of the estimated length of sleep, sleep latency, wakefulness during the night and number of awakenings during the night. The patients were also asked to state whether the awakenings were due to breathing problems (including problems with cough and phlegm) or to causes not related to breathing.

The patients filled in a diary card twice daily, morning and evening. PEF was measured with a Mini-Wright peak flow metre and the highest value of three attempts was recorded. The patients were instructed not to use inhaled bronchodilators later than 5 hours prior to PEF measurements if possible. Asthmatic symptoms and adverse experiences were recorded with scores of 0 (none) to 3 (severe). The number of puffs of bronchodilators was also noted by the patient on the diary card.

At the end of the 6-week study the patients were asked which treatment period (if either) they had preferred with respect to sleep and asthmatic symptoms.

Statistics

It was estimated before the study that 20 patients would be needed to reach a statistical power of 80% in order to detect a difference of 40 minutes between the treatments in mean estimated sleep time provided that the standard deviation of the difference was 60 minutes.

The Wilcoxon signed rank test was used to test for treatment differences in the sleep questionnaire score, diary recordings and lung function variables during the last week of each treatment period. A difference with a two-tailed p value of < 0.05 was regarded

as statistically significant. A cross-over analysis, addressing questions of carry-over effects and period effects, was performed. No significant period or carry-over effects on the diary data (both sleep and lung function) were found.

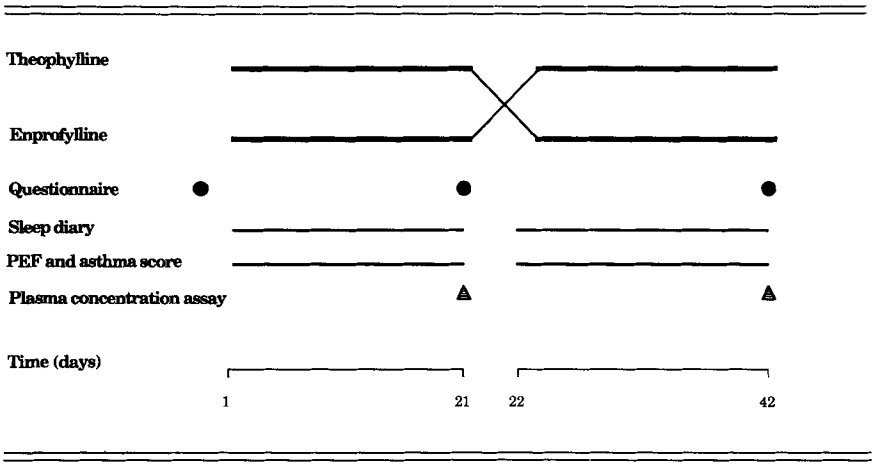

Figure 1. The study design.

RESULTS

Thirty-two patients entered the study, but ten patients did not complete the entire study period and were therefore not included in the final analysis. Of the ten withdrawals, seven took place during enprofylline treatment (adverse experiences, n=5; asthma exacerbation, n=1; or personal reasons, n=1), and three during theophylline treatment (adverse experiences, n=1; and asthma exacerbations, n=2).

The final statistical analysis thus comprised 22 patients (13 men and 9 women, mean age 53 years, range 30-66). All patients had had their asthma for at least 4 years (mean duration 21 years). All patients were taking oral theophylline and inhaled β_2-agonists, and in addition 20 patients were using topical corticosteroids, 19 oral β_2-agonists and seven oral corticosteroids. Three patients used hypnotics occasionally before entry into the study. The patients had taken oral theophylline for an average of 6 years (range 1-9 years). Two patients were taking 450 mg of theophylline b.i.d. and were thus given this dose in the study, and the remaining patients were taking 300 mg of theophylline b.i.d. Before the study six patients reported that they experienced sleep problems after drinking coffee in the evening and they were thus regarded as caffeine-sensitive in this respect (8). The mean plasma enprofylline concentration at the end of the study period was 28.4 µmol/l (range 6.2 - 56.1) and the mean plasma theophylline concentration was 47.3 µmol/l (range 21.7 - 71.1).

The patients had significantly lower scores of daytime sleepiness, early morning awakening, nightmares and uneasiness during the last week of both treatment periods than in the pre-treatment questionnaire (Table 1). There were, however, no significant differences in sleep complaints or daytime performance (questionnaire results) or in the length of sleep and the number of awakenings (diary results) between the theophylline and enprofylline treatment periods, either in the total study population or in the subgroup of caffeine-sensitive patients (Tables 1 and 2). Seven patients preferred the theophylline period and four the enprofylline period regarding effects on sleep, while 11 patients had no preference (statistically not significant (N.S.)).

Table 1 Sleep questionnaire results. Percentage of patients reporting moderate and severe complaints before the study (B), during the theophylline treatment period (T) and during the enprofylline treatment period (E)[†](n=22).

	B	T	E
Difficulties in inducing sleep	41	36	32
Difficulties in maintaining sleep	50	45	50
Nightmares	23	14*	18*
Early morning awakenings	64	45**	50*
Daytime sleepiness	68	32**	36*
Morning tiredness	95	77**	86
Impairment of concentration	59	41•	54
Uneasiness	68	32**	41*

[†] * ($p<0.05$) and ** ($p<0.01$) denote that the scores are statistically significantly different from these in B. No statistically significant differences were found between T and E.

Table 2. Sleep diary results (mean±SD).

	Theophylline	Enprofylline
Estimated sleep time (min/night)	368±66	378±67
Sleep latency (min/night)	45±43	43±34
Nightime wakefulness (min/night)	55±50	52±42
Breathing-related awakenings/week	3±6	3±6
Non-breathing-related awakenings/week	6±5	6±5

The mean evening PEF was significantly higher and the bronchodilator aerosol consumption during the daytime and night-time significantly lower during the theophylline period than during the period with enprofylline (Table 3). The mean morning PEF and mean asthma score were approximately the same with both treatments. Nine patients

preferred the theophylline and five the enprofylline period regarding the effect on asthmatic symptoms, while eight patients had no preference (N.S).

Table 3 Effects on lung function, bronchodilator aerosol consumption and asthmatic symptoms (mean±SD).

		Theophylline	Enprofylline	
Peak flow (l/min)	morning	305±112	300±101	
	evening	361±119	342±108	p<0.01
Aerosol consumption (No. of puffs)	night	3.6±4.9	4.2±4.3	p<0.05
	day	4.5±4.2	4.9±4.3	p<0.05
Asthmatic symptoms (mean score)	night	0.8±0.9	0.9±0.9	
	day	1.0±0.9	0.8±0.9	

The adverse experiences reported, during both treatments, were mainly headache and nausea. During the first two weeks of treatment these two symptoms were of higher frequency and intensity with enprofylline than with theophylline, but during the third week the reported adverse experiences were fewer, with no significant differences between the treatments (Table 4).

Table 4. Frequency and mean score of headache and nausea during the treatment periods (n=22).

			Theophylline		Enprofylline	
			n	mean score	n	mean score
Headache	Week	1	5	2.0	13	2.3
		2	7	1.9	12	1.9
		3	8	1.6	8	1.5
Nausea	Week	1	2	1.5	4	1.75
		2	1	-	5	2.0
		3	1	-	1	-

DISCUSSION

In a previous study we have reported that the prevalence rate of DIS, DMS and daytime sleepiness were about twice as high among asthmatic patients than in the healthy population (9). With its characteristic nocturnal cough and breathing difficulties, the disease itself is a well established cause of sleep disturbances (4). Theophylline, which has CNS effects similar to those of caffeine (6) has, however, also been reported to decrease the quality of sleep in some patients (8,16). The patients selected for participation in this study represented the large number of

asthmatics who are treated with theophylline and who have significant problems with their sleep. It would be of value to know whether theophylline significantly disturbs sleep in this category of patients, since if so, a change of anti-asthmatic therapy might improve the quality of sleep in this large group of patients.

In the present study the patients reported fewer problems with daytime sleepiness and early morning awakenings during both the theophylline and enprofylline treatment period than in the pre-study questionnaire. This might partly have been an effect of more regular use of the anti-asthmatic medication due to our monitoring. No significant difference in the quality of sleep was found, however, between the theophylline and enprofylline periods. Thus there was no tendency towards better sleep with enprofylline, but rather the contrary. This result considerably weakens the possibility that the CNS-excitatory actions of theophylline, which are not produced by enprofylline, was a cause of these patient's sleep disturbances.

According to the inclusion criteria, the patients in this study were receiving theophylline medication before recruitment. Sensitive subjects experiencing severe sleep problems when once started on theophylline may either have stopped their treatment and thus not been in the selected group or have developed a tolerance to this particular side effect. A comparison between the effects of starting doses of theophylline and enprofylline on sleep in such sensitive subjects may be warranted. Most of the patients were also taking oral ß2-agonists, which would account for the rather low plasma theophylline concentration during the theophylline treatment period (17). It is therefore not certain that our results are valid for patients receiving theophylline as monotherapy, who would be taking higher doses in order to have a good anti-asthmatic effect. Finally, it is possible that if we had studied a larger number of patients or had used more sophisticated methods for sleep measurements, such as polysomnography, we might have found some differences favouring enprofylline. It is unlikely, however, that these differences would have been large enough to justify switching therapy in a clinical situation.

Enprofylline has been found to have the same anti-asthmatic efficacy as theophylline in experimental studies and in a large-scale long-term multi-centre study, where the same doses were used as in this study (3). The plasma concentrations at the end of each study period were at levels at which the two drugs should have an equal anti-asthmatic effect (2). The differences between enprofylline and theophylline in this study regarding peak expiratory flow, aerosol consumption and asthmatic symptoms were considered marginal and should not invalidate the comparative aspect of effects on sleep. In particular there was no difference in morning peak flow values and in symptoms.

The comparison between the treatments was made during the third week of each treatment period. During this third week enprofylline and theophylline did not differ concerning side effects such as nausea and headache. Contributing to the difference in tolerance during the first two weeks of treatment may have been the fact that all patients were used to and well acquainted with the effects of theophylline and that the

pharmacology of the two xanthines regarding headache and nausea may differ somewhat owing to their different abilities to antagonize adenosine.

By virtue of its property of being a xanthine derivative without adenosine antagonism, enprofylline has proved to be a valuable tool in delineating the roles of endogenous adenosine in man (13,15). Accordingly, since enprofylline and theophylline did not differ regarding associated sleep problems, the results of this study suggest that adenosine receptor antagonism may not be a significant cause of sleep disturbances in asthmatic patients who are receiving maintenance treatment with theophylline. Other factors than the arousal actions of theophylline, such as effects of the disease itself, are probable causes of sleep problems in this category of patients.

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Correspondence to Christer Janson
Department of Lung Medicine
Akademiska sjukhuset
S-751 85 Uppsala