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An evaluative study of the short-term effects of once-daily, sustained-release theophylline on sleep in nocturnal asthmatics

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Objective. To examine the effects of once-daily, sustained-release theophylline on sleep patterns in nocturnal asthmatics.

Design. Double-blind, randomised, cross-over, placebo-controlled trial over 22 days. Seven-day period to establish therapeutic levels of theophylline (11.8 ± 3 mg/l); 8-day cross-over period of 4 days' placebo or theophylline; 7-day baseline period. Electrophysiological sleep patterns, overnight bronchoconstriction and arterial O_2 saturation monitored on nights 7, 11 and 15.

Setting. Sleep Laboratory, Medical School, University of the Witwatersrand.

Patients. Twelve volunteers who met the criteria for asthma, had previously used theophylline, were clinically stable and had a history of nocturnal awakenings caused by asthma were enrolled.

Outcome measures. Sleep-onset latency (SOL), within-sleep wakefulness (WSW), rapid eye movement sleep (REM), slow-wave sleep (SWS), peak expiratory flow rate (PEFR) and arterial oxygen saturation.

Results. SOL increased on theophylline — 12 minutes (range 7 - 9 minutes) compared with placebo — 6 minutes (range 3 - 11 minutes); WSW increased from 33 minutes (range 17 - 66 minutes) on placebo to 72 minutes (range 35 - 150 minutes) on theophylline. REM sleep was unaltered. SWS decreased in 10 - 12 patients, but this difference was not significant. Early morning PEFR was significantly better on theophylline in all study limbs.

Conclusion. Our findings show that while once-daily, sustained-release theophylline improves bronchodilation in nocturnal asthmatics, it increases nocturnal wakefulness and decreases sleep efficiency during short-term treatment. This may, however, not be a long-term effect.

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Early morning 'dipping' in asthmatic patients is related to circadian rhythms and frequently fails to respond to treatment.[1] With conventional twice-daily theophylline administration, serum theophylline concentrations drop during the early hours of the morning and nocturnal asthma attacks are therefore not always prevented.[2] However, improved control of nocturnal asthma has been reported with the use of once-daily, sustained-release, evening-administered theophylline.[1]

The influence of theophylline on sleep is not clear and studies examining the effect of sustained-release preparations, either once- or twice-daily regimens, have yielded conflicting results.[3,4] While some studies report no influence of theophylline on sleep in both asthmatics and normal volunteers over periods of 5 - 14 days, others found increased wakefulness and decreased sleep efficiency in similar groups over comparable time periods.[3-6]

We examined the quality and efficiency of sleep as well as changes in lung function in nocturnal asthmatics in a double-blind, randomised, cross-over, placebo-controlled study. Once-daily, sustained-release, evening-administered theophylline was compared with placebo while concurrent anti-asthma medication (inhaled β-agonists, beclomethasone, prednisone, nedocromil sodium) was maintained. Fifteen adults (age range 20 - 51 years), diagnosed as asthmatics according to criteria of the American Thoracic Society and with a history of asthma-induced awakenings, entered the study. Twelve patients (7 men, 5 women) completed the 22-day trial, 3 patients having withdrawn due to adverse events. During the initial 7 days of the study, serum was obtained at 07h00 and therapeutic levels of theophylline (11.8 ± 3 mg/l) were established. The following 8 days comprised a cross-over period of 4 days each on placebo or theophylline. Baseline recordings were made on the final 7 days. Electrophysiological sleep recordings, overnight bronchoconstriction and arterial oxygen saturation were measured on nights 7, 11 and 15 in the Edblo Sleep Laboratory, University of the Witwatersrand. Night 7 served as a period of acclimatisation, while nights 11 and 15 were either placebo or theophylline evaluations. Daily diary charts were kept by the patients, who noted peak expiratory flow rate (PEFR) at 22h00 and 06h00, subjective sleep and mood assessments and concurrent medication.

The sleep and lung function parameters were analysed by means of the analysis of variance for a cross-over design after logarithmic transformation of the data. Geometric mean and 95% confidence intervals (CIs) were calculated for the ratio of population medians of theophylline and placebo.

Evening-administered, sustained-release theophylline significantly improved early morning bronchodilation, as measured by PEFR, but resulted in a general increase in wakefulness. The time taken to fall asleep (sleep-onset latency (SOL)) doubled on theophylline (12 minutes, range 7 - 19 minutes) compared with placebo (6 minutes, range 3 - 11 minutes), while wakefulness after sleep onset (WSW) increased from 33 minutes (range 17 - 66 minutes) to 72 minutes (range 35 - 150 minutes) (Fig. 1). The increased wakefulness on theophylline resulted in a decreased sleep efficiency which may have contributed to the lower subjective ratings of morning alertness. The times spent in rapid eye movement (REM) sleep and slow-wave sleep (SWS) (stages 3 and 4 of non-REM sleep) were not

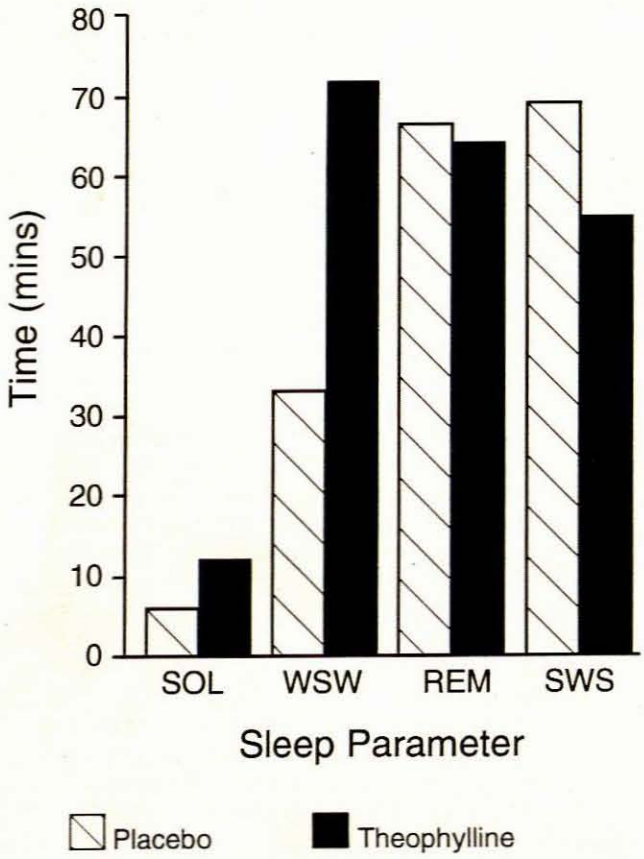

Fig. 1. Geometric means for selected sleep parameters (minutes) over a 7-hour recording period, after 4 days of treatment with theophylline or placebo in 12 symptomatic adult asthmatics. Four days of theophylline treatment increased both the time taken to fall asleep (SOL) and subsequent wakefulness (WSW) when compared with placebo.

significantly different with placebo than with theophylline treatment.

The acute stimulant effect of theophylline resulted in increased wakefulness after 4 days of use. The stimulatory effects are expected to subside with long-term use.[2] However, following 10 days of twice-daily treatment[6] and 11 days of continuous theophylline treatment in 4 of our 12 patients, increased wakefulness was still present. These findings may not be representative of the long-term effects of once-daily sustained-release theophylline, and studies over longer time periods are required to clarify this issue.

Our findings show that once-daily, evening-administered, sustained-release theophylline improves control of nocturnal asthma but increases nocturnal wakefulness during short-term treatment.

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Asthma in goldminers

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Objectives. To determine whether asthma in goldminers is caused by or contributed to by their working environment.

Design. A case-control study in which men with asthma working underground in goldmines were compared with underground goldminers without asthma in relation to their age, duration of exposure to the underground environment, atopy and family history of asthma.

Setting. An in- and outpatient facility providing for the medical needs of approximately 90 000 miners employed on goldmines in the Free State.

Outcome measures. Occupational history, atopy and family history of asthma were compared in the two groups. The age of onset of asthma and duration of occupational exposure were examined in the men with asthma.

Results. The study sample included 78 underground miners with asthma and 46 without asthma. The men in the two groups were of similar age, but those with asthma had worked underground for a longer period than the men without asthma. Twenty of the asthmatic and none of the control group had been exposed to paint and cement in the course of their work. Fifty of the asthmatic and only 3 of the control group were atopic. The mean age of onset of asthma (± SD) was 30.6 ± 10.73 years. Six of the men had developed asthma before starting to work in the mines, and the disease had developed 13.4 ± 8.22 years after starting to work underground in the remaining 72.

Conclusion. The late age of onset and the onset after exposure to the underground environment suggest that the disease was work-related.

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