The Therapeutic Effect of Theophylline on Sustained Attention in Patients with Obstructive Sleep Apnoea Under nCPAP-therapy

A Büttner
KH Rühle

Klinik Ambrock, Klinik für Pneumologie, Allergologie und Schlafmedizin, Universität Witten-Herdecke, 58091 Hagen, Ambrocker Weg 60, Germany

1. Background
Patients with obstructive sleep apnea syndrome suffer from frequent O₂-desaturations (hypoxia) and severe sleep fragmentation due to frequent respiratory arousals leading to daytime sleepiness and reduced attention. Reduced sleep quality also influences the capability to drive motor vehicles.

Analysis of components of attention are performed using MSLT, MWT and self-assessment of sleepiness e.g. through questionnaires (e.g. Epworth Sleepiness Scale ESS), vigilance, selective and divided attention measured by neuropsychological tests; driving simulators can also be employed for this purpose.

Under nCPAP therapy, apnea frequency and duration is improved significantly, but in a few cases, daytime sleepiness improves only to some extent, so that this problem requires further therapeutic measures.

Application of caffeine as a xanthine derivative with an effect on healthy persons significantly increases sustained attention during daytime.

In different testing methods, caffeine led to a reduction of daytime sleepiness and improvement of sustained attention.

As the application of caffeine can lead to uncomfortable side effects, e.g. in the form of restlessness, the use of theophylline to reduce daytime sleepiness in case of OSAS as a model study was suggested due to its sustained release, the possibility of monitoring the blood level and minor side effects. However, theophylline administered in the evening does not have positive effects on the apnea frequency and additionally deteriorates sleep quality.

We therefore investigated the following questions:
- To what extent is sustained attention, measured by driving simulator, reduced for OSAS patients?
- Is it possible to improve sustained attention by application of delayed-action theophylline in the morning and at noon?
- Is it possible to improve sustained attention measured with a driving simulator by treating OSAS patients with slow-release theophylline during daytime?

2. Objectives and Methodology
2.1. Measuring Devices
   a. Driving simulator
      The newly developed driving simulator is a menu-controlled Turbo Pascal program, which runs on a usual personal computer.
In this test, a road with shoulder, median and curves is simulated in polychromatic images. On the right side of the road, obstacles in the form of "No Through Road!" signs can be shown which are visible only for a short time (e.g. 200 msec). Their times of appearance are randomized, varying numbers of events can be set for a five-minute simulation period. The patient's task is now to use a steering wheel to steer his/her car on the right lane (tracking) and, using two buttons (which both have the same function) located on the steering console, to react to the obstacles appearing (visual search).

The program registers tracking deviations, measuring the duration of the individual deviations in seconds, which are added up over the entire driving simulation period. In this study only tracking deviations were evaluated.

b. Questionnaires
In the study, the Epworth Sleepiness Scale (ESS) questionnaire and a patient questionnaire were employed. The questionnaires served, on the one hand, to register subjective assessment of daytime sleepiness or the tendency to fall asleep during the day, and on the other hand to register demographic and clinical details as well as data concerning driving skills.

2.2. Study Design
Our study consists of two steps: first: testing of untreated patients with obstructive sleep apnea syndrome (pilot study); second: one year later, these patients, now under therapy, are tested again, as they still have problems with residual symptoms in the daytime.

To establish the diagnosis of OSAS and to characterize the disorder, a polysomnography was carried out according to the criteria established by Rechtschaffen and Kales and the DGSM (Deutsche Gesellschaft für Schlafforschung und Schlafmedizin [German Sleep Research Association]).

In the pilot study, a placebo-controlled sample of untreated OSAS patients (n = 50) were given placebo or theophylline in a randomized order on two consecutive days (Bronchoretard 6mg/kg body weight) 8:00 and 12:00 hrs, the aim was a serum level of theophylline > 10 µg/ml.

The clinical symptoms questionnaire was handed out and daytime sleepiness estimated by Epworth Sleepiness Scale (ESS) on the first day of admission.

The driving simulator test was performed at 16:00 hrs. It takes place in a sound-proof, unlit, dark room (the computer monitor is the only source of light). The test instructions are standardised and invariably given by the same person.

In the main study, one year later, all the patients from the pilot study are contacted, and 9 of these patients are tested again according to the same design and under the same conditions, but now under nCPAP-therapy, because these patients still show reduced sustained attention.

2.3. Inclusion Criteria
Patients referred to our hospital with complaints of sleepiness and suspicion of sleep apnea were consecutively enrolled in the study. Patients with concomitant heart and lung diseases, neurological and psychiatric diseases were excluded. In particular, the patients
should not have consumed any drinks containing alcohol or caffeine for 4 to 6 hours prior to the test, not be hungry or thirsty and not have taken any medication impairing their attention.

3. Results and Analysis

3.1. Patients
First, we tested 50 consecutive OSAS patients not under therapy. A polysomnography was carried out to establish a diagnosis for these patients, of whom 49 were male and 1 female (age: 49.7 ± 7.7 years, BMI: 30.1 ± 5.9; AHI: 28.6/h ± 20.6/h; mean AH duration: 49.8 sec ± 20.1 sec; SaO₂min: 79.8% ± 7.7%). The patients reported a moderate daytime sleepiness (ESS score: 11.6 ± 4.9) and sustained attention.

One year later, we researched 9 of these patients with OSAS according to the same design, but now under nCPAP-therapy, as these patients still suffered from reduced sustained attention. The male patients were studied (age: 52.6 ± 7.9 years, BMI: 36.2 ± 10.4; AHI: 4.8/h ± 2.8/h; mean AH duration: 36.4 sec ± 33.0 sec; SaO₂min: 83.3% ± 10.7%). The patients reported residual symptoms, especially reduced sustained attention. The ESS score was at 6.7 ± 3.7. The serum level of theophylline under placebo at the beginning of the measurement was 2.7 µg/ml ± 7.8 µg/ml and under theophylline medication 11.7 µg/ml ± 7.8 µg/ml.

The patients achieved a total sleep time of 313.6 ± 79.0 min, with 249.5 ± 37.5 min non-REM sleep and 32.0 ± 21.0 min REM sleep. Patients' sleep latency was at 20.0 ± 12.3 min, their REM latency at 201.6 ± 26.6 min, the arousal index at 20.2/h ± 17.5/h and sleep efficiency at 75.7% ± 16.5%. Sleep stage 1 was at 52.4 ± 19.9, stage 2 at 121.9 ± 51.0, stage 3 at 59.1 ± 42.6 and stage 4 at 16.1 ± 11.9 minutes.

3.2. Attention Results
For evaluation of sustained attention under the effect of theophylline, the "Carsim" tracking deviations were analysed. The duration of tracking deviations under placebo was 50.9 ± 107.8 sec., and significantly decreased to 22.1 ± 52.6 sec. under theophylline (T value = 2.285; p = 0.027*; in healthy persons, in an earlier study, we determined the 95% tolerance limit with 13.2 sec of tracking deviations). In 34/50 patients, sustained attention improved after theophylline administration.

In the second part of our study, the duration of tracking deviations under placebo was found to be 119.4 ± 23.6 sec., and it significantly decreased to 7.8 ± 9.9 sec. under theophylline (T value = 15.59; p < 0.001***; Fig. 1). In 9/9 patients, sustained attention improved after theophylline administration: all patients improve on the theophylline.
**Figure 1:** Therapeutic effect of theophylline on tracking deviation by nCPAP-treated patients

![Graph showing the effect of theophylline on tracking deviation](image)

**Legend:** The application of theophylline resulted in a significant improvement of sustained attention, measured by the duration of track deviations.

4. Discussion

We could demonstrate that under therapeutic theophylline levels, one marker of sustained attention, measured by a driving simulator, can be improved. However, 34 of 50 patients in the pilot study and 9 of 9 patients in the main study did improve. Parameters characterizing the severity of the disease, namely AHI, mean AH duration and SaO2min, were not different in the group of responders and non-responders (in both parts of the study).

It must be pointed out that theophylline does not influence mean and minimal O2-saturations during sleep in patients with SAS [6]. However, sleep architecture and sleep quality, which may be disturbed, should not be influenced by theophylline administered in the morning, as the theophylline serum level has gone down by the evening and should therefore no longer have any relevant effect on sleep quality. By using a cross-over study design, even this small influence on sustained attention can be neglected.

Reduced attention and vigilance are relevant symptoms of obstructive sleep apnea. Sustained attention should be investigated according to its components (some of which are selective and divided attention, sustained attention, processing speed).

Thus, various studies have been published which investigate the association between the sleep apnea syndrome and frequency of car accidents. Objectification of divided attention as well as its improvement in the course of nCPAP therapy is of great importance [5, 7, 13, 14].

We therefore developed an easy-to-operate driving simulator ("Carsim"), which requires low levels of fine motor skills and cognitive standards. Among the various test modifications (length of steering, test duration, number of bends and events presented), a 30-minute test with 5-minute practising phase and the presentation of 18 visual events and 6 curves varying in time length was found to be suitable [5]. In an earlier study, we could prove that learning effects are not relevant when repeating the driving test on two consecutive days [4].
In a comparison between a healthy control group and untreated patients with obstructive sleep apnea, great differences in the duration of tracking and tolerance deviations were found [4]. These findings also correspond to the results by Findley et al. [7], George et al. [9], Gerdesmeyer et al. [11] and Randerath et al. [15].

56.7% of OSAS patients showed more than 13.2 sec of tracking deviations (95% tolerance limit for healthy persons; [3]). This percentage is comparable to the tracking errors in the 21 patients of George et al. [8], who used a tracking task with visual search. Half of their patients performed worse than the control subjects, some showing a performance even worse than normals impaired by alcohol.

In a further study, the majority of patients were re-examined with “Carsim” after > 6 months of nCPAP therapy. A clear improvement of the duration of tracking deviations on the driving simulator could be observed, i.e. under nCPAP therapy, the duration of tracking deviations improved significantly [2]. Similar results were also found by Gerdesmeyer et al. [11] and Randerath et al. [15] in their respective studies.

Yet despite nCPAP therapy, about 25% of OSAS patients still showed a reduction of sustained attention, i.e. they were beyond the normal values for persons with undisturbed sleep [2].

Modafinil is a wake-promoting substance producing significant improvements in daytime sleepiness in narcoleptic patients. In a study additionally using Modafinil in 30 OSAS patients who remained sleepy during CPAP, small improvements of alertness could be demonstrated by means of the MWT (Kingshott et al. 2001 [12]), but no significant improvements of cognitive performance or quality of life were found. The authors concluded therefore that this agent could have a certain, limited use for sleepy patients to reduce the regular employment of CPAP.

The driving simulator can identify patients with poor performance. We used the test to document the reduced sustained attention which is characteristic for the disease and to prove the positive effects of theophylline.

Theophylline increases the activity of wake-active neurons in the forebrain by antagonising the effect of adenosine [1]. The application of theophylline resulted in a significant improvement of sustained attention, the performance under theophylline was near the range of healthy persons. It could therefore be considered to employ theophylline in the same way as Modafinil, as an adjunct therapy for patients who in spite of nCPAP therapy show reduced sustained attention.

It is actually not possible to compare the mechanisms of Modafinil and theophylline. Modafinil is a novel wake-promoting agent with central effects not yet fully understood to treat the excessive daytime sleepiness in narcolepsy. Both drugs are effective in treating patients with OSAS and sleepiness, but it is unclear how long and in which intervals the drugs can be used, as in case of prolonged application, tachyphylaxia could develop.

5. Conclusion
The administering of theophylline shows a significant improvement of sustained attention, but Therapy of OSAS with theophylline alone cannot be recommended, as nCPAP therapy represents the causal principle to prevent the obstruction of the upper airways. In many cases, this therapy on its own leads to a normalisation of sleep architecture and consecutively to normal daytime vigilance.
References


