Temazepam 10 mg does not affect breathing and gas exchange in patients with severe normocapnic COPD

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Keywords
Benzodiazepines; Chronic Obstructive Pulmonary Disease; Gas exchange; Insomnia; Sleep; Temazepam

Summary
Background: Benzodiazepines can improve sleep quality, but are also thought to cause respiratory depression in patients with chronic obstructive pulmonary disease (COPD). The aims of this study were to assess the effects of temazepam on indices of circadian respiratory function, dyspnea, sleep quality, and sleepiness in patients with severe COPD and insomnia.

Methods: In a double-blind, randomized, placebo-controlled, cross-over study in 14 stable patients with COPD (mean FEV1 0.99 ± 0.3 L) with insomnia, polysomnography with continuous transcutaneous capnography and oximetry, arterial gas sampling, hypercapnic ventilatory response, multiple sleep latency test, Epworth Sleepiness Scale, dyspnea and sleep visual analogue scales (VAS) were performed at baseline, after one week of temazepam 10 mg at bedtime and after one week of placebo.

Results: Temazepam did not cause statistically significant changes in mean transcutaneous carbon dioxide tension during sleep compared to placebo (5.9 ± 1.0 kPa vs. 6.3 ± 1.4 kPa).

Abbreviation list: ABG, arterial blood gas; AHI, apnea–hypopnea-index; COPD, chronic obstructive pulmonary disease; DI, desaturation index; HCV, hypercapnic ventilatory response; HR, heart rate; PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; PetCO2, end-tidal partial pressure of carbon dioxide; PtcCO2, transcutaneous partial pressure of carbon dioxide; PSG, polysomnography; REM, rapid eye movements; SaO2, arterial saturation of oxygen; SpO2, functional saturation of oxygen; TST, total sleep time; VAS, visual analogue scale.

* This study was registered at www.ClinicalTrials.gov as ‘Effects of temazepam in patients with chronic pulmonary obstructive disease’ (ID number NCT00245661).

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Introduction

The sleep of patients with chronic obstructive pulmonary disease (COPD) is often of poor quality. Up to fifty-three percent of these patients report sleep-related complaints characterized by a longer sleep latency, more frequent arousals and awakenings, and more daytime sleepiness than healthy individuals.

Sleep disturbances can substantially reduce patients' quality of life and, as a result, patients often consult their physician for hypnotics. Twenty-eight percent report frequent use of hypnotics compared to 10% in age-matched controls. Polysomnographic recordings show reductions in total sleep time (TST) and duration of slow wave and rapid eye movement (REM) sleep, more sleep state changes, and an increase in number and severity of arousals during sleep. Benzodiazepines are proven to influence sleep quality beneficially and are the first-choice hypnotics nowadays.

However, ATS/ERS-guidelines state that hypnotics should be avoided in patients with severe COPD. Benzodiazepines may negatively affect breathing during sleep in these patients in several ways; they may decrease the central sensitivity to hypoxic and hypercapnic stimuli, they decrease the arousal response following hypoxaemia or hypercapnia, and they increase upper airway resistance, mainly due to myorelaxation. Other studies, by contrast, did not show any adverse effects of benzodiazepines in patients with COPD.

Several problems occur when interpreting and comparing these studies due to methodological flaws like a single night of drug usage (a possible carry-over effect may be overlooked), inclusion of subjects with varying severity of COPD, the use of different benzodiazepines, and the use of different respiratory outcome variables. Furthermore, none of these studies were performed in COPD patients with insomnia, precisely the patients one might prescribe a hypnotic to. So although several studies have been published about both the benefits and the risks of the use of benzodiazepines in patients with COPD, their use still remains controversial. The effects of temazepam on breathing have, to our knowledge, not been studied in patients with COPD.

The primary objective of this study was therefore to examine whether prolonged usage of the benzodiazepine temazepam influences indices of breathing and gas exchange during sleep in patients with severe COPD who experience insomnia. Secondary objectives were to assess the effects of prolonged usage of temazepam on diurnal breathing, gas exchange, and dyspnea in patients with severe COPD and insomnia. In addition, sleep quality and diurnal sleepiness were examined in these patients.

Methods and materials

Subjects

Subjects were recruited at the outpatient centre of the Respiratory Medicine Department of the Rijnstate Hospital, Arnhem, the Netherlands. Patients were eligible for inclusion if they had COPD GOLD stage 3 or 4 without an exacerbation in the past 6 weeks, and if they experienced insomnia. GOLD stages 3 or 4 were chosen because these patients were anticipated to show the most profound adverse effects when these would occur. Exclusion criteria were the use of any medication influencing sleep architecture within 4 weeks before inclusion, a history of alcohol, benzodiazepine or other drug dependence, allergy to a benzodiazepine, a clinically relevant sleep apnea syndrome (defined as having an apnea–hypopnea-index (AHI) \( \geq 15 \), either measured before enrolment or at the baseline polysomnography (PSG)), and dependency on long-term oxygen therapy. Written and oral informed consent was obtained from all participants and the study was approved by our Institutional Review Board.

Study design

All subjects were studied for three weeks in a double-blind, randomized, cross-over design. Subjects were randomized after the baseline measurements to use 10 mg temazepam or placebo once a day orally, both during one week, separated by a washout-period of one week. Randomization was done by the hospital pharmacy. Subjects were instructed to take the study medication 30 min before they went to bed. Temazepam was proven to improve sleep quality previously.

The rationale for selecting the benzodiazepine temazepam was based on its efficacy, its frequent use as a hypnotic and Dutch guidelines, which advise the use of temazepam 10 mg (or nitrazepam) as first choice hypnotic due to its intermediate half-life and minimal daytime side effects. The temazepam and placebo were provided by the hospital pharmacy as a solution, which was produced as previously described.
Measurements

Before enrolment, all subjects underwent pulmonary function testing with reversibility (after 400 μg salbutamol). A baseline polysomnography (PSG) and a multiple sleep latency test (MSLT) were done for acclimatization purposes and to screen for any possible sleeping disorders. At days 7 and 21 all subjects participated in the following measurements: an arterial blood gas (ABG) was taken at rest, the ventilatory response to hypercapnia (HCVR) was measured, in normoxic conditions, by the steady state method, an MSLT consisting of 4 naps at 2-h intervals was performed, subjective dyspnea, sleepiness, sleep latency and sleep quality in the past week were assessed with 10-point visual analogue scales (VAS) and the Epworth Sleepiness Scale (ESS) was used to evaluate subjective sleepiness after temazepam and placebo use. Higher ESS scores indicate a greater sleepiness, and a cut-off point of 10 is often used to distinguish between normal (<10) and excessive (≥10) daytime sleepiness.

To assess sleep quality with temazepam and placebo, a PSG was performed at night 7 and night 21, which included continuous electro-oculography (EOG), submental muscle electromyography (EMG) and electro-encephalography (EEG) (Sleepscreen, Viasys Healthcare, Hoechberg, Germany). Together with the PSG, heart rate and rhythm were measured by a continuous electrocardiography and oxygen saturation (SpO₂) and transcutaneous carbon dioxide (PtcCO₂) were continuously measured (TOSCA 500, Linde Medical Sensors, Basel, Switzerland) to assess gas exchange during sleep. Furthermore, airflow- and respiratory effort were measured with a nasal/oral thermistor and thoracic and abdominal piezoelectric belts. A bilateral anterior tibialis EMG was performed to exclude periodic leg movements.

Definitions

An apnea was defined as a cessation of oronasal airflow lasting ≥10 s, a hypopnea was defined as a decrease in airflow and/or chest wall movement of 50% or more occurring simultaneously with an oxygen desaturation, the AHI was defined as the number of apneas and hypopneas per hour sleep, an oxygen desaturation was defined as a reduction in oxygen saturation of ≥4% from baseline and the desaturation index (DI) was defined as the number of desaturations per hour sleep. Parameters to describe sleep quality were the total sleep time (TST), sleep-onset latency and sleep quality as measured by PSG. Both the slope (Δminute ventilation (VE)/end-tidal carbon dioxide tension (PetCO₂)) and intercept (L/min) of the HCVR were analyzed. Sleep latency was manually staged according to standard methods by two qualified sleep technicians blinded to the subject’s treatment status. Data are expressed as means (SD) for quantitative variables or as means ± SEM when percentages are compared. We used a Student’s t test for paired series and χ² – test for continuous and discrete variables respectively to compare between the data obtained after a week temazepam and the data obtained after a week placebo. P values <0.05 were considered statistically significant. All statistical analyses were carried out using the SPSS version 12.0 statistical package (SPSS, Inc., Chicago, IL).

Results

Subjects

Fig. 1 shows a flow diagram of the selection of the subjects. Seventeen patients were enrolled in the study, but 3 subsequently dropped out. One subject appeared from the first PSG to have an obstructive sleep apnoea–hypopnoea syndrome and was therefore excluded; another subject developed an exacerbation of his COPD during the study and was excluded, and a third subject withdrew from participation due to the burden of the measurements. Fourteen subjects completed the study-protocol; their demographic data and characteristics are presented in Table 1. The sleep-related complaints of the subjects were difficulty maintaining sleep (experienced by 8 subjects), a prolonged sleep-onset latency (experienced by 7 subjects), extensive daytime sleepiness (experienced by 6 subjects), and nocturnal dyspnea (experienced by 2 subjects).

Respiratory and sleep variables

The effects of temazepam and placebo on diurnal and nocturnal respiratory variables are listed in Table 2; their effects on variables concerning sleep architecture and sleep quality are listed in Table 3 and their effects on daytime sleepiness are listed in Table 4. None of the changes were statistically significant, except for the TST (increased), the amount of stage 2 sleep (increased), and the VAS-scale on sleep latency (improved).

Discussion

The main finding of the present study is that prolonged usage of temazepam 10 mg in the evening did not influence indices of gas exchange and breathing during sleep in our patients with severe normocapnic COPD who experience insomnia. Furthermore, it seems that diurnal gas exchange, respiratory centre control, subjective dyspnea, objective and subjective daytime sleepiness were not affected by

Analysis

We aimed to detect a 0.5 kPa difference in PtcCO₂ (based on previous studies) at the 5% significance level for a one-sided test with 80% power. With a crossover design, this would require 14 patients. To anticipate possible dropouts, we planned to include 17 patients.

The primary outcome parameters were the PtcCO₂ and SpO₂ levels during sleep, and secondary parameters were the AHI and DI, the HCVR, the ABG values, the levels of subjective and objective sleepiness (represented by VAS-scales, ESS and MSLT outcomes), dyspnea sensation (VAS), sleep latency (VAS), sleep quality (VAS), and the sleep quality as measured by PSG. Both the slope (Δminute ventilation (VE)/end-tidal carbon dioxide tension (PetCO₂)) and intercept (L/min) of the HCVR were analyzed. Sleep latency was manually staged according to standard methods by two qualified sleep technicians blinded to the subject’s treatment status.
temazepam compared to placebo, while TST and subjective sleep latency improved in these patients.

Neither the indices of gas exchange during sleep ($P_t\text{CO}_2$ and $\text{SpO}_2$), nor the indices of breathing during sleep (AHI and DI) were affected by temazepam compared to placebo. Evidence that diurnal gas exchange, respiratory centre control, and subjective dyspnea are not affected by temazepam is that daytime $\text{PaCO}_2$, $\text{PaO}_2$, HCVR, and VAS scales remained unchanged with temazepam.

Our findings are consistent with those of prior reports, but contrary to those found in other studies. These studies were all randomized clinical trials with a sample size ranging from 9 to 24 subjects. One study had a study population of healthy subjects, the other five only included patients with COPD (FEV1 predicted ranging from 17 to 76%). The study drugs were diazepam, flunitrazepam, nitrazepam, triazolam, zolpidem, and zopiclone.

The differences in outcomes might be explained by one of the following reasons. First, outcomes are likely to be influenced by the pharmacological profiles of the used benzodiazepines. This is, to our knowledge, the first study to evaluate temazepam in the present context. Comparisons to other studies should therefore be done with care.

Second, our outcomes might have been different when a higher dose of temazepam would have been used. Although larger doses (15–20 mg temazepam) are sometimes prescribed for insomnia, we chose to use the smallest dose likely to be effective. Further studies are needed to assess the adverse effects of larger doses.

Third, the designs of studies and duration of drug use (a single night vs. one week) might play a role in outcomes. With the prolonged use as was done in this study, a possible carry-over effect could be examined. Fourth, it might be that our study was too under-powered to demonstrate an

### Table 1 Characteristics of the 14 subjects enrolled in the study.

<table>
<thead>
<tr>
<th>Patient data</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>61.6 ± 8.0</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/4</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>0.99 ± 0.3</td>
</tr>
<tr>
<td>FEV1, % predicted (%)</td>
<td>33.5 ± 9.2</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>32.7 ± 13</td>
</tr>
<tr>
<td>Reversibility of FEV1, % predicted (%)</td>
<td>3.34 ± 3.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.2 ± 5</td>
</tr>
<tr>
<td>Baseline $\text{PaCO}_2$, kPa</td>
<td>5.4 ± 0.4</td>
</tr>
<tr>
<td>Baseline $\text{PaO}_2$, kPa</td>
<td>9.6 ± 0.7</td>
</tr>
<tr>
<td>Smoking status, pack-years</td>
<td>43.1 ± 15.9</td>
</tr>
<tr>
<td>Former, n</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Current, n</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Medication, N (%)</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>13 (93)</td>
</tr>
<tr>
<td>$\beta_2$ agonists</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Other antihypertensiva</td>
<td>4 (29)</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index; FEV1 = Forced Expiratory Volume in 1 s; FVC = Forced Vital Capacity; $\text{PaCO}_2$ = Arterial pressure of carbon dioxide; $\text{PaO}_2$ = Arterial pressure of oxygen. Data are expressed as mean ± SD or N. (%) unless otherwise stated.
effect. This might especially concern any secondary variables, since the present sample size was based on the primary variables PtcCO₂ and SpO₂. Outcomes in secondary variables might have been different with a larger sample size. Due to the crossover design, this study was capable to detect a 0.5 kPa difference in PtcCO₂ and a 4% difference in nocturnal SpO₂, both with 80% power, with only 14 subjects.

Temazepam beneficially influenced the sleep quality by lengthening the TST, it improved the subjective sleep latency, and increased the amount of stage 2 nREM sleep. It did not significantly influence other parameters of sleep quality and sleep architecture nor did it improve objective and subjective daytime sleepiness in our population.

A strong point of this study is the measurement of PtcCO₂ during sleep. To our knowledge, this is one of the first studies where PtcCO₂ was measured to assess the effects of a benzodiazepine on gas exchange during sleep. Nocturnal measurements of PtcCO₂ have rarely been performed due to the insufficient accuracy and risk of burns associated with older capnometers. The current

### Table 2 Respiratory variables.  

| Variables | Baseline | Temazepam | Placebo | p Value  
|-----------|----------|-----------|---------|----------
| PtcCO₂ during sleep, kPa | | | |  
| Mean  | 6.2 ± 0.6 | 5.9 ± 1.0 | 6.3 ± 1.4 | 0.27  
| Highest | 6.9 ± 0.6 | 6.4 ± 1.1 | 7.3 ± 2.0 | 0.13  
| Lowest | 5.3 ± 0.7 | 4.9 ± 1.2 | 5.5 ± 1.0 | 0.08  
| % TST with PtcCO₂ > 7 kPa | 9.9 ± 22.1 | 7.8 ± 26.5 | 8.0 ± 26.5 | 0.75  
| SaO₂ during sleep, % | 92 ± 2 | 92 ± 3 | 92 ± 2 | 0.31  
| Lowest | 82 ± 5 | 81 ± 4 | 83 ± 5 | 0.24  
| % TST with SaO₂ < 90% | 8.3 ± 19.3 | 7.2 ± 11.0 | 6.1 ± 16.4 | 0.96  
| AHI, /h TST | 5.4 ± 5.9 | 6.8 ± 6.3 | 5.1 ± 5.2 | 0.40  
| DI, /h sleep | 10.1 ± 8.8 | 8.9 ± 8.6 | 7.9 ± 6.3 | 0.61  
| HCVR | | | |  
| Slope (L/min/kPa) | 4.0 ± 4.4 | 5.6 ± 4.5 | 5.7 ± 4.8 | 0.99  
| Intercept (L/min) | −6.7 ± 23.4 | −13.7 ± 20.7 | −13.4 ± 21.5 | 0.96  
| Daytime PaCO₂, kPa | 5.4 ± 0.4 | 5.5 ± 0.6 | 5.5 ± 0.5 | 0.62  
| Daytime PaO₂, kPa | 9.6 ± 0.7 | 9.3 ± 1.0 | 9.6 ± 0.9 | 0.14  
| Subjective dyspnea (VAS), pts | 3.8 ± 2.6 | 4.2 ± 2.9 | 4.1 ± 2.5 | 0.90  

AHI = Apnea–hypopnea-index; DI = Desaturation Index; HCVR = Ventilatory response to hypercapnia; PtcCO₂ = Transcutaneous partial pressure of carbon dioxide; SaO₂ = Oxygen saturation; TST = Total sleep time; VAS = Visual analogue scale.

Note that normal values of HCVR in healthy subjects are as follows: slope 13.9 ± 7.1 L/min/kPa, intercept −62.9 ± 36.8 L/min.  

Data are expressed as mean ± SD.

For comparisons between temazepam and placebo.
Temazepam and severe COPD

Table 4 Variables on objective and subjective diurnal sleepiness. a

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Temazepam</th>
<th>Placebo</th>
<th>p Value b</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSLT, min.</td>
<td>16.5 ± 4.6</td>
<td>15.8 ± 4.6</td>
<td>14.7 ± 4.6</td>
<td>0.38</td>
</tr>
<tr>
<td>ESS, pts.</td>
<td>6 ± 4</td>
<td>5 ± 4</td>
<td>6 ± 4</td>
<td>0.13</td>
</tr>
<tr>
<td>Daytime sleepiness (VAS), pts</td>
<td>4.7 ± 3.0</td>
<td>4.7 ± 3.2</td>
<td>4.8 ± 2.6</td>
<td>0.86</td>
</tr>
</tbody>
</table>

ESS = Epworth Sleepiness Scale; MSMT = Multiple sleep latency test; VAS = Visual Analogue Scale. a Data are expressed as means ± SD. b For comparisons between temazepam and placebo.

transcutaneous device, by contrast, has been reported to accurately assess PCO2 in routine respiratory practice, 29 in critically ill adults, 30 in newborns, 31 and during cardiopulmonary exercise testing 32 without the occurrence of any major complications. Although this apparatus has not yet been validated during sleep, we think that it can accurately measure nocturnal PtcCO2 since its use on an intensive care unit is also for an extended period of time.

Other strong points are the inclusion of subjects with only severe COPD (FEV1 predicted <50%), who in addition experienced insomnia, the study period of 7 days instead of a single day or night, and the timing of the measurements; unlike several previous studies, we not only examined the subjects awake, but also while they were asleep.

Limitations of this study are present as well. We did not compare temazepam to other benzodiazepines or a non-benzodiazepine benzodiazepine-receptor agonist (NBBRA). An intermediate-acting benzodiazepine was chosen since long- and short-acting benzodiazepines are not recommended for the short-term management of insomnia, and because only minor differences in efficacy exist between NBBRA’s and benzodiazepines, 33 these two groups of hypnotics were not compared with each other.

Another limitation is the relatively low dosage of temazepam, used for reasons mentioned above. Furthermore, at the start of the second study week the stability of the COPD was not objectively confirmed with spirometry, but only assessed on clinical grounds.

Temazepam caused no adverse respiratory events for the group as a whole, but it is possible that these events occur on an individual scale, because some individuals, like patients with other, unfavorable pharmacodynamics, patients who may take extra doses of temazepam, or patients with other sleep disturbances, might be more susceptible to adverse events than others. Therefore, the sample size may have been too small to include some of those ‘more susceptible’ patients. Studies with larger sample sizes will be needed to include some of those more susceptible patients as well.

Our conclusions cannot safely be applied to other, related situations such as the use of other benzodiazepines, larger doses of temazepam, periods longer than our study period of one week, or to patients with an exacerbation of their COPD, to hypercapnic COPD patients, to patients with COPD plus a sleep-apnea syndrome or to patients with other pulmonary diseases. In the mentioned situations and patients groups, use of temazepam is still to be seen as experimental.

In the light of the mentioned limitations, this study is best to be seen as a preliminary explorative study for assessing the feasibility to perform a larger study on this topic, and the clinical implications of this study are very limited. Larger studies would be necessary to determine the role of benzodiazepines and NBBRA’s in the pharmacological management of insomnia during an exacerbation in patients with (severe) COPD and in the aforementioned situations and patients groups. Until those studies are performed, guidelines on this subject like the ATS–ERS guideline 10 should not be more liberate and temazepam and other benzodiazepines should still be used with great caution in these situations and patients. Also, temazepam should only be used in patients with COPD when other, non-pharmacological therapies for insomnia have failed, and then only for a short period. Its use should carefully be watched and reevaluated when the patient develops an exacerbation of the COPD or worsens for other reasons.

Physicians should be aware that the prevalence of insomnia in patients with COPD can be as high as 50%, 2 and that insomnia can have a major negative impact on the quality of life of these patients. Hence, by improving sleep quality physicians have a tool to presumably improve the quality of life of their patients with COPD.

In conclusion, in this preliminary study repeated doses of temazepam did not adversely affect nocturnal respiratory function in our severe but stable normocapnic COPD patients without complications, but it did improve TST and sleep-onset latency. Furthermore, temazepam did not affect diurnal gas exchange, diurnal central respiratory centers, and subjective dyspnea.

Temazepam can, in our view, not automatically be dismissed from patients with stable, normocapnic COPD who experience insomnia and consequently have a reduced quality of life, but it remains to be seen as a last resort when other, non-pharmacological remedies have failed.

Acknowledgements

The authors owe much gratitude to the participants of this study, to the Clinical Neurophysiology Department at the Rijnstate Hospital and Sleep Laboratory at Velp Hospital for their assistance in the study logistics and data collection, and to GlaxoSmithKline for the financial support. The funding agency did not have any involvement in the study design, data collection, data analysis, interpretation of data, manuscript preparation and/or in the decision to submit the paper for publication.

Conflict of interest statement

None declared.

Funding

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*Table 4*  Variables on objective and subjective diurnal sleepiness. a

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