Does oral alprazolam affect ventilation? a randomised, double-blind, placebo-controlled trial

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Abstract

The respiratory effects of benzodiazepines have been controversial. This investigation aimed to study the effects of oral alprazolam on ventilation. In a randomised, double-blind cross-over protocol, 20 healthy men ingested 1 mg of alprazolam or placebo in random order, 1 week apart. Ventilation was unobtrusively monitored by inductance plethysmography along with end-tidal PCO2 and pulse oximetry 60-160 min after drug intake. Subjects were encouraged to keep eyes open. Mean \(\sqrt{\text{I(1/2)}/\text{I}}\) was similar (6.21 +/- 0.71 vs 6.41 +/- 1.12 L/min, P = NS). End-tidal PCO2 and oxygen saturation did also not differ between treatments. However, coefficients of variation of minute ventilation after alprazolam exceeded those after placebo (43 +/- 23% vs 31 +/- 13%, P < 0.05). More encouragements to keep eyes open were required after alprazolam than after placebo (5.2 +/- 5.7 vs 1.3 +/- 2.3 calls, P < 0.05). In a multiple regression analysis, higher coefficients of variation of minute ventilation after alprazolam were related to a greater number of calls. Oral alprazolam in a mildly sedative dose has no clinically relevant effect on ventilation in healthy, awake men. The increased variability of ventilation on alprazolam seems related to vigilance fluctuations rather than to a direct drug effect on ventilation.
Respiratory Effects of Alprazolam in Healthy Men.

A Randomized, Double-Blind, Placebo-Controlled Trial

By

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Running head: Respiratory effects of alprazolam

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Abstract

The respiratory effects of benzodiazepines have been controversial. We therefore investigated the effects of alprazolam, an anxiolytic benzodiazepine, on ventilation. In a randomized cross-over protocol 20 healthy men (mean age ±SD 28±9y), ingested 1 mg of alprazolam or placebo in random order, 1 week apart. Ventilation was unobtrusively monitored by inductance plethysmography along with end-tidal carbon dioxide tension, pulse oximetry and ECG during 2 periods of 20 minutes starting 40 and 100 min after drug intake. Subjects rested supine and were encouraged to keep their eyes open. Minute ventilation 40 and 100 minutes after alprazolam intake was 6.53±0.87 and 6.21±0.71 L/min, corresponding values on placebo were 6.45±1.29 and 6.41±1.12 L/min, P=NS, all instances. End-tidal carbon dioxide tension and oxygen saturation did not differ between alprazolam and placebo. However, coefficients of variation of minute ventilation were greater during alprazolam than during placebo sessions, i.e., 51±41% and 43±23%, vs. 30±16% and 31±13%, P<0.05. Encouragements to keep eyes open were required more frequently during alprazolam than during placebo sessions (5.5±5.8 and 5.2±5.7 calls, vs. 1.2±2.7 and 1.3±2.3 calls, P<0.05). In a multiple regression analysis the higher coefficients of variation of minute ventilation during alprazolam sessions were related to a greater number of calls suggesting a reduced vigilance. In conclusion, oral alprazolam in a mildly sedative dose has no clinically relevant effect on ventilation in healthy, awake men. The increased variability of ventilation on alprazolam seems to derive from vigilance fluctuations rather than from a direct drug effect on ventilation.

Key words: anxiety, drug treatment, side effect, ventilation, apnea, hypoventilation, benzodiazepine, alprazolam
INTRODUCTION

Benzodiazepines are widely used for treatment of anxiety and sleep disorders in hospitalized patients and outpatients. Nevertheless, their respiratory effects are incompletely understood. When ingested in high doses or administered intravenously, benzodiazepines may induce hypoventilation in normal subjects and in patients with chronic obstructive lung disease (COPD). In patients with obstructive sleep apnea syndrome (OSA) intravenous benzodiazepines may trigger upper airway obstruction with apnea during sleep. Conversely, clinical experience suggests that relevant respiratory depressant effects of low dose oral benzodiazepines are rare. However, there are very few and partly controversial trials to support this impression. For example, Mak and colleagues found no reduction of the ventilatory response to carbon dioxide in 6 normal subjects after oral midazolam or diazepam administration. In 11 and 15 patients with mild to moderate obstructive sleep apnea nitrazepam and temazepam, respectively, did not alter nocturnal oxygen saturation nor induce apnea. In 14 patients with mild to moderate hypoxemic, nonhypercapnic COPD oral nitrazepam and flunitrazepam did not impair nocturnal oxygenation but in 12 awake patients with severe COPD oral flunitrazepam slightly reduced minute ventilation and the ventilatory response to carbon dioxide. Interestingly, Dodson and colleagues found an unchanged slope of the ventilatory response to carbon dioxide in 11 healthy subjects after ingestion of lorazepam but the position of the response curve was shifted to the left implying ventilatory stimulation. Studies in rats and observations in mountaineers at high altitude and in patients with central sleep apnea due to heart failure suggested that benzodiazepines may decrease the occurrence of central sleep apnea. In summary, studies on respiratory effects of orally administered benzodiazepines are scant, have a limited statistical power and have provided conflicting results. We therefore performed a randomized, double-blind, placebo controlled cross-over study on the respiratory effects of alprazolam, an anxiolytic widely used...
in clinical practice. The purpose was to evaluate the hypothesis that alprazolam at an anxiolytic oral dose would not suppress or even stimulate ventilation in awake healthy subjects. To avoid the well known effect of airway instrumentation on breathing pattern and ventilation 16 we employed respiratory inductive plethysmography, an unobtrusive technique, to monitor ventilation 17.

**MATERIALS AND METHODS**

**Subjects**

Twenty healthy non-smoking men, mean ±SD age 28 ±9 years, with normal spirometry (FEV1 99 ±10 % predicted, FVC 100 ±9 % predicted) were recruited. They had no evidence of anxiety disorder (Beck anxiety Inventory, BAI, 4 ± 3) 18. Subjects gave written informed consent and the study was approved by the Hospital Ethics Committee. The trial was registered at the Swiss Agency for Therapeutic Products (#2005DR2056).

**Assessments**

A general medical history was obtained. Height, weight, blood pressure, and pulse rate were measured. Symptoms of anxiety in the last 30 days were evaluated with the Beck Anxiety Inventory (BAI) 18. Anxiety before and during the investigations was monitored using the short version of the Spielberger State-Trait-Anxiety Inventory (STAI-K) 19,20 and a visual analogue scale (VAS) ranging from completely relaxed (0 mm) to extremely nervous (100 mm). Spirometry was performed according to standard techniques 21.

Ventilation and the patterns were recorded by calibrated respiratory inductive plethysmography a technique that accurately monitors lung volume changes without the need for instrumentation of the airway 22,23. The inductance plethysmograph (Respirace PT, Non-
Invasive Monitoring Systems, Miami Beach, FL, USA) incorporated a pulse oximeter and an ECG. The rib cage and abdominal inductance sensors were placed at the level of the nipples and the umbilicus, respectively, and secured with tape. The relative gain of their signals was determined by the Qualitative Diagnostic Calibration (QDC) method during natural breathing and the sum of the two signals was calibrated against the integrated output of a flow meter. Validation of the calibration at the end of studies revealed a $\leq 10\%$ deviation of mean tidal volume by inductance plethysmography from corresponding flow meter values in all instances. End-tidal carbon dioxide concentration (Normocap, Datex-Ohmeda, Helsinki, Finland) derived from the nares, and transcutaneous carbon dioxide tension measured by a probe at the volar side of the forearm (Microgas 7650, Kontron Instruments, Schlieren, Switzerland) were recorded as surrogates of the arterial PCO$_2$ and calibrated at the beginning and end of the recordings. Sampling rate for all signals was 50 Hz.

**Protocol**

This was a randomized, double-blind, placebo-controlled, cross-over study. The hospital pharmacy prepared sets of 2 identically looking capsules with one containing 1 mg alprazolam (Xanax®, Pfizer AG, Zurich, Switzerland) and the other placebo. Each set was labeled with a number code that identified the capsule prepared for session one and two, respectively. To obtain a balanced design 10 sets contained placebo and 10 alprazolam in the capsule for the first session. The code was not broken until completion of data analysis.

On the study days, subjects were allowed to drink no more than 1 cup of coffee or black tea on that morning, but to do the same at both investigation days. At 11 am. they reported to the laboratory, completed the anxiety questionnaires and ingested the capsule for the first session. Once the monitoring equipment was prepared subjects took place in a comfortable supine position on a bed in the sound-proof laboratory. They were instructed to rest quietly and keep their eyes open. Measurements started at 11:40 a.m., lasted for 40 min during which
subjects watched a documentary video, and were repeated after a 20 min break at 12:40 p.m.. Anxiety questionnaires were completed after each measurement period. During the measurements subjects were constantly observed by a technician from the adjacent control room by a video camera. If the technician had the impression that a subject did not concentrate on the video or tended to sink the eye lids she encouraged him to watch the video via a microphone-loud-speaker system and recorded the time of the call.

One week after the first recording session, at the same time of the day, the same protocol was repeated after administering the second capsule.

**Data analysis and statistics**

Breathing pattern variables were determined breath by breath by specialized software (RespiEvents, Noninvasive Monitoring Systems, USA)\(^23\). Medians of physiologic variables during the final 20 minutes of each recording, i.e. at 12 noon and at 1 p.m., were computed. For the group, data from verum and placebo sessions were expressed as means ±SD, and compared by paired t-tests. Variances were compared by Levene’s test for equality of variance. A probability of <0.05 was considered statistically significant. Based on previous studies\(^23;26\) a sample size of >17 subjects was required to detect clinically relevant differences in PtcCO2 of 4 mmHg, in SpO2 of 3% and in minute ventilation of 0.6 L/min with a power of 0.8 (alpha=0.05).

**RESULTS**

Table 1 summarizes the main outcomes. As expected, alprazolam had a sedative effect as demonstrated by the higher number of calls required to draw the subjects’ attention to the
video. The anxiety visual analog scores and the STAI-K scores were already very low during placebo sessions and no further decrease was noted with alprazolam.

Neither the mean minute ventilation, nor any other breathing pattern variable were altered by alprazolam compared to placebo. In addition, arterial oxygen saturation and transcutaneous and end-tidal carbon dioxide tensions remained unchanged as well (table 1). However, inspection of individual recordings revealed that the breathing patterns during alprazolam were more irregular than during placebo (figure 1). To quantify this irregularity, the coefficients of variation (i.e. the SD in percent of the mean value) of breath-by-breath breathing pattern variables were computed. The results confirmed a significantly greater intra-individual variability of minute ventilation, tidal volume and breath rate with alprazolam than with placebo (table 2). A graphical display of the distribution of individual results further revealed a greater inter-individual scatter of data during alprazolam compared to placebo sessions for minute ventilation, tidal volume and end-tidal carbon dioxide tension (Figure 2).

To investigate the determinants of the breathing pattern variability, a multiple regression analysis was performed with the coefficients of variation of minute ventilation as dependent and alprazolam or placebo, vigilance level (represented by the number of encouraging calls needed to maintain subjects awake), the first or second measurement period and anxiety level (VAS scores at the end of measurement periods) respectively, as independent variables. This analysis revealed that the greater variability of minute ventilation during alprazolam sessions (Beta = 0.14, P=0.24) was related to a reduced vigilance, i.e. a greater number of encouraging calls (Beta = 0.39, P=0.002), even if controlled for the measurement period (Beta = -0.49, P=0.63) and the anxiety level (Beta = -0.10, P=0.38). The model explained 21% of the variance in the outcome (R = 0.46, SEE=24, P=0.001).
DISCUSSION

We performed a randomized, double-blind, placebo-controlled trial of the respiratory effects of alprazolam administered orally in a dose commonly used to treat anxiety in outpatients. Alprazolam did not affect mean ventilation, arterial oxygen saturation, carbon dioxide tension and heart rate in healthy men although fluctuations in vigilance under the influence of alprazolam were associated with an increased variability of ventilation. The findings are novel and important since alprazolam is widely used for treatment of anxiety and since its respiratory effects have not been rigorously studied. The absence of a clinically relevant ventilatory depressant effect of alprazolam is reassuring since it contrasts to some reports on other benzodiazepines administered intravenously or in high doses.

Zacharias and coworkers found a transient reduction in mean minute ventilation from 7.4 L/min to 4.0 L/min lasting for approximately 5 min after intravenous premedication by midazolam in 17 male and 17 female otherwise healthy patients undergoing a dental treatment. Although arterial oxygen saturation was not significantly altered a potential change in alveolar ventilation could not be assessed since arterial PCO₂ was not measured. Some degree of initial hyperventilation due to anxiety before the dental procedure and a subsequent reduction of ventilation to normal or only slightly reduced values under the influence of the benzodiazepine could not be ruled out either. Mora and coworkers monitored ventilation by a pneumotachograph attached to a facemask during sedation by an intravenous midazolam infusion in 16 patients in normal cardiorespiratory health undergoing colonoscopy. Although there was a slight increase in the end-tidal carbon dioxide tension over baseline after midazolam administration, the values remained well within the normal range, i.e. 42 mmHg at the end of the infusion, and minute ventilation and the ventilatory response to CO₂ were unchanged. Dodson and coworkers observed an unchanged slope of the ventilatory response to CO₂ in 11 volunteers after oral administration of 1 mg and of 2.5 mg of
lorazepam. Interestingly, the position of the CO₂ response curve was shifted to the right suggesting even a slight ventilatory stimulant action of the benzodiazepine.

The current investigation helps to resolve the partly contradictory findings from previous studies on the respiratory effects of benzodiazepines. By using respiratory inductive plethysmography to monitor breathing patterns we were able to avoid the well known stimulatory effect of airway instrumentation on ventilation. In addition, we estimated arterial PCO₂ from end-tidal and transcutaneous measurements without the need for an arterial puncture or catheterization which might also have stimulated ventilation by the associated pain and inconvenience. Even in the absence of such irritation and in slightly sedated subjects who had to be encouraged to keep their eyes open we did not observe a depressant effect of alprazolam on ventilation and gas exchange. These negative findings are well corroborated by the rigorous design of our randomized, placebo controlled and appropriately powered study.

Alprazolam sessions were associated with an increased variability of breath rate, tidal volume and minute ventilation (table 2). However, multiple regression analysis revealed, that alprazolam was not an independent predictor of an increased variability of the breathing pattern when the number of calls to keep the eyes open we taken into account. Therefore, the apparent ventilatory destabilizing effect of alprazolam seemed to be related to fluctuations in vigilance or arousal state rather than by a direct action of alprazolam on control of breathing. The greater between-subject variation of breathing pattern characteristics with alprazolam compared to placebo (figure 2) might reflect individual differences in the response to the drug.

The results of our study cannot be extrapolated to patients with severe and hypercapnic chronic obstructive pulmonary disease (COPD) in whom oral triazolam and flunitrazepam induced a rise in PaCO₂ and a fall in minute ventilation. In addition, caution with the use of benzodiazepines is also warranted in patients with the obstructive sleep apnea syndrome since
they might experience an increased tendency to collapse their upper airway \textsuperscript{29}. Conversely, preliminary data indicate that benzodiazepines may have a stabilizing effect on ventilation in patients with central sleep apnea \textsuperscript{15}, and on the periodic breathing with central apneas observed in healthy subjects at high altitude \textsuperscript{30}.

In conclusion, we found that alprazolam, a drug widely used to treat anxiety in outpatients, does not have a clinically relevant effect on ventilation in healthy, awake men when administered in an oral dose that induces sedation.
REFERENCES


Figure Legends

**Figure 1**

Example of a time series of inductive plethysmographic rib cage (RC), and abdominal volume signals (AB) along with their sum which corresponds to instantaneous lung volume changes (Sum) during placebo-session (*top*) and alprazolam-session (*bottom*). Note particularly the periodical breathing, which was often observed. Increase of ventilation is against to interpret as a seldom effect. Alprazolam was associated with a greater variability of breathing patterns than placebo.

**Figure 2**

Distribution of individual results (triangles) of end-tidal carbon dioxide partial pressure (PetCO₂) and breathing pattern variables along with mean values (horizontal lines). During alprazolam sessions (Alpr), the scatter of data was significantly greater than during placebo sessions (Plac) for PetCO₂, minute ventilation, and tidal volume (Levene’s test for equality of variance P<0.05).
figure 1
Figure 2

(A) Minute Ventilation (L/min)

(B) Tidal Volume (L)

(C) Breath Rate (1/min)

(D) PetCO₂ (mmHg)

Data points are plotted for times 12 noon and 1 p.m. for each day.

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*Note: The figure illustrates the variability in respiratory parameters over time.*
Table 1. Effects of Alprazolam on Ventilation, Breathing Patterns and Anxiety

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Alprazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 noon</td>
<td>1 p.m.</td>
</tr>
<tr>
<td>Minute ventilation (V'I), L/min</td>
<td>6.53 (0.87)</td>
<td>6.21 (0.71)</td>
</tr>
<tr>
<td>Tidal volume (VT), L</td>
<td>0.43 (0.08)</td>
<td>0.40 (0.07)</td>
</tr>
<tr>
<td>Breath rate, breaths/min</td>
<td>15.8 (2.5)</td>
<td>16.2 (2.6)</td>
</tr>
<tr>
<td>Duty cycle (Tl/Ti)</td>
<td>0.41 (0.03)</td>
<td>0.41 (0.04)</td>
</tr>
<tr>
<td>VT/Ti, ml/seconds</td>
<td>247 (97)</td>
<td>236 (91)</td>
</tr>
<tr>
<td>Apneas/hypopneas (events/20 min)</td>
<td>0.40 (0.99)</td>
<td>0.30 (0.66)</td>
</tr>
<tr>
<td>SpO2, %</td>
<td>97.6 (1.00)</td>
<td>97.7 (0.81)</td>
</tr>
<tr>
<td>PtcCO2, mmHg</td>
<td>46 (2)</td>
<td>48 (4)</td>
</tr>
<tr>
<td>PetCO2, mmHg</td>
<td>45 (2)</td>
<td>44 (3)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>62.4 (8.4)</td>
<td>61.7 (8.9)</td>
</tr>
<tr>
<td>Vigilance (calls during 20min)</td>
<td>1.2 (2.7)</td>
<td>1.3 (2.3)</td>
</tr>
<tr>
<td>Anxiety – VAS</td>
<td>12 (8)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Anxiety – State Anxiety inventory</td>
<td>8.5 (2.0)</td>
<td>8.0 (1.9)</td>
</tr>
</tbody>
</table>

Means ±SD, n=20; VT/Ti: mean inspiratory flow; SpO2: oxygen saturation by pulse oximetry; PtcCO2 and PetCO2: transcutaneous and end-tidal CO2 tension; VAS: visual analog scale ranging from 0 to 100 mm. * P<0.05 vs. placebo;
### Table 2. Variability of Ventilation During Alprazolam and Placebo Sessions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Alprazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 noon</td>
<td>1 p.m.</td>
</tr>
<tr>
<td>CV minute ventilation (V'I), %</td>
<td>30 (16)</td>
<td>31 (13)</td>
</tr>
<tr>
<td>CV tidal volume (VT), %</td>
<td>34 (20)</td>
<td>35 (17)</td>
</tr>
<tr>
<td>CV breath rate, %</td>
<td>18 (8)</td>
<td>18 (8)</td>
</tr>
</tbody>
</table>

N=20; values are mean (SD) coefficients of variation (CV = SD/mean, percent) for within subjects variability during the measurement periods; * P<0.05 vs. corresponding value on placebo.