Effect of alprazolam (0.5 mg) on driving performance of anxiety patients and healthy controls

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Abstract

Background
Alprazolam is a widely prescribed anxiolytic for the treatment of anxiety, panic disorder, and depression. Current literature suggests that alprazolam impairs driving performance (e.g. Verster et al., 2002; Vermeeren et al., 2009).

Aims
In the present study the major objective was to investigate the effect of alprazolam in treated and untreated anxiety patients compared to a healthy control group after oral alprazolam administration (0.5 mg) (acute phase) in a simulated environment. Primary variables were the vehicle variables (driving performance measures). The secondary objective was to compare multiple cognitive and subjective measures collected for each participant in order to establish the whole range of driving impairment.

Methods
In this study, the alprazolam effect (0.5 mg) on drivin performance was investigated in three experimental groups: a) treated anxiety patients, b) untreated anxiety patients, and c) control group. 51 (38.2 ±10.5 years old) participants completed two driving tasks; a lane tracking and a car following scenario with a semi-dynamic passenger car simulator. Impaired weaving control was observed in all groups after alprazolam administration. Increase in brake reaction time (sec) was found in treated and untreated anxiety patients when driving in the car following scenario. Healthy participants showed riskier close following behaviour after alprazolam administration compared to treated and untreated anxiety patients ($p<.001$). A significant decrease in alertness -measured in computerised attention tests -was found only in healthy participants ($p=.015$). Untreated patients and healthy participants reported decreased vigilance.

Discussion and conclusions
This study clearly showed an alprazolam effect (0.5mg) in driving performance in treated, untreated anxiety patients and healthy participants.

Introduction

Alprazolam (Generic Xanax®) is a benzodiazepine derivative mainly prescribed for the treatment of generalised anxiety, panic disorder, and depression. It is the most often prescribed psychoactive substance (Verster et al., 2002). The usual clinical dosages of alprazolam, administrated in divided doses, range from 0.5 mg to 4 mg/day for the treatment of anxiety disorder and from 6 to 10 mg/day for the treatment of panic disorders. Reported adverse effects after alprazolam intake include sleepiness, sedation, drowsiness, and reduced alertness.

Current studies advocate that alprazolam might have detrimental effects on driving performance. Verster and colleagues (2002) investigated the acute effects of alprazolam (1mg) on driving performance during real traffic in conjunction with laboratory tests related

to driving skills. Statistically significant differences were found between the alprazolam and placebo groups with regards to Standard Deviation of Lateral Position (SDLP), Standard Deviation of Speed (SDS) accompanied by impairment in laboratory tests. Vermeeren and colleagues (2009) reviewed related literature on axiolytics' effect on driving. Their discussion on over-the-road driving points out that the mean increase of SDLP in this study was comparable to BAC=1.5mg/ml (Louwerens et al., 1987). Subjective assessment showed also impairment in driving quality, decrease in alertness, lower mental activation, and increased mental effort. Verster and colleagues (2005) carried out a literature review on 14 placebo controlled and double blind studies which investigated the effects of anxiolytic drugs on on-the road tests. Standard Deviation of Lateral Position (SDLP) was the main driving parameter. They concluded that among other types of benzodiazepines a single dose of alprazolam might impaired driving performance (i.e. increased weaving was recorded). The authors suggested patients treated with alprazolam should be cautioned when driving a car and that it might not be safe to drive while under alprazolam therapy.

In general, relevant studies have shown detrimental impairment due to alprazolam administration on driving performance (e.g. Snyder et al., 2005), controlled laboratory settings (e.g. Seppala et al., 1986) and subjective scales (Vermeeren et al. 2009).

Methods

This section describes the participants' demographics and the sample selection process.

Participants
In total, 51 participants (38.2 ±10.5 years old) were recruited in the experiment. The following table presents age and gender distribution for each group.

Table 1: Group characteristics

Group	**Age (Mean±SD)**	**Gender (M/F)**
Treated **(Group A; N=15)**	42.4±13.9	8/7
Untreated **(Group B; N=18)**	36.9±8.9	9/9
Control **(Group C; N=18)**	35.4±8.8	8/10

All participants were screened prior participation and were medically examined by two collaborating doctors. Correct medical diagnosis was ensured by the collaborating doctors. In the patients groups (Groups A and B), the participants were diagnosed with anxiety and, specifically, with a Hamilton Anxiety Rating Scale equal or greater than 20 (HAM-A: mild to moderate severity) (Hamilton, 1959). Patients in Group A were systematically using alprazolam for at least 2 months before the testing day. Patients in Group B did not receive any kind of treatment for at least two months before the testing day. Participants in Group C had no medical history of anxiety or alcohol abuse and were free of medication. Participants were experienced drivers and were currently active drivers. Volunteers received reimbursement for their participation.

Study design
The present study utilises a mixed design for the comparison of patient and control experimental groups in question. The independent variable was the alprazolam administration with two levels: (baseline and alprazolam 0.5 mg intake). Dependent variables were: a) the driving performance (simulated environment), b) attentional performance (computerised tests in winTAP), and c) subjective assessments. The aim was to investigate the acute effect of alprazolam administration (0.5mg) and the potential of additive effects (treated) in two driving tasks.

Procedure
At arrival participants completed a driving background questionnaire and written consent was obtained after detailed briefing. Both alcohol screening (with breathanalyser) and urine drug screening were performed before testing takes place. Participants had a familiarisation drive in order to get used to the driving simulator. Participants had to complete two tasks at the driving simulator (Figure 1); a lane tracking scenario for about 20 minutes in a highway environment maintaining a constant speed of 90 km/h and a car following scenario for about 20 minutes in a highway environment maintaining a safe distance from the lead vehicle that was moving with a steady speed of 90 km/h. Four instances of abrupt breaking (leading vehicle) occurred randomly. Participants received instructions for each driving scenario. For the lane tracking scenario participants were instructed to maintain steady lateral position. For the car following scenario they were instructed to maintain a safety distance from the lead vehicle. Scenarios were counter-balanced between the two phases and among participants.

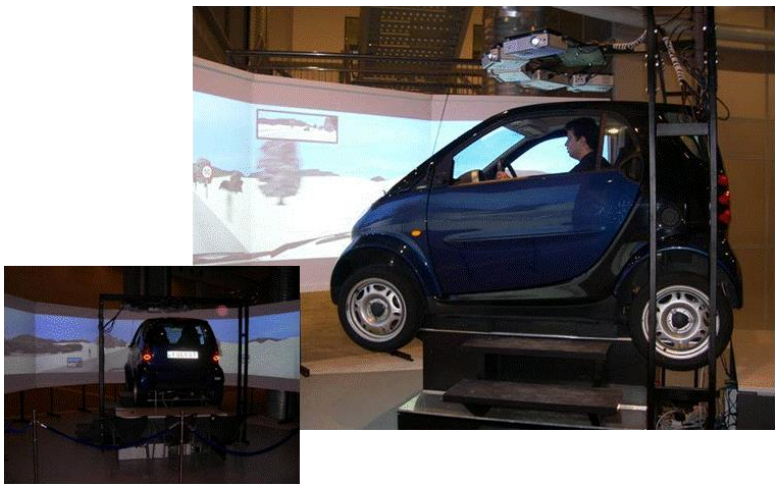

Figure 1: Passenger car driving simulator

Following the simulator driving scenarios, participants completed a computerised alertness choice test (winTAP, Zimmerman and Fimm, 1993) and reaction times (msec), omissions and errors were recorded. Sleepiness was subjectively rated before and after each driving scenario and before and after the computerised tests. Higher scoring meant less vigilance and subsequently increased sleepiness [The Karolinska Sleepiness Scale (KSS) is a universally accepted, validated and standardised scale (Åkerstedt and Gillberg, 1990)].

Blood collection lasted approximately 10-15 minutes and usually participants wanted to relax and take a small break before the driving tasks. Participants started the driving tasks almost 15 minutes after blood collection (10 ml tubes of whole blood, serum and blood spot specimens) and about an hour after alprazolam intake. The time interval between

administration and driving was adequate before testing takes place and was based on relevant studies (e.g. Leufkens et al., 2007).

Statistics
Within and between participants comparisons were carried out with repeated measures of General Lineral Models (GLM) and one-way ANOVAs. In case of violation of homogeneity and homoscedacity assumptions, non-parametric equivalents were administered (Friedman and Wilcoxon rank test, respectively). The α level was set at .05. Statistical analyses were performed with the statistical programme Statistical Package for the Social Sciences (SPSS) (version 18.0 for Windows; SPSS, Chicago, IL).

Results

Alprazolam intake impaired driving performance in all groups. In particular, increased weaving (SDLP= 5.8 cm) has been found in treated anxiety patients when driving an hour after alprazolam intake (F (1, 14) =11.31, p=.005). Similarly, untreated anxiety patients showed a significant increase of 4 cm after alprazolam intake (F (1, 17) =5.28, p=.035). On the same track, healthy participants showed the greatest increase in weaving (ΔSDLP=6.8 cm; F (1, 17) =36.34, p<.001).
The following bar charts (Figure 2) present the percentages (%) of impaired/improved driving performance as a function of alprazolam serum concentration levels (ng/mL). It appears that alprazolam is associated with impairment in lateral position keeping even in low concentrations in treated patients (100% ; <5) and controls (80%; <5).

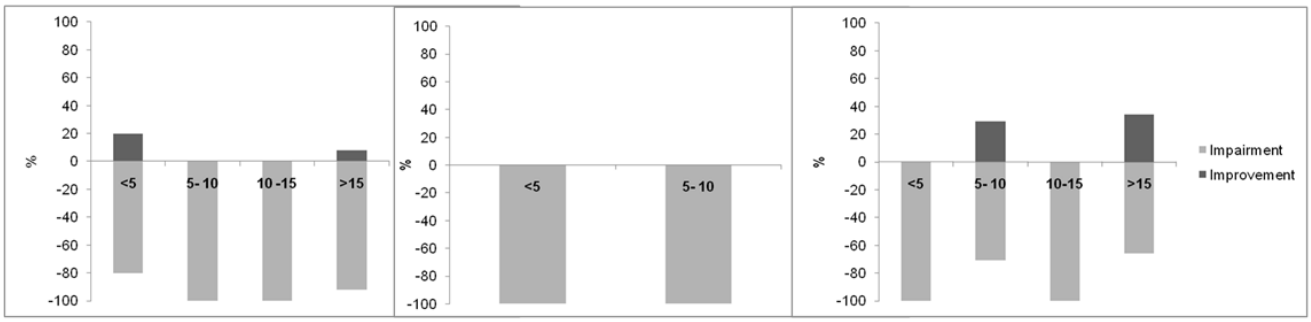

Figure 2: Percentage of impairment/improvement as a function of serum concentration (ng/mL) for the control, untreated, and treated groups (from left to right)

For the untreated anxiety patients only two concentration levels (<5 and 5-10 ng/mL) were detected and impairment with regards to lateral position keeping was observed. Increased impairment was noted in the treated anxiety group for the serum concentration groups of 5-10 and >15 ng/mL. For the other two groups, almost in all cases impairment was observed. Therefore, impairment is present even in small concentrations regardless of group type (i.e. presence of anxiety disorder or not).

Significant increase in brake reaction time was observed in treated (0.5 sec; p<.05) and untreated patient groups (1 sec; p<.05) but not in the control group (0.3 sec) in the car following scenario. The attention test revealed significant decrease in alertness (mean difference: 31.92 msec) only in the control group (p=.015) after alprazolam intake. Untreated patients felt significantly less vigilant in the alprazolam condition (p=.001). Similarly, healthy participants felt significantly less vigilant after alprazolam intake (p=.018).

Discussion

The findings of this study support the main hypothesis that alprazolam will impair driving performance in all three groups. Indeed significant increase in weaving (SDLP) was found in all groups after alprazolam administration. Specifically, alprazolam's detrimental effects were evident in weaving in all groups with higher lateral deviation in the control group by more than 6 cm. Therefore vehicle lateral control is affected by alprazolam intake. Relevant literature is in agreement with these findings. Alprazolam intake deteriorates lateral control but acute effect (Curran, 1986; Leufjkens et al., 2007) is greater than chronic administration due to tolerance in the sedating effects because of repeated use as it seems to be the case with lateral deviation in the treated anxiety patients' group in this study. Likewise, most alprazolam studies have found high increments of SDLP. Verster and colleagues (2002) observed increments of SDLP of approximately 9 cm.

However, lane deviations in real traffic deviate from corresponding measurements in a simulated environment. Thus ramification and extrapolation of results should be made with this difference taken into consideration. Respective between groups' comparisons showed no significant differences among groups after alprazolam oral administration ($p<.05$). Therefore impairment may be comparable among groups as the difference among groups was approximately around 2-2.5 cm. Only in treated patients' group a percentage of improvement was observed. The other two groups had almost solely impaired weaving. This improvement may depict (overall ≈20% improvement) tolerance. Non-sedative antidepressants were found not to affect SDLP values (Ramaekers, 2003). Furthermore, alprazolam affected brake reaction time in treated and untreated anxiety patients. As treated group showed the greatest overall deterioration in reaction time (0.95±0.24 sec), additive effect of alprazolam intake may be greater than acute for reaction time (untreated: 0.9±0.02; control: 0.83±.03). Serum concentrations revealed that impairment is present in all groups even in small concentrations and, thus, leading to the conclusion the effect might be present regardless the concentration. However, the size of the effect for each concentration level might be important for defining the level of impairment.

It appears that additive effects are more powerful and treated anxiety patients do not show tolerance effects in psychomotor tests or psychomotor related driving skills, without of course, isolating them from the rest of parameters. Subjective assessments of treated anxiety patients are in favour of the tolerance proposition as there was no significant difference in their evaluation of sleepiness during driving scenarios in the simulated tasks. On the contrary, untreated and healthy participants reported increased sleepiness after alprazolam administration which reflects their driving performance. It is important to keep in mind, though, that anxiety patients are overly self-conscious, pay high self-attention after the activity, or have high performance standards for themselves. It should be borne in mind that anxiety patients' subjective assessments of their driving behaviour may be influenced also by their symptomatology.

Alprazolam significantly affected alertness in the control group but no other significant impairment was observed for the neuropsychological tests. Relevant studies have found differences. The greater effect was the acute effect in healthy individuals. It is important to note that this battery is standardised to driving behaviour but has not been applied in drug related research before. Subjective scales confirmed the effect perceived by participants. Treated patients did not perceive any difference in vigilance. On the contrary, the other two groups-not used in alprazolam medication-reported that they felt significantly less vigilant (untreated and control) and that they drove badly (untreated). It is alarming that treated

patients did not report any difference or change in the way they drive which might imply that their everyday driving performance is affected and they may not be aware of it and their risk of accidents due to lack of awareness may be increased.

The effect of alprazolam in healthy participants was stronger than in treated and untreated patients. Alprazolam intake (0.5 mg) might improve the driving performance of anxiety patients but might have deteriorative effect in healthy controls' driving performance. This study clearly showed an alprazolam effect (0.5mg) in driving performance in treated, untreated anxiety patients and healthy participants. Conclusively, the main findings of this study are in agreement with current research that people under alprazolam medication should be informed about the potential detrimental effects of alprazolam administration to their everyday activities and driving. Likewise, physicians and medical practitioners should be educated and trained on how the adverse effects of alprazolam prescriptions may affect driving performance.

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