Psychopharmacology (2007) 191:951–959
DOI 10.1007/s00213-006-0669-8

ORIGINAL INVESTIGATION

Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg

Tim R. M. Leufkens · Annemiek Vermeeren · Beitske E. Smink · Peter van Ruitenbeek · Johannes G. Ramaekers

Received: 8 August 2006 / Accepted: 6 December 2006 / Published online: 12 January 2007

Abstract
Rationale Alprazolam extended-release (XR) is approved for the treatment of panic disorder. This sustained formulation is absorbed in a delayed manner and is therefore expected to produce fewer and less severe side effects than its immediate release equivalent (alprazolam IR). The effect of alprazolam XR on potentially dangerous daily activities, such as driving a car, is expected to be less as compared to alprazolam IR.
Objectives The present study was designed to compare the effects of alprazolam XR (1 mg) and alprazolam IR (1 mg) on actual driving ability and cognitive function.
Method Eighteen healthy volunteers (aged 20–45 years) participated in a double-blind, placebo-controlled, three-way crossover study. At 4 h post-dose, subjects performed a standardized driving test on a primary highway in normal traffic. Cognitive and psychomotor tests were assessed 1, 2.5, and 5.5 h post-dose. Memory functioning was measured only 1 h after administration.
Results Both formulations severely impaired driving performance between 4 and 5 h after administration. The magnitude of impairment in the driving test observed with alprazolam XR was about half that observed with alprazolam IR. Laboratory test results were in line with the driving data.
Conclusions The acute impairing effects of alprazolam XR 1 mg on driving and psychomotor functions were generally less, as compared to its immediate-release equivalent, but still of sufficient magnitude to increase the risk of becoming involved in traffic accidents.

Keywords Alprazolam XR · Driving · Cognition · Psychomotor performance · Serum concentration · Formulation

T. R. M. Leufkens · A. Vermeeren · P. van Ruitenbeek · J. G. Ramaekers
Experimental Psychopharmacology Unit, Brain and Behavior Institute, Faculty of Psychology, Maastricht University, Maastricht, The Netherlands

B. E. Smink
Department of Toxicology, The Netherlands Forensic Institute (NFI), The Hague, The Netherlands

T. R. M. Leufkens (✉)
Department of Neurocognition, Faculty of Psychology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands
e-mail: t.leufkens@psychology.unimaas.nl

Introduction

Daytime sedation and impairment of psychomotor and cognitive functioning is one of the main problems associated with the use of benzodiazepine anxiolytics. This poses a crucial problem for users of these drugs who must operate vehicles. Epidemiological studies have shown that use of benzodiazepines is associated with an increased risk of car accidents (Barbone et al. 1998; Neutel 1995, 1998). Experimental studies have shown, however, that effects on driving performance vary depending on the drug, dose, and the formulation used (c.f. Vermeeren 2004).

Alprazolam is the most frequently used benzodiazepine in the treatment of panic disorder and anxiety (Isbister et al. 2004; Moroz 2004; RxList 2005; Verster et al. 2002). It is a 1,4 triazolobenzodiazepine and available in two formulations, an immediate release (IR) formulation and an extended release (XR) formulation. Alprazolam IR is

rapidly absorbed and has a relatively short elimination half-life ranging between 10 and 18 h (Greenblatt and Wright 1993; Moroz 2004). After oral administration of alprazolam IR 1 mg, peak plasma concentrations ranging from 12 to 22 μg/l are reached within 0.7 to 1.8 h after intake (Greenblatt and Wright 1993). Alprazolam IR is mainly prescribed in units of 0.25, 0.50, or 1.00 mg three times daily for patients suffering from anxiety, but daily doses can be raised to 10 mg for patients suffering from panic disorder (Busto et al. 2000).

Patients using alprazolam IR report benzodiazepine-related adverse events, such as drowsiness, dizziness, and reduced alertness (Verster and Volkerts 2004b). A vast amount of studies have shown that alprazolam IR in doses of 0.5 mg and higher impairs a variety of cognitive and psychomotor skills such as memory, speed of responses, and tracking performance (Bertz et al. 1997; Ellinwood et al. 1985; Greenblatt et al. 1988; Kroboth et al. 1998; Scavone et al. 1992; Smith et al. 1984; Subhan et al. 1986; Vermeeren et al. 1995; Verster et al. 2002).

Alprazolam XR was developed to reduce the adverse events associated with alprazolam IR. It produces peak plasma concentrations that are about 50% of a similar dose of the IR formulation and occur between 5 and 12 h after administration (Busto et al. 2000; Eller and Della-Coletta 1990; Fleishaker et al. 1989; Glue et al. 2006). Alprazolam XR produced fewer and less severe side effects than its IR equivalent. Moreover, it has been shown that cognitive and psychomotor performance is less impaired after alprazolam XR than after alprazolam IR (Busto et al. 2000; Mumford et al. 1995; Rickels 2004).

It is unclear, however, if a reduction in performance impairment observed in laboratory tests of psychomotor function and cognition after alprazolam XR will have any implications for drivers who are being treated with alprazolam. In general, the validity of short psychomotor tests for predicting actual driving performance is limited. At best, drug-induced impairments in psychomotor tests are only moderately correlated to drug-induced impairment in driving performance as assessed in on-the-road driving tests. Consequently, it is widely accepted in the drug and driving community that experimental studies for establishing the driving hazard of a medicinal drug should proceed from conventional psychomotor tests to driving simulators and actual driving tests. Therefore, the final conclusions concerning a drug's impairing effect on driving should be based on combined results from these studies (ICADTS 1999).

The present study was designed to establish the effects of alprazolam XR on actual driving performance as assessed in a standard on-the-road driving test (O'Hanlon 1984). This test has been used repeatedly for assessing medicinal drug effects on actual driving in a large number of studies (reviews: Ramaekers 2003; Vermeeren 2004). Recently, it was applied in a study to assess the effect of a single dose of alprazolam IR 1 mg and placebo on actual driving performance in 20 healthy young volunteers (Verster et al. 2002). That study showed that alprazolam IR produced severe impairment of road tracking control equivalent to the effect produced by a blood alcohol concentration (BAC) of 1.5 g/l.

The primary purpose of the current study was to compare the effects of alprazolam XR with those of alprazolam IR on performance of healthy subjects in a standardized highway driving test. It was expected that driving impairment would be less after alprazolam XR as compared with alprazolam IR, due to differences in the pharmacokinetic profiles of both formulations. The secondary purpose was to compare the effects on cognitive and psychomotor functioning related to driving in a controlled laboratory setting.

Methods and materials

Subjects

Eighteen healthy volunteers (nine men and nine women) were recruited by means of advertisements in local newspapers and public buildings. Their mean ±SE age was 32.3± 2.0 years. Volunteers were screened by a telephone interview, health questionnaire, and medical examination. The medical examination included blood hematology and chemistry, urinalysis, drug and pregnancy screening, and a 12-lead electrocardiogram. Inclusion criteria were age between 21 and 45 years, good physical and mental health, body mass index between 18 and 28 kg/m^2, possession of a driving license for more than 3 years, and average driving experience of at least 5000 km/year. Volunteers with any cardiovascular, endocrine, psychiatric, and/or neurological condition were excluded, as were subjects with a history of drug abuse or currently using psychoactive medication, hypotension (<90/50 mmHg), liver disorder, pregnancy or lactation, and drinking more than 20 alcoholic consumptions per week.

From 1 week before participation in the study until completion of the last treatment period, subjects were not allowed to use any prescribed medicines or drugs of abuse. During the study period, it was not allowed to participate in any other biomedical research. Subjects had to refrain from alcohol and caffeine 24 h before testing. On test days, subjects were not allowed to consume any food 3 h before arrival. During testing, smoking was prohibited.

The study's approval was obtained from the medical ethics committee of Maastricht University. The study was conducted according to the code of ethics on human

experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). After complete description of the study to the subjects, written informed consent was obtained.

Design and treatment

The study was conducted according to a double-blind, placebo-controlled, three-way crossover design. Treatments were single oral doses of alprazolam 1 mg IR, alprazolam 1 mg XR, and placebo. Study medication was supplied in three capsules (double dummy) at 9 A.M. of each test day. Treatment orders were balanced by randomly assigning six treatment orders to 18 subjects. The minimum period between successive treatments was 7 days.

Testing procedure

Before the first treatment period, all subjects received a comprehensive training of the driving and laboratory tasks. The standardized highway driving test was undertaken between 4 and 5 h after dosing, i.e., the time plasma concentrations of the XR formulation were expected to be at a maximum. The Stop Signal Task and a Divided Attention Task were performed at 1, 2.5, and 5.5 h after dosing. A Word Learning Task was performed at 1 h post-dose. Subjects consumed two standardized light meals 0.5 h before and 3.5 h after drug intake.

Driving and laboratory tasks

In the 1-h driving test (O'Hanlon 1984), subjects operate a specially instrumented vehicle over a 100-km (61-mi) primary highway circuit while maintaining a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. Subjects are accompanied by a licensed driving instructor with access to dual controls. During the test, the car's speed and lateral position with respect to left lane-line are continuously recorded. These signals are edited off-line to yield the Standard Deviation of Lateral Position (SDLP in centimeters) which is taken as the primary outcome variable. SDLP is a measure of road tracking error or 'weaving'. SDLP has proven to be sensitive to the sedative and stimulating effects of various psychoactive drugs such as anxiolytics (O'Hanlon et al. 1995; Verster et al. 2005), hypnotics (Vermeeren 2004), antidepressants (Ramaekers 2003), and antihistamines (O'Hanlon and Ramaekers 1995; Verster and Volkerts 2004a).

The Divided Attention Task measures the ability to perform two tasks simultaneously during 12 min (Moskowitz 1973). The primary subtask is a compensatory tracking task set at a constant level of difficulty. The secondary subtask is a visual search task in which the subject has to monitor 24 asynchronously changing single digits presented in the four corners of a screen. The subjects are instructed to remove their foot from a pedal as rapidly as possible whenever they detect the digit '2'. The main performance parameters are average tracking error (in mm) and number of control losses in the tracking task and number of misses and speed of target detection (in ms) in the visual search task. These parameters are transformed to standard (z) scores for each task. Performance in this test has proven sensitive to the effects of many sedative drugs such as doses of alcohol, antidepressants, antipsychotics, antihistamines, and the residual effects of hypnotics (Ramaekers et al. 1999; Robbe and O'Hanlon 1995; Vermeeren et al. 2002; Vuurman et al. 1994).

The Stop Signal Task assesses inhibitory control, defined as the ability to stop a pending thought or action (Logan 1994). The paradigm consists of two concurrent tasks, i.e., a stop and a go task. The current test was adapted from an earlier version by Fillmore et al. (2002) and has been validated for showing stimulant and sedative drug effects (Ramaekers and Kuypers 2006). The go signals are four letters (A, B, C, or D) presented one at a time in the center of a computer screen. Subjects are required to respond to each letter as quickly as possible by pressing one of two response buttons by either the left (A or C) or right (B or D) index finger. In the stop task, subjects are required to withhold any response in case a stop signal (a visual cue appearing in one of the four corners of the screen) is presented. Stop signals are presented 12 times at each of the four delays after the onset of a letter: 50, 150, 250, 350 ms The dependent variables are reaction times to go signals (Go RT), the average delay needed to inhibit successfully the ongoing response (stop signal reaction time, SSRT) and the total number of false alarms.

The Word Learning Task assesses memory for verbal information (Rey 1964). In this test, 15 monosyllabic nouns are sequentially presented on a computer screen for 2 s, and the subject is required to read the words aloud. At the end of the sequence, the subject is asked to recall as many words as possible in any order. This procedure is repeated five times, and the total number of correct recalls in five trials is referred to as the Immediate Recall Score (IRS). After a delay of at least 20 min, the subject is again required to recall as many words as possible. During this trial, the nouns are not presented. The total number of correct recalls is referred to as the Delayed Recall Score (DRS). Finally, a sequence of 30 monosyllabic nouns is presented, containing 15 nouns from the original set and 15 new nouns in random order. The subject has to indicate whether a noun originates from the old or from the new set. The total number of correct indications is referred to as the Recognition Score (RS). The reaction time of decision is

measured and is referred to as the Recognition Reaction Time (RRT). Performance in this test has previously been shown to be sensitive to the effects of alprazolam IR in doses of 0.5 and 1 mg (Vermeeren et al. 1995).

Serum concentrations

Alprazolam was determined by measuring serum concentrations. Blood samples were collected at 55 min and 6 h after ingestion of the drug. Samples were centrifuged after a clotting period, and serum was frozen at −20°C until analyses for pharmacokinetic assessments. Serum was analyzed for serum concentrations of alprazolam and its metabolite α-hydroxy-alprazolam using a Liquid Chromatography-Tandem Mass Spectometry Method (LC-MS-MS) with Electrospray Interface (ESI).

Internal standards, d5-alprazolam and d5-α-hydroxy-alprazolam, were added to 1.0 ml serum sample before solid-phase extraction (Oasis HLB®, Waters, Etten-Leur, The Netherlands). The analytes were eluted from the cartridges with 1.5 ml acetonitrile after washing with 2 ml water and 2 ml acetonitrile/water 10% v/v. The serum extracts were evaporated and reconstituted in 50 µl acetonitrile/water 20% v/v before analysis.

The LC-MS system consisted of a TSP Spectra System (Finnigan, Breda, The Netherlands), including an SN4000 controller, a vacuum degasser (SCM 1000), a pump (P4000), and an auto sampler (AS3000), connected to an ion trap mass spectrometer (LCQ, Finnigan). Chromatographic data were acquired and processed using X-calibur™ 1.2 software (Finnigan). The method used an Atlantis C18 column (150×2.1 mm, Waters, Etten-Leur, The Netherlands). Injection volume was 10 µl. The gradient used in this LC-MS (MS) method was acetonitrile/formic acid (0.005 M), 10% to 90% v/v acetonitrile. The time course of the gradient was as follows: t=0–1 min (10–40% v/v acetonitrile), t=1–7 min (40 v/v % acetonitrile), t=7–8 min (40–90% v/v acetonitrile), t=8–9 min (90% v/v acetonitrile), t=9–10 min (90–10% v/v acetonitrile). Parent ions (m/z 309, 314, 325, and 330 for alprazolam, d5-alprazolam, α-hydroxy-alprazolam, and d5-α-hydroxy-alprazolam, respectively) and product ions (m/z 274 and 281 for alprazolam, m/z 279 and 286 for d5-alprazolam, m/z 279, 297, and 307 for α-hydroxy-alprazolam, and m/z 284, 302, and 312 for d5-α-hydroxy-alprazolam) were detected after collision.

The linear range for the assay was 1–10 ng/ml for alprazolam and 0.5–5 ng/ml for α-hydroxy-alprazolam. The limit of quantification (concentration with an intra-day standard deviation of 20%) was 1 ng/ml for alprazolam and 0.5–1 ng/ml for α-hydroxy-alprazolam. The accuracy was satisfactory (deviation from calibrated external control 10%). Inter-day precision was not determined, because in forensic case work, calibration curves are included in each analytical run.

Statistical analyses

Sample size was based on a power calculation for detecting a clinically relevant effect of 2.4 cm in the primary measure of this study, the SDLP. This change corresponds to the effects of alcohol on SDLP, whereas BACs are 0.5 g/l as measured in a previous study (Louwerens et al. 1987). Given that test–retest reliability of the driving test is at least r=0.70, a group of 18 subjects should permit detection of a mean change in SDLP of 2.0 cm, with a power of at least 90% and an α risk of 0.05.

The global model used in the analysis of variance (ANOVA) of all cognitive and psychomotor parameters included *subject*, *period*, *treatment*, and *time of testing*. In case of a significant overall effect of treatment, a subsequent analysis for comparing separate drug treatments was conducted using three simple contrasts.

All statistical analyses were done by using the Statistical Package for the Social Sciences (SPSS) statistical program (version 12.0.1 for Windows; SPSS, Chicago, IL).

Results

A summary of the cognitive, driving, and psychomotor tests is shown in Table 1.

Missing data

Word Recognition Test data were incomplete for five subjects and Stop Signal Task data were incomplete for six subjects due to technical problems. Only complete data sets entered the analysis.

Road tracking test

Ten driving tests (18.5% out of 54 comprising the complete data set) were terminated prematurely because the driving instructors judged the subject to be too drowsy to continue safely. They terminated seven rides (38.9% out of 18 comprising one condition) in the IR condition and three rides (16.7%) in the XR condition. The SDLP scores were calculated from the data collected until termination of each ride.

There was a significant treatment effect [F(2,16)=31.89, p<0.001]. Contrast analysis revealed that both drug formulations significantly increased SDLP [IR: F(1,17)=67.44, p<0.001; XR: F(1,17)=36.86, p<0.001]. However, mean SDLP after alprazolam XR was significantly lower as compared to alprazolam IR [F(1,17)=34.37, p<0.001].

Table 1 Summary of the results of the Road Tracking Test and Cognitive and Psychomotor Tests in healthy subjects in a crossover trial of alprazolam IR (1 mg), alprazolam XR (1 mg), and placebo (n=18)

Measure	Time	Mean (SE)			Simple contrast analysis		
		Placebo	Alprazolam XR	Alprazolam IR	PLA vs XR p	PLA vs IR p	XR vs IR p
Road Tracking Test							
SDLP (cm)	4.0	19.50 (0.79)	23.44 (0.44)	27.68 (1.40)	***	***	***
SDS (km/h)	4.0	2.18 (0.19)	2.48 (0.18)	3.01 (0.34)	–	–	–
Divided Attention Test							
z-AE + z-ln(cl)	1.0	−0.94 (0.28)	−0.21 (0.34)	0.71 (0.46)	*	***	*
	2.5	−0.74 (0.33)	−0.01 (0.35)	1.08 (0.40)	*	***	*
	5.5	−0.73 (0.32)	0.43 (0.34)	0.40 (0.46)	**	**	NS
z-RT + z-ln(mi)	1.0	−0.96 (0.33)	−0.62 (0.35)	0.47 (0.51)	NS	**	*
	2.5	−0.55 (0.32)	0.21 (0.40)	1.30 (0.54)	*	**	*
	5.5	−0.69 (0.37)	0.19 (0.37)	0.66 (0.53)	*	*	NS
Stop Signal Task							
Go RT (ms)	1.0	645 (36)	642 (28)	704 (52)	–	–	–
	2.5	640 (32)	645 (30)	716 (40)	NS	***	***
	5.5	622 (32)	620 (34)	670 (39)	–	–	–
Stop RT (ms)	1.0	284 (15)	279 (12)	391 (13)	NS	***	***
	2.5	268 (9)	285 (11)	343 (21)	NS	**	*
	5.5	263 (9)	277 (9)	302 (19)	NS	*	NS
FA	1.0	8.92 (2.78)	9.00 (3.00)	8.17 (2.63)	–	–	–
	2.5	6.58 (2.41)	8.17 (2.51)	7.08 (1.96)	–	–	–
	5.5	5.58 (1.53)	7.33 (2.13)	7.42 (2.18)	–	–	–
Word Learning Test							
IRS	1.0	57.6 (1.11)	54.9 (1.64)	50.7 (1.83)	NS	***	NS
DRS	1.0	11.9 (0.58)	11.2 (0.55)	9.7 (0.84)	NS	**	*
RS	1.0	28.7 (0.49)	27.9 (0.80)	28.3 (0.52)	–	–	–
RRT (ms)	1.0	784 (21)	800 (24)	883 (49)	–	–	–

PLA Placebo, *IR* alprazolam Immediate Release, *XR* alprazolam Extended Release, *NS* not significant, *SDLP* standard deviation of lateral position, *SDS* standard deviation of speed, *IRS* immediate recall score, *DRS* delayed recall score, *RS* recognition score, *RRT* recognition reaction time, *FA* false alarms, *z-AE* z-score of average tracking error, *z-ln(cl)* z-score of log transformed total number of control losses, *z-RT* z-score of reaction time, *z-ln(mi)* z-score of log transformed total number of misses

*p<0.05

**p<0.01

***p<0.001

Figure 1 shows that SDLP increased with approximately 8 cm in the IR condition and 4 cm in the XR condition as compared to placebo.

No overall differences between placebo and drug were found on mean speed and speed variability.

Divided attention task

The distributions of control losses and misses were highly skewed. Therefore, they were transformed to their natural log (ln) scores before transformation to z-scores. ANOVA of the sum score of the z-scores of the average error and natural log of the total number of control losses revealed a significant overall treatment effect [$F(2,16)$= 11.74, p<0.001]. Effects of treatments were further analyzed at separate times after drug intake. These analyses showed that tracking performance was significantly impaired at 1, 2.5, and 5.5 h after administration of alprazolam IR 1 mg [1 h: $F(1,17)$=15.88, p<0.001; 2.5 h: $F(1,17)$= 15.14, p<0.001; 5.5 h: $F(1,17)$=12.40, p<0.01] and alprazolam XR 1 mg [1 h: $F(1,17)$=6.31, p<0.05; 2.5 h $F(1,17)$=7.00, p<0.05; 5.5 h: $F(1,17)$=12.26, p<0.01]. The effects of the XR formulation were less severe, however, than those of the IR formulation at 1 h [$F(1,17)$=15.42, p<0.05] and 2.5 h post-dose [$F(1,17)$=21.32, p<0.05] but no longer at 5.5 h post-dose.

A significant overall treatment effect in target detection performance, as measured by the sum of the z-scores of the reaction time and natural log of total number of misses, was found [$F(2,16)$=5.72, p<0.05]. Analyses at separate times after administration revealed a significant impairment on target detection by alprazolam IR compared to placebo at

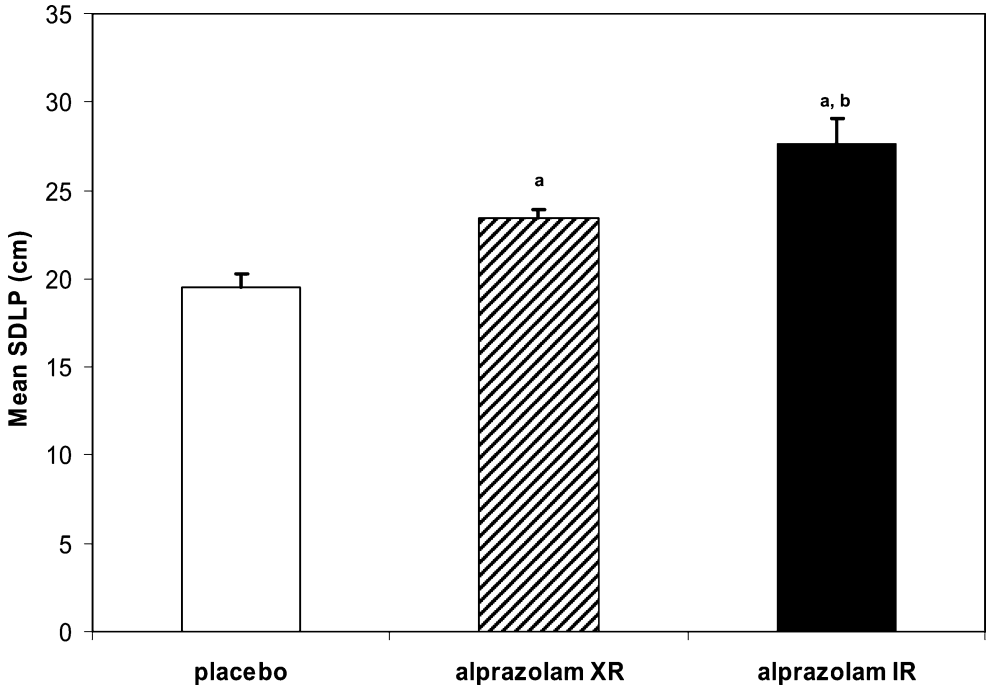

Fig. 1 Mean (±SE) Standard Deviation of Lateral Position (SDLP) in each drug condition. **a** is significantly different from placebo ($p<0.001$) and **b** is significantly different from alprazolam XR ($p<0.001$)

all times of measurement [$F(1,17)=6.89$, $p<0.05$]. Alprazolam XR did not differ significantly from placebo 1 h post-dose. On 2.5 and 5.5 h post-dose, target detection differed significantly between placebo and alprazolam XR [respectively, $F(1,17)=4.46$, $p<0.05$; $F(1,17)=6.49$, $p<0.05$]. Comparisons between both treatment conditions revealed significant differences at 1 h and 2.5 h post-dose [respectively, $F(1,17)=5.84$, $p<0.05$; $F(1,17)=6.72$, $p<0.05$]. At 5.5 h after ingestion, target detection was not significantly different between both treatment conditions.

Stop signal task

Analysis revealed a significant overall treatment effect on the go reaction time [$F(2,10)=6.20$, $p<0.05$]. Separate analyses for each time of testing revealed significant differences between treatments at 2.5 h post-dose. At that time, relative to placebo, the go reaction time was significantly longer after alprazolam IR [$F(1,11)=22.87$, $p<0.001$] but not after alprazolam XR. Moreover, the increment in reaction time after alprazolam IR was also significantly different from that after alprazolam XR [$F(1,11)=23.70$, $p<0.001$]. No interaction was found between treatment and time of measurement.

A significant interaction effect between treatment and time of measurement in SSRT was found [$F(2,10)=58.94$, $p<0.001$]. Placebo drug comparisons for each time of testing showed that alprazolam IR increased SSRT significantly at each time of testing [$F(1,11)=6.01$, $p<0.05$], whereas alprazolam XR did not. SSRT after alprazolam XR was significantly faster than after alprazolam IR 1 and 2.5 h after ingestion [$F(1,11)=109.92$, $p<0.001$; $F(1,11)=6.44$, $p<0.05$, respectively] but no longer at 5.5 h post-dose.

For the total number of false alarms data, analyses revealed no significant effects.

Word learning test

Analysis of the total number of words correctly recalled over five memory trials, as reflected by the IRS, showed a significant overall treatment effect [$F(2,16)=9.08$, $p<0.01$]. Placebo-drug comparisons revealed a significant impairing effect of alprazolam IR at 1 h after administration but not of alprazolam XR. No significant difference was found between alprazolam IR and alprazolam XR.

The DRS also revealed a significant overall treatment effect, as delayed recall under the alprazolam IR condition was significantly lower than under the placebo condition [$F(1,17)=10.22$, $p<0.01$]. Delayed recall after alprazolam XR ingestion did not significantly differ from placebo. The difference between alprazolam IR and alprazolam XR was significant [$F(1,17)=4.64$, $p<0.05$].

No significant effects were found on performance in the recognition test.

Serum concentrations

Mean (SE) serum concentrations for alprazolam at 55 min post-dose were 4.9 (1.0) μg/l after alprazolam IR administration and 1.7 (0.2) μg/l after alprazolam XR administration. After approximately 6 h of drug ingestion, mean (SE) serum concentrations for alprazolam were 10.6 (0.5) μg/l

after alprazolam IR and 9.0 (0.6) μg/l after alprazolam XR. The alprazolam metabolite α-hydroxy-alprazolam was not detectable in the serum. The metabolite is expected to be present in plasma in unconjugated form at less than 10% of the alprazolam level (Smith and Kroboth 1987).

Discussion

Results from the present study show that both alprazolam 1 mg formulations administered as single doses to healthy nonanxious volunteers significantly impair performance on the standardized highway driving test. The IR formulation produced a mean increase in SDLP of 8.2 cm and the XR formulation produced an increase of 3.9 cm. Although the magnitude of effect on SDLP was reduced by about 50% after alprazolam XR, the impairment was still severe. The acute effects of alprazolam IR and alprazolam XR would be the equivalents of driving with a BAC above the legal limit for alcohol in most industrialized countries, i.e., 0.5 g/l (Louwerens et al. 1987). BACs of above 0.5 g/l have been shown to progressively increase the risk of becoming involved in a serious traffic accident by a factor of 2 or more (Borkenstein 1974). The number of driving tests that were prematurely terminated supported the SDLP data. Under the alprazolam XR condition, three (16.7%) subjects were not able to complete the driving test. Alprazolam IR caused an early ending of the test in seven (38.9%) subjects. The most frequent reason for aborting the test prematurely was excessive sleepiness.

The detrimental effect of alprazolam IR on driving in the present study is similar to that found in a previous study employing the same standardized highway driving test. In that study, Verster et al. (2002) found a mean increment in SDLP of approximately 9 cm between 1–2 h after a single dose of alprazolam IR 1 mg. This indicates that sensitivity of the subjects in the present study to the effects of alprazolam was normal.

Although the laboratory tests are not expected to strongly predict driving performance, they usually provide some insight as to what extent driving is affected after drug intake. Driving ability is not one distinct skill but a combination of a series of mental and behavioral functions (Vermeeren and De Gier 1995). Therefore, performance in laboratory tests assessing different aspects of driving can provide insight into what aspects of driving behavior are most sensitive to the effects of a particular drug, although performance in any single test is not highly correlated to driving performance itself. As expected, alprazolam IR significantly impaired performance on all tasks as compared with placebo. It impaired tracking and peripheral visual search in the divided attention task, response speed and inhibitory control in the stop signal task, and immediate and delayed recall in the word learning task. In contrast, alprazolam XR only impaired performance in the divided attention task but not in the stop signal and memory tests, indicating a reduction in adverse effects.

This reduction in impairing effects was most pronounced within the first 4 h after administration of both formulations, when blood levels of alprazolam XR were still rising and those of alprazolam IR were at their peak, as shown by the serum concentrations. Within this time period, the effects of alprazolam XR were significantly less severe in the majority of the tests as compared with those of alprazolam IR. At 5.5 h, post-dosing performance effects and serum concentrations became comparable. At this point in time, alprazolam XR achieves peak plasma concentrations, whereas alprazolam IR plasma levels are already descending. Thus, peak effects of alprazolam XR are less severe than those of alprazolam IR.

A potential limitation of the present study might be that the effects were assessed only after a single dose administration of study treatments. Alprazolam-induced impairment may become less severe after chronic administration of alprazolam, as it is well known that tolerance to the sedating effects of benzodiazepines can develop after repeated use (Curran 1986). However, it has also been shown that tolerance to the impairing effects of benzodiazepines is never complete. An epidemiological study by Neutel (1995) demonstrated that benzodiazepines increase the relative risk of becoming involved in traffic accidents during the first week of treatment and that this risk remains, albeit to a lesser extent with passage of time. During the first week of treatment, the benzodiazepine users' relative risk was 13.5. After 1 month, the relative risk had declined to 2.6. The implication thus seems to be that benzodiazepine impairment persists over time but to a lesser degree as observed after initial dosing. A similar pattern was found in an experimental study assessing the effects on driving performance of diazepam 5 mg treatment during 4 consecutive weeks in 12 patients with generalized anxiety disorder (Van Laar et al. 1991). Diazepam significantly impaired driving performance as reflected by an elevated SDLP in the first 3 weeks of treatment. Therefore, it was concluded that driving performance of patients will be affected at least during early, chronic treatment.

It might be argued that performance of healthy subjects may be different from performance of patients suffering from anxiety of panic disorder. Moreover, as healthy volunteers do not have a history of benzodiazepine use, the effect of alprazolam may be stronger than that in patients who have already been using alprazolam for an extended period of time. Yet, these notions have never been confirmed in scientific research. On the contrary, O'Hanlon et al. (1995) have shown that driving performance after both single and repeated doses of benzodiazepine anxio-

lytics did not differ in healthy volunteers and patients. Moreover, these authors showed that baseline and placebo performances were comparable between both groups. This implies that healthy volunteer models can be used for predicting drug effects on driving in patient populations. Therefore, if the effects of both formulations of alprazolam observed in the present study also apply to anxious individuals receiving the medications as clinical treatment, the risk of becoming involved in a car accident may be increased.

In conclusion, the impairing effects of alprazolam XR 1 mg on driving and cognition were generally less as compared to its IR equivalent but still of sufficient magnitude to increase the risk of becoming involved in traffic accidents.

Acknowledgment This research was supported by a grant from Pfizer, New York, USA.

We like to thank Anita van Oers, Janneke Guijaux, Roland Otten, Henk Brauers, Willy Jeurissen, Irma Brauers and Cees van Leeuwen for their assistance in data collection.

References

Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352:1331–1336

Bertz RJ, Kroboth PD, Kroboth FJ, Reynolds IJ, Salek F, Wright CE, Smith RB (1997) Alprazolam in young and elderly men: sensitivity and tolerance to psychomotor, sedative and memory effects. J Pharmacol Exp Ther 281:1317–1329

Borkenstein RF (1974) The role of the drinking driver in traffic accidents, the Grand Rapids study. Blutalkohol 11

Busto UE, Kaplan HL, Wright CE, Gomez-Mancilla B, Zawertailo L, Greenblatt DJ, Seller EM (2000) A comparative pharmacokinetic and dynamic evaluation of alprazolam sustained-release, bromazepam, and lorazepam. J Clin Psychopharmacol 20:628–635

Curran HV (1986) Tranquillising memories: a review of the effects of benzodiazepines on human memory. Biol Psychol 23:179–213

Eller MG, Della-Coletta AA (1990) Absence of effect of food on alprazolam absorption from sustained release tablets. Biopharm Drug Dispos 11:31-37

Ellinwood EH Jr, Heatherly DG, Nikaido AM, Bjornsson TD, Kilts C (1985) Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. Psychopharmacology 86:392–399

Fillmore MT, Rush CR, Hays L (2002) Acute effects of oral cocaine on inhibitory control of behavior in humans. Drug Alcohol Depend 67:157–167

Fleishaker JC, Phillips JP, Eller MG, Smith RB (1989) Pharmacokinetics and pharmacodynamics of alprazolam following single and multiple oral doses of a sustained-release formulation. J Clin Pharmacol 29:543–549

Glue P, Fang A, Gandelman K, Klee B (2006) Pharmacokinetics of an extended release formulation of alprazolam (Xanax XR) in healthy normal adolescent and adult volunteers. Am J Ther 13:418–422

Greenblatt DJ, Wright CE (1993) Clinical pharmacokinetics of alprazolam. Therapeutic implications. Clin Pharmacokinet 24:453–471

Greenblatt DJ, Harmatz JS, Dorsey C, Shader RI (1988) Comparative single-dose kinetics and dynamics of lorazepam, alprazolam, prazepam, and placebo. Clin Pharmacol Ther 44:326–334

ICADTS (1999) Guidelines on experimental studies undertaken to determine a medicinal drug's effect on driving or skills related to driving. Bundes Anstalt fuer Strassenwesen (BASt), Köln

Isbister GK, O'Regan L, Sibbritt D, Whyte IM (2004) Alprazolam is relatively more toxic than other benzodiazepines in overdose. Br J Clin Pharmacol 58:88–95

Kroboth PD, Folan MM, Bauer KS, Tullock W, Wright CE, Sweeney JA (1998) Do alprazolam-induced changes in saccadic eye movement and psychomotor function follow the same time course? J Clin Pharmacol 38:337–346

Logan GD (1994) On the ability to inhibit thought and action: a users' guide to the Stop Signal Paradigm. In: Dagenbach D, Carr TH (eds) Inhibitory processes in attention, memory, and language. Academic, San Diego, pp 189–239

Louwerens JW, Gloerich ABM, de Vries G, Brookhuis KA, O'Hanlon JF (1987) The relationship between drivers' blood alcohol concentration (BAC) and actual driving performance during high speed travel. Alcohol Drugs Traffic Saf 86:183–186

Moroz G (2004) High-potency benzodiazepines: recent clinical results. J Clin Psychiatry 65(Suppl 5):13–18

Moskowitz H (1973) Laboratory studies of the effects of alcohol on some variables related to driving. J Saf Res 5:185–199

Mumford GK, Evans SM, Fleishaker JC, Griffiths RR (1995) Alprazolam absorption kinetics affects abuse liability. Clin Pharmacol Ther 57:356–365

Neutel CI (1995) Risk of traffic accidents injury after prescription for a benzodiazepine. Ann Epidemiol 5:239–244

Neutel I (1998) Benzodiazepine-related traffic accidents in young and elderly drivers. Hum Psychopharmacol Clin Exp 13:S115–S123

O'Hanlon JF (1984) Driving performance under the influence of drugs: rationale for, and application of, a new test. Br J Clin Pharmacol 18(Suppl 1):121s–129s

O'Hanlon JF, Ramaekers JG (1995) Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989–94. Allergy 50:234–242

O'Hanlon JF, Vermeeren A, Uiterwijk MM, van Veggel LM, Swijgman HF (1995) Anxiolytics' effects on the actual driving performance of patients and healthy volunteers in a standardized test. An integration of three studies. Neuropsychobiology 31:81–88

Ramaekers JG (2003) Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. J Clin Psychiatry 64:20–29

Ramaekers JG, Kuypers KPC (2006) Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on behavioral measures of impulsivity: alone and in combination with alcohol. Neuropsychopharmacology 31:1048–1055

Ramaekers JG, Louwerens JW, Muntjewerff ND, Milius H, de Bie A, Rosenzweig P et al (1999) Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. J Clin Psychopharmacol 19:209–221

Rey A (1964) L'examen clinique en psychologie. Presses Universitaires de France, Paris

Rickels K (2004) Alprazolam extended-release in panic disorder. Expert Opin Pharmacother 5:1599–1611

Robbe HW, O'Hanlon JF (1995) Acute and subchronic effects of paroxetine 20 and 40 mg on actual driving, psychomotor performance and subjective assessments in healthy volunteers. Eur Neuropsychopharmacol 5:35–42

RxList (2005) Top 200 prescriptions for 2005 by number of US prescriptions dispensed. http://www.rxlist.com/top200.htm

Scavone JM, Greenblatt DJ, Goddard JE, Friedman H, Harmatz JS, Shader RI (1992) The pharmacokinetics and pharmacodynamics of sublingual and oral alprazolam in the post-prandial state. Eur J Clin Pharmacol 42:439–443

Smith RW, Kroboth PD (1987) Influence of dosing regime non alprazolam and metabolite serum concentrations and tolerance to sedative and psychomotor effects. Psychopharmacology 93:105–112

Smith RB, Kroboth PD, Vanderlugt JT, Phillips JP, Juhl RP (1984) Pharmacokinetics and pharmacodynamics of alprazolam after oral and iv administration. Psychopharmacology 84:452–456

Subhan Z, Harrison C, Hindmarch I (1986) Alprazolam and lorazepam single and multiple-dose effects on psychomotor skills and sleep. Eur J Clin Pharmacol 29:709–712

Van Laar MW, Volkerts ER, Van Willigenburg APP (1991) Therapeutic effects and effects on actual driving performance of chronically administered buspirone and diazepam in anxious outpatients. J Clin Psychopharmacol 12:86–95

Vermeeren A (2004) Residual effects of hypnotics: epidemiology and clinical implications. CNS Drugs 18:297–328

Vermeeren A, De Gier JJ (1995) Methodological guidelines for experimental research in drugs and driving: accomplishments and future needs. In: Krüger HP, Kohnen R, Schoch H (eds) Medicamente im Strassenverkehr: Auftreten, Risiken Konsequenzen. Gustav Fisher Verlag, Stuttgart, pp 49–59

Vermeeren A, Jackson JL, Muntjewerff ND, Quint PJ, Harrison EM, O'Hanlon JF (1995) Comparison of acute alprazolam (0.25, 0.50 and 1.0 mg) effects versus those of lorazepam 2 mg and placebo on memory in healthy volunteers using laboratory and telephone tests. Psychopharmacology 118:1–9

Vermeeren A, Riedel WJ, van Boxtel CJ, Darwish M, Paty I, Patat A (2002) Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. Sleep 25:224–231

Verster JC, Volkerts ER (2004a) Antihistamines and driving ability: Evidence from on-the-road driving studies during normal traffic. Ann Allergy Asthma Immunol 92:294–305

Verster JC, Volkerts ER (2004b) Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. CNS Drug Rev 10:45–76

Verster JC, Volkerts ER, Verbaten MN (2002) Effects of alprazolam on driving ability, memory functioning and psychomotor performance: a randomized, placebo-controlled study. Neuropsychopharmacology 27:260–269

Verster JC, Veldhuijzen DS, Volkerts ER (2005) Is it safe to drive a car when treated with anxiolytics? Evidence from on-the-road driving studies during normal traffic. Curr Psychiatry Rev 1:215–225

Vuurman EF, Uiterwijk MM, Rosenzweig P, O'Hanlon JF (1994) Effects of mizolastine and clemastine on actual driving and psychomotor performance in healthy volunteers. Eur J Clin Pharmacol 47:253–259