A study of the effects of long-term use on individual sensitivity to temazepam and lorazepam in a clinical population

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Aims The central effects of benzodiazepines may be attenuated after chronic use by changes in pharmacokinetics, pharmacodynamics or both. This attenuation may be influenced by the dosing pattern and the characteristics of the user population. The objectives of this study were to evaluate drug sensitivity in long-term users of temazepam and lorazepam in a clinical population.

Methods The sensitivity to benzodiazepine effects in chronic users (1–20 years) of lorazepam ($n=14$) or temazepam ($n=13$) was evaluated in comparison with age and sex matched controls. Drug sensitivity was evaluated by plasma concentration in relation to saccadic eye movement parameters, postural stability and visual analogue scales.

Results Pharmacokinetics of lorazepam and temazepam did not differ between patients and control subjects. Chronic users of lorazepam showed clear evidence of reduced sensitivity, indicated by lack of any pharmacodynamic difference between patients and controls at baseline, when drug concentrations were similar to the peak values attained in the control subjects after administration of 1–2.5 mg of lorazepam. In addition, there was a two- to four fold reduction in the slopes of concentration-effect plots for measures of saccadic eye movements and body sway (all; $P \leq 0.01$). By contrast, sensitivity in chronic users of temazepam was not different from controls. The difference between the temazepam and the lorazepam group appears to be associated with a more continuous drug exposure in the latter, due to the longer half-life and a more frequent intake of lorazepam. This pattern of use may be partly related to the more anxious personality traits that were observed in the chronic users of lorazepam.

Conclusions Chronic users of lorazepam show evidence of tolerance to sedative effects in comparison with healthy controls. Tolerance does not occur in chronic users of temazepam. The difference may be related to pharmacological properties, in addition to different patterns of use, associated with psychological factors.

Keywords: benzodiazepines, patients, tolerance, age, concentration-effect relationships, psychomotor effects

Introduction

Despite the fact that benzodiazepines are generally only indicated for a limited period, a considerable number of patients become chronic users [1]. The continuing therapeutic efficacy of long term treatment with benzodiazepines is uncertain [2], while an increased risk of accidents has been demonstrated in patients using benzodiazepines [3–6]. The benefit-risk ratio of long term treatment with benzodiazepines may be affected by changes in sensitivity with increasing age or by development of tolerance with prolonged use.

Studies on the development of tolerance to benzodiazepine effects have yielded conflicting results [7, 8] and have been largely restricted to healthy subjects receiving treatment for several weeks at the most. Individual concentration-effect relationships, which allow pharmacokinetic- and pharmacodynamic changes to be distinguished, have not been evaluated in clinical studies of tolerance development.

In the present study, saccadic eye movements and body sway were selected as objective effect parameters of benzodiazepine effects, while visual analogue scales were used to evaluate subjective drug effects. The maximal velocity of saccadic eye movements is a highly sensitive parameter for sedative benzodiazepine effects in individual subjects [9, 10]. Furthermore, changes in the level of wakefulness induced by other interventions affect saccadic peak velocity in a consistent manner [11–13]. Body sway provides a measure of postural stability, which is affected by benzodiazepines [14–16] and has been shown to be associated with the occurrence of falls and accidents in the elderly [17–20]. Visual analogue scales have been shown to be a sensitive measure of benzodiazepine effects in healthy volunteers [21].

The objectives of this study were to evaluate drug sensitivity in long-term users of temazepam or lorazepam in comparison with age- and sex-matched controls.

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Methods

Patients using benzodiazepines for a period of at least 3 months and control subjects (male or female, aged 18 years or older) were recruited by advertisement in local papers. Chronic users of temazepam or lorazepam were selected for the study of tolerance development since these were the drugs most frequently used. Exclusion criteria were: patients using more than one benzodiazepine, controls having used benzodiazepines within 3 months prior to the start of the study, use of other drugs known to affect CNS-performance tests within 4 weeks prior to the start of the study, evidence of psychiatric disease, evidence of active clinical abnormalities as assessed by medical history, physical examination, ECG, and routine laboratory assessments, pre-menopausal female controls not using reliable anticonception, pregnancy, drug abuse or evident abuse of alcohol. All participating subjects were mobile and living independently. The protocol for the study was approved by the Ethics Review Board of the Leiden University Hospital. Signed informed consent was obtained from all subjects following written and oral explanation about the study. Patients and controls were paid for their participation in the study.

The effects of chronic use of temazepam and lorazepam on plasma concentration-effect relationships were evaluated in an open, parallel, cross-sectional study with age- and sex-matched pairs of chronic users and control subjects. Thirteen chronic users of temazepam and fourteen chronic users of lorazepam were enrolled in the study. Patient/control pairs were tested with the benzodiazepine used by the patient.

Plasma concentrations and drug effects were measured following a single oral dose of temazepam or lorazepam. Temazepam was administered as soft gelatine capsules (Normison®) at a dose of 20 mg for subjects up to 60 years and 10 mg for subjects over 60 years of age. Lorazepam was administered as tablets (Temesta®) at a dose of 2.5 mg for subjects up to 60 years and 1 mg for subjects over 60 years of age. Pharmacodynamic measurements were performed at −50, −30, −10, 10, 30, 50, 70, 90, 120, 150, 180, 240, 300, 360, and 480 min relative to drug intake for subjects receiving temazepam and at −50, −30, −10, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 360, and 480 min for subjects receiving lorazepam. Plasma samples (10 ml) were taken before drug intake and prior to each pharmacodynamic assessment after drug intake.

Subjects were not allowed to use alcoholic beverages from the evening preceding the study day until 36 h after intake of medications. Patients were instructed to continue their usual benzodiazepine dosage schedule, but not to take benzodiazepines after 23.00 h on the evening preceding the study day. Smoking and the use of caffeinated drinks or chocolate were not allowed on study days. Subjects received a light breakfast at −75 min and a sandwich lunch at 190 min relative to drug intake.

Plasma concentrations of temazepam were measured by use of high pressure liquid chromatography (h.p.l.c.), with u.v. detection at 230 nm (detection limit: 2 ng ml^{-1}). Plasma concentrations of lorazepam were measured by use of reverse phase h.p.l.c. with u.v. detection at 235 nm (detection limit: 2 ng ml^{-1}).

All pharmacodynamic assessments were made in a quiet room with subdued lighting. Prior to the study subjects practised the pharmacodynamic tests three times on one occasion. The registration of saccadic eye movements was performed as previously described [21]. The average peak velocity and latency of all artifact-free saccades in a session were calculated.

Measurements of antero-posterior sway [22] were made for 2 min with the eyes open ($Sway_{EO}$) and for 2 min with the eyes closed ($Sway_{EC}$). During measurements subjects were standing with their feet slightly apart wearing comfortable low heeled shoes.

Subjective drug effects were assessed by use of visual analogue scales [23] for alertness (VAS-alertness) and feeling of psychic tension (VAS-tension). The visual analogue lines were 10 cm wide without indications of scale. The dimensions of the lines scales were: *alert-drowsy* and *relaxed-tense*.

The state- and trait anxiety of subjects was assessed by use of the validated Dutch version of the Spielberger State-Trait Anxiety Inventory (STAI-DY) [24]. The inventory was presented to the subjects after arrival at the centre, prior to any further activities. In addition, personality variables were assessed with the Dutch Personality Inventory, resulting in scores for inadequacy, social inadequacy, rigidity, hostility, self-sufficiency, dominance and self esteem [25]. Subjects completed the personality inventory on study days, prior to the last session of pharmacodynamic tests.

The maximal measured plasma concentrations were used as an estimate of C_{max} for temazepam and lorazepam. Areas under the plasma concentration-time curve between 0 and 8 h (AUC(0,8h)) were calculated by use of the trapezoidal rule [26]. For pharmacodynamic parameters the area under the effect curve between 0 and 8 h (AUEC(0,8h)) was calculated for changes from baseline values. After visual inspection of concentration-effect plots a linear model was chosen to describe the concentration-effect relationships of temazepam and lorazepam.

Statistical analysis was performed for values of C_{max} and AUC(0,8h) of temazepam and lorazepam and for baseline values, AUEC(0,8h) and slopes of concentration-effect plots of pharmacodynamic parameters. Differences between groups were evaluated by analysis of covariance, with the covariates age and sex for baseline-values and slopes and with the covariates age, sex and dose for values of C_{max}, AUC(0,8h) and AUEC(0,8h). Differences in anxiety scores and psychological parameters were evaluated by analysis of covariance with the covariates age and sex. For these parameters separate analyses were performed for overall differences between patients and controls and for differences between patients using temazepam and patients using lorazepam. Slopes of the best fitting regression lines in individual subjects were calculated by use of the statistical software package BMDP (BMDP Statistical Software Inc. Los Angeles, CA). All statistical analyses were performed by use of the statistical software package SPSS/PC+ V-4.0.1. (SPSS Inc., Chicago, Illinois, US).

Results

All subjects completed the study. No matching control was found for one female patient using lorazepam and an age matched male volunteer was included instead.

Demographic characteristics

The demographic data for chronic users and matched controls are shown in Table 1. The temazepam and lorazepam group had different clinical characteristics. The medical diagnosis varied between the groups which resulted in a different selection of benzodiazepine; temazepam was prescribed for insomnia and lorazepam primarily for anxiety. Lorazepam was more frequently dosed than temazepam; once ($n=7$, 50%) to thrice ($n=3$, 21.4%) daily. One patient (7.1%) used lorazepam three to four times a week. All temazepam users took their medication once per day, except two patients (15.4%) who used temazepam three to four times per week.

In the temazepam group seven patient-control pairs (over 60 years of age) received 10 mg temazepam and six pairs received the 20 mg dose, during the study day. In the lorazepam group, three patient-control pairs (over sixty years of age) received a 1 mg dose and 11 pairs received 2.5 mg.

Pharmacokinetics

Chronic users of lorazepam had average baseline plasma concentrations which were close to the maximal values in the control group, while the average baseline plasma concentrations for patients using temazepam were approximately one third of the maximal values reached in controls (113 *vs* 377 ng ml^{-1}; Table 2). Significant differences in C_{max} and AUC(0,8h) were found between patients and controls receiving lorazepam but not temazepam. There were no significant effects of age or sex on values of C_{max} and AUC(0,8h) for temazepam and lorazepam in the analysis of matched groups.

Pharmacodynamics and concentration-effect relationships

The average AUEC(0,8h) values in matched groups of patients and controls receiving temazepam or lorazepam are shown in Table 3, with 95% confidence intervals for drug effects in each separate group and P values indicating differences between matched groups. Table 4 shows the average slopes of concentration effect plots in matched groups of patients and controls. The average effect curves and the average concentration-effect plots for saccadic peak velocity following temazepam are shown in Figure 1. Concentration-effect plots of temazepam showed no significant differences between patients using temazepam and controls in baseline values, AUEC(0,8h) or slopes (Tables 3 and 4). Visual analogue scales of alertness improved similarly in patients and controls, after temazepam. Feelings of tension did not change.

The average effect curves and the average concentration-effect plots in chronic users and controls after lorazepam are shown in Figure 2 for saccadic peak velocity and Figure 3 for body sway with eyes closed. Average baseline lorazepam concentrations in patients were comparable with peak levels attained in controls (15.8 *vs* 19.0 ng ml^{-1}; Table 2). At that time, values of the pharmacodynamic measures did not differ between chronic lorazepam users and their matched control subjects. In contrast to the temazepam results, the AUEC(0,8h) values (Table 3) and slopes (Table 4) of concentration effect plots for saccadic peak velocity, saccadic latency, and body sway were significantly smaller in patients using lorazepam as compared with control subjects (all; $P \leq 0.01$). No differences between patients and controls were found on visual analogue scales of subjective alertness (improved) and feeling of tension (unchanged).

Table 1 Demographic data; chronic users and matched controls.

	Temazepam patients (n = 13)	*Temazepam controls* (n = 13)	*Lorazepam patients* (n = 14)	*Lorazepam controls* (n = 14)
Age (years), (range)	60.7 (36–76)	60.8 (38–76)	53.9 (33–64)	55.5 (47–66)
Weight (kg), (range)	65.8 (50–86)	71.3 (58–88)	72.7 (52–103)	75.5 (54–87)
Sex (M/F)	2/11	2/11	4/10	5/9
Level of education (score[a]), (range)	2.6 (1,4)	2.2 (1,3)	2.6 (2,4)	2.4 (1,4)
Smokers Number of subjects, (%)	5 (39%)	1 (8%)	9 (64%)	5 (36%)
Subjects using alcohol Number of subjects, (%)	7 (54%)	7 (54%)	4 (29%)	12 (86%)
Concurrent disease (diagnoses/number of subjects)	18/9	4/3	14/9	5/5
Subjects using concurrent medication; number of subjects (%)	10 (77%)	4 (31%)	10 (71%)	4 (29%)
Duration of benzodiazepine use (years), (range)	5.5 (1–20)		9.0 (1–20)	
Average daily dose (mg), (range)	17.3 (5–40)		2.5 (0.5–7.5)	
Indication for use (number)				
1) hypnotic	13		4	
2) anxiolytic	0		7	
3) hypnotic + anxiolytic	0		2	
4) other	0		1	

a) Elementary school = 1, secondary school = 2, vocational training = 3, higher education = 4.

Table 2 Pharmacokinetic parameters following administration of temazepam and lorazepam to chronic users and controls.

	Temazepam patients (n = 13)	*Temazepam controls* (n = 13)	*Lorezepam patients* (n = 14)	*Lorazepam controls* (n = 14)
$C_{(t=0)}$ (ng ml^{-1})	113 ± 134	0	15.8 ± 8.0	0
C_{max} (ng ml^{-1})	441 ± 211	377 ± 203	36.5 ± 8.6[a]	19.0 ± 5.7
AUC(0,8 h) (ng ml^{-1} h)	118 ± 58	86 ± 46	13.8 ± 3.6[a]	6.4 ± 2.1

$C_{(t=0)}$ = concentration at baseline.

a) Lorazepam patients significantly different from controls, $P < 0.001$.

Table 3 Pharmacodynamic effects (AUEC(0, 8 h) values; change from baseline) following administration of temazepam and lorazepam to chronic users and controls. The 95% confidence intervals for estimated drug effects in each group are given in parentheses. The statistical significance for difference between patients and controls is indicated in a separate column.

	Temazepam patients (n = 13)	*Temazepam controls* (n = 13)	*Difference patient/control*	*Lorazepam patients* (n = 14)	*Lorazepam controls* (n = 14)	*Difference patient/control*
Saccadic peak velocity (°/s h)	−44 (−62, −26)	−54 (−67, −40)	NS	−42 (−60, −24)	−84 (−103, −65)	$P < 0.01$
Saccadic latency (ms h)	8 (−0.3, 15)	−0.6 (−9, 8)	NS	13 (5, 21)	39 (27, 52)	$P < 0.01$
$Sway_{EO}$ (mm/2min h)	24 (−15, 63)	49 (13, 85)	NS	48 (16, 79)	200 (112, 288)	$P < 0.01$
$Sway_{EC}$ (mm/2min h)	61 (−46, 169)	74 (24, 125)	NS	98 (43, 153)	280 (158, 402)	$P = 0.01$
VAS-alertness (mm h)	−8 (−16, 0.5)	−11 (−18, −3)	NS NS	−13 (−23, −2)	−16 (−26, −6)	NS
VAS-tension (mm h)	−7 (−13, −0.8)	−6 (−17, 5)	NS	−4 (−16, 8)	4 (−2, 10)	NS

Table 4 Pharmacodynamic effects (slopes concentration-effect plots) following administration of temazepam and lorazepam to chronic users and controls. The 95% confidence intervals for the estimated slopes in each group are given in parentheses. The statistical significance for difference between patients and controls is indicated in a separate column.

	Temazepam patients (n = 13)	*Temazepam controls* (n = 13)	*Difference patient/control*	*Lorazepam patients* (n = 14)	*Lorazepam controls* (n = 14)	*Difference patient/control*
Saccadic peak velocity (°/s (ng ml^{-1})$^{-1}$)	−0.36 (−0.63, −0.09)	−0.28 (−0.34, −0.21)	NS	−3.4 (−4.3, −2.5)	−5.8 (−6.9, −4.6)	$P < 0.01$
Saccadic latency (ms (ng ml^{-1})$^{-1}$)	0.04 (−0.01, 0.08)	0.03 (0.01, 0.06)	NS	1.2 (0.6, 1.8)	2.6 (2.1, 3.1)	$P < 0.01$
$Sway_{EO}$ (mm/2min (ng ml^{-1})$^{-1}$)	0.2 (−0.1, 0.5)	0.4 (0.2, 0.5)	NS	4.2 (1.7, 6.6)	17.9 (11.8, 24.0)	$P < 0.01$
$Sway_{EC}$ (mm/2min (ng ml^{-1})$^{-1}$)	0.5 (0.1, 1.0)	0.6 (0.1, 1.1)	NS	8.6 (3.0, 14.3)	26.7 (17.3, 36.1)	$P < 0.01$
VAS-alertness (mm (ng ml^{-1})$^{-1}$)	−0.05 (−0.09, −0.00)	−0.06 (−0.11, −0.02)	NS	−1.1 (−1.8, −0.5)	−1.3 (−2.2, −0.5)	NS
VAS-tension (mm (ng ml^{-1})$^{-1}$)	0.00 (−0.03, 0.04)	0.02 (−0.02, 0.06)	NS	−0.05 (−1.01, 0.90)	0.58 (0.30, 0.87)	NS

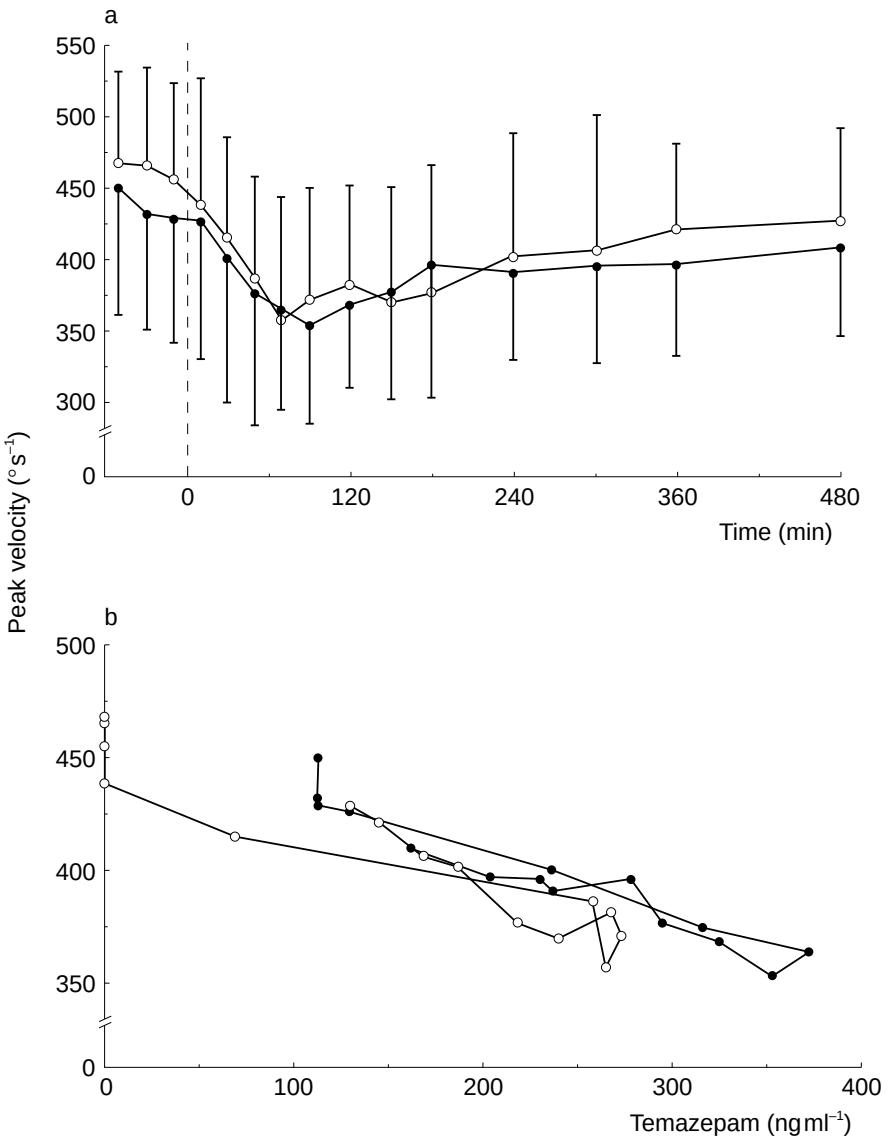

Figure 1 Average time course (a) and concentration effect curves (b) of saccadic peak velocity (s.d.) in chronic users of temazepam (●) and and controls (○) following administration of temazepam. (Dashed line indicates time of administration of temazepam).

Psychological characteristics

Significant differences between patients using lorazepam or temazepam and control subjects were found for state anxiety (patients (average ± s.d.); 40 ± 9, controls; 34 ± 9, $P<0.05$), trait anxiety (patients; 45 ± 10, controls; 35 ± 9, $P<0.001$), inadequacy (patients; 19 ± 9, controls; 11 ± 8, $P<0.01$) and self esteem (patients; 26 ± 4, controls 29 ± 5, $P<0.05$). Patients using temazepam differed significantly from patients using lorazepam for trait anxiety (temazepam; 41 ± 8, lorazepam; 49 ± 10, $P<0.05$), dominance (temazepam; 19 ± 6, lorazepam; 13 ± 5, $P<0.05$) and hostility (temazepam; 19 ± 6, lorazepam; 24 ± 5, $P<0.05$).

Discussion

This study aimed to compare the pharmacodynamic effects of benzodiazepines among chronic users of two of the most commonly prescribed benzodiazepines, lorazepam and temazepam. It can be argued that the reliability of the outcome of this open study is limited by differences in patient characteristics and actual patterns of use between lorazepam- and temazepam-users. At the same time however, such differences would be relevant to practical benzodiazepine therapy, and they have not been studied systematically before. Therefore, this open study in actual patient populations was preferred to a long-term prospective double-blind trial, with all the ethical and practical problems associated with chronic benzodiazepine usage.

In this study, chronic users of lorazepam showed no objective effects at baseline, despite average lorazepam plasma concentrations that were similar to the peak plasma levels reached in control subjects. This is a clear indication for tolerance to lorazepam. Furthermore, the slopes of concentration-effect plots demonstrated a reduced sensitivity to the effects of the subsequent dose of lorazepam, which is also a sign of reduced drug sensitivity. By contrast, the concentration-effect relationships in chronic users of temazepam and control subjects were indistinguishable. The difference in sensitivity to lorazepam and temazepam may be related to the use or the properties of the two benzodiazepines (pharmacological); or related to the characteristics of the user populations (demographic).

Chronic users of lorazepam had clearly higher baseline drug concentrations than long term temazepam users (relative to levels attained in controls). This suggests that exposure to lorazepam is more prolonged than to temazepam. In the present study, lorazepam was taken twice or thrice

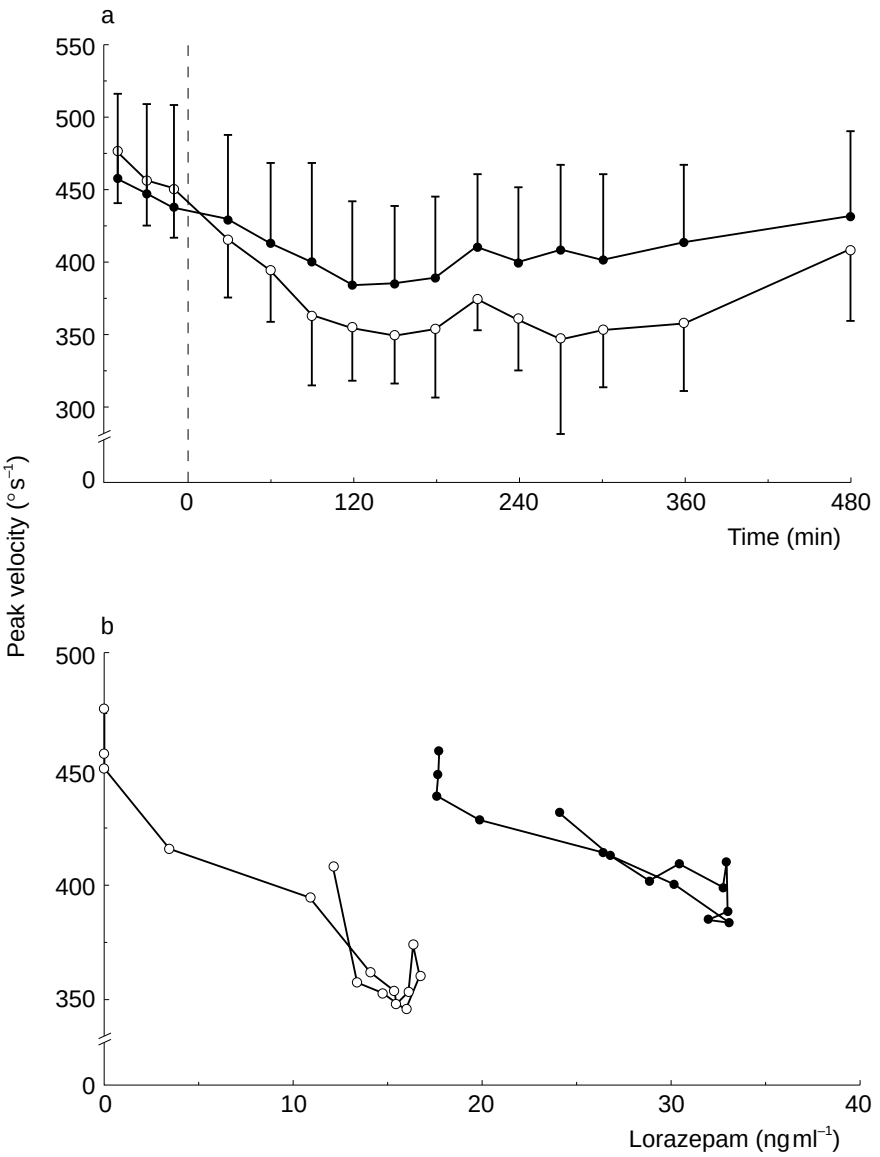

Figure 2 Average time course (a) and concentration-effect curves (b) of saccadic peak velocity (s.d.) in chronic users of lorazepam (●) and controls (○) following administration of lorazepam. (Dashed line indicates time of administration of lorazepam).

daily by 50% of the users whereas all temazepam users took their drug once per day. Moreover, the plasma half-life of lorazepam is generally longer than for temazepam (8–25 h *vs* 5.3–11.5 h, respectively [27]). In addition, lorazepam has a higher receptor affinity than temazepam [28]. All these factors may have led to a more continuous exposure to lorazepam than to temazepam, and hence to a difference in the liability to development of tolerance.

Tolerance to the effects of lorazepam has previously been reported after short term administration to healthy volunteers [29], and in psychiatric patients using high doses of various benzodiazepines [30]. However, there have been no studies evaluating tolerance in out-patients using lorazepam. The present study was performed in a clinical population, and was hence inevitably unrandomized. Randomization to chronic intake of temazepam or lorazepam and a prospective follow-up were considered unethical in healthy volunteers, and impracticable in patients; and experienced users would probably readily sense the difference between placebo and their usual benzodiazepine medication, obviating the use of placebo control. Hence, the study was substantiated by a cross-sectional comparison of chronic users to age- and sex-matched controls, by the use of methods that are well established in benzodiazepine research, and by a detailed inventory of known confounding factors in each study group.

Despite measures to control the comparability of the study groups, subjects were selected from different patient populations, which may have affected the outcomes of the study. The sensitivity to benzodiazepines may be influenced by concomitant disease and use of medication, which was more frequent in chronic benzodiazepine users in the literature [1, 31] and in our study group (Table 1). However, these factors were very similar among patients using temazepam or lorazepam in the present study, and patients with conditions or drugs likely to affect the pharmacodynamic measures or effects of benzodiazepines were excluded. Heavy smoking [32] and frequent use of alcohol [33] have been reported to reduce the sensitivity to benzodiazepines. These factors were not entirely evenly distributed among the study groups, but the differences were not significant, and it is unlikely that they are responsible for the considerable differences in drug sensitivity observed in this study. The different pharmacodynamic effects found between the study groups could be related to differences in prevailing psychological state (anxiety levels), or to more stable personality traits. Patients with panic disorder show a reduced sensitivity to benzodiazepines [34, 35]. In the present study, chronic

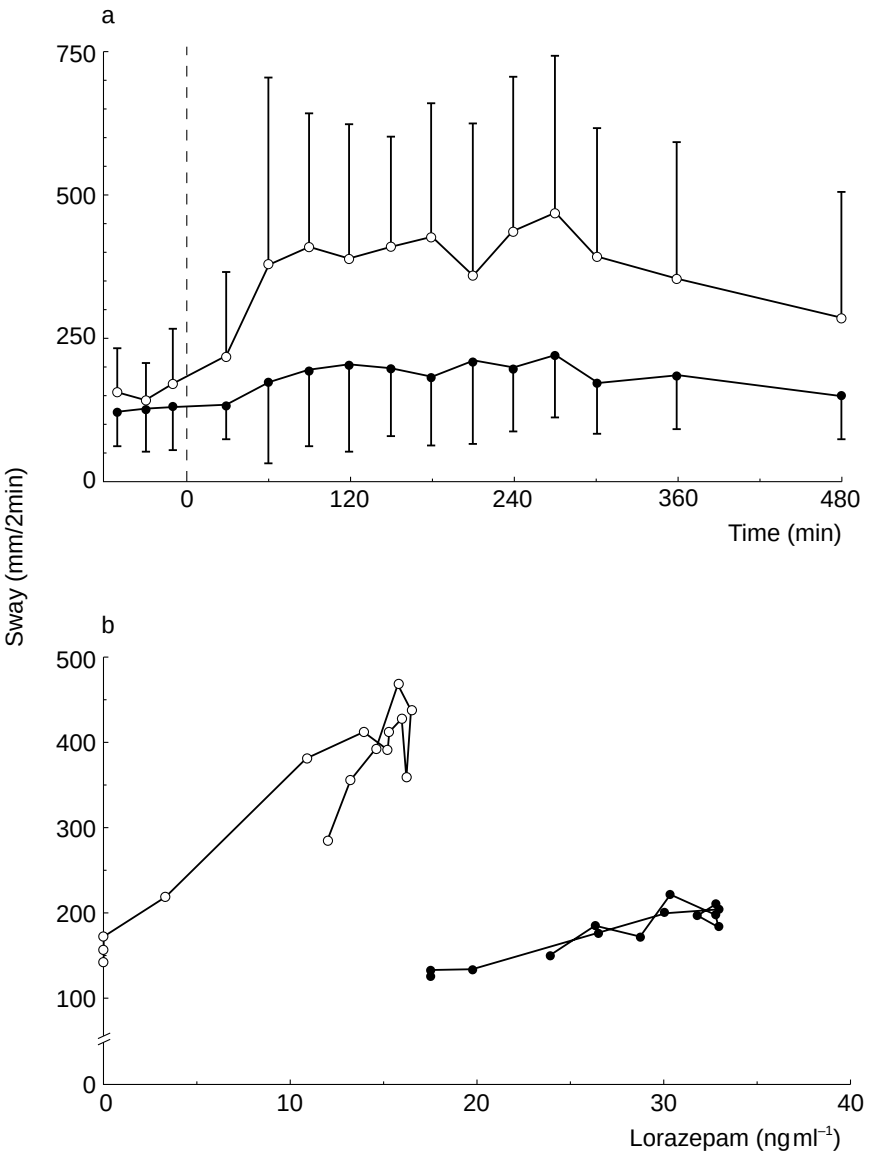

Figure 3 Average time course (a) and concentration effect curves (b) of body sway (eyes open) (s.d.) in chronic users of lorazepam (●) and controls (○) following administration of lorazepam. (Dashed line indicates time of administration of lorazepam).

users of lorazepam and temazepam were more anxious at baseline than control subjects, shown by differences in state- and trait anxiety. Increased alertness, associated with anxiety, could partly explain the reduced sensitivity to benzodiazepines in patients compared with their more relaxed control subjects. However, both groups of patients were equally anxious during the study day (state anxiety) and acute psychological effects are therefore unlikely to explain the differences in benzodiazepine sensitivities between the two patient groups. Long term users of lorazepam were characterized by more tense personality traits than patients using temazepam, shown by their significantly higher trait anxiety- and hostility levels and lower dominance-scores. These differences in personality traits may have affected the use of lorazepam and temazepam under ambulant conditions, e.g. a more frequent use of lorazepam by the more anxious patients in this group compared to the temazepam group. Certain personality traits have been shown to predispose to chronic use of benzodiazepines [36]. In this way, differences in patient selection could be related to the observed pharmacological differences between lorazepam and temazepam, discussed previously.

Several reviews report that tolerance develops to sedative, but not to anxiolytic effects during prolonged use of benzodiazepines [37–39]. However, such studies are poorly comparable because of differences in design, patient selection [39] and other methodological problems [2]. Often, an increase in anxiety caused by withdrawal symptoms (due to an abrupt switch to placebo after chronic use) is attributed to slackening of the anxiolytic effects of the discontinued drug, and hence as proof of its prolonged efficacy [37]. The present study has shown that development of tolerance in a clinical population depends on the efficacy parameter, the pattern of use, and the selected patient population. Despite clear indications for tolerance, lorazepam still caused significant effects on saccadic eye movements, postural stability and subjective alertness. Therefore, the advice not to drive or operate machinery within hours after intake of lorazepam remains valid in chronic users. Temazepam also still impaired performance in chronic users. This could be a risk factor for accidents in insomniac patients when they get up during the night after taking a sleeping pill. Contrary to temazepam, lorazepam did not improve the visual analogue scale for psychic tension, and subjects were anxious despite high lorazepam levels at baseline or after lorazepam administration. This could be due to the development of tolerance to the anxiolytic effects of lorazepam, but not of temazepam. The efficacy of lorazepam or temazepam as a hypnotic after

chronic use cannot be determined from this study, although this was the most frequent self-admitted indication for use. Benzodiazepine hypnotics are recommended for no more than 4 weeks [40–42]. Continuing effects on objective sleep parameters have been reported after temazepam use for up to 5 weeks [43], but not after benzodiazepine use for over 6 months [44].

Differences between chronic users of temazepam and lorazepam indicate that results obtained for one benzodiazepine cannot be simply extrapolated to another. Benzodiazepines can have a reduced efficacy on at least some parameters after long term administration, which is at least partly associated with the continuity of drug exposure. This continuity is not only due to the pharmacological properties of the benzodiazepine involved, but also to the pattern of use, and hence to the characteristics of the users.

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