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ORIGINAL INVESTIGATION

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Effects of alprazolam and lorazepam on catecholaminergic and cardiovascular activity during supine rest, mental load and orthostatic challenge

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Abstract Effects of oral alprazolam (0.5 and 1 mg) and lorazepam (2 mg) on sympathetic adrenomedullary activity and sedation were studied during supine rest, mental load (Color Word Test, CWT) and active standing (OCT), in 12 male volunteers in a randomized double-blind placebo-controlled cross-over design. Compared to placebo, alprazolam significantly increased subjective sedation, reduced plasma adrenaline and noradrenaline concentrations and mean blood pressure (MBP) during supine rest, and attenuated plasma adrenaline responses during the CWT and the OCT; these effects during the CWT and OCT appeared to be dose-dependent. In comparison with lorazepam (2 mg), alprazolam (1 mg) showed reduced MBP levels during supine rest, whereas lorazepam showed a higher heart rate level during supine rest, a reduced plasma noradrenaline response to the OCT and a performance deterioration to the CWT. There were no differences between alprazolam (1 mg) and lorazepam regarding subjective sedation. Although the benzodiazepines were similar regarding their increase of sedation, alprazolam and lorazepam induced differential effects on sympathetic adrenomedullary activity during rest and stress, whereby suppression of adrenomedullary activity may be specific for alprazolam.

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Introduction

Activation of the sympathetic adrenomedullary system is of great importance for the physiological adaptation to a range of mental and physical situations. During stressful situations, activation of the sympathetic nervous system may be accompanied by changes in subjective mood such as anxiety, irritability or dysforia (Lader and Bruce 1986). Moreover, chronic increased sympathetic activity due to stressful situations may be relevant for the pathogenesis of anxiety states and cardiovascular diseases such as hypertension (Brown and MacQuin 1981; Charney et al. 1984).

Treatment of anxiety symptoms in patients with cardiovascular dysfunction often includes benzodiazepines. Because suppression of stress-induced sympathetic adrenomedullary activation may be desirable in patients with stress related cardiovascular disorders, a benzodiazepine with such properties is of great interest. Alprazolam is a benzodiazepine similar to other benzodiazepines in its anxiolytic properties (Dawson et al. 1984), but different in other respects. In the rat, it antagonizes stress-induced increases in adrenaline and noradrenaline concentrations (Vogel et al. 1984). Alprazolam also protects against stress-induced cardiac damage in hamsters with cardiomyopathy (Tapp et al. 1989) and in rats treated with isoproterenol (Berkowitz et al. 1988). Some of these effects may be related to stimulation of α_2-receptors by alprazolam, although it does not seem to bind directly to these receptors (Rick-Brand and Müller 1988). Unlike diazepam, alprazolam

antagonizes the reserpine-induced increase in β-receptors, which may be related to the antidepressant effects of alprazolam (Sethy and Hodges 1982). In humans, alprazolam may suppress adrenergic as well as noradrenergic function, although conflicting data exist (Stratton and Halter 1985; Risby et al. 1989; Linnoila et al. 1990; McLeod et al. 1990; Breier et al. 1992; Osman et al. 1993). Studies in humans have also suggested that there are differences between benzodiazepines with respect to sedative properties: alprazolam may induce less sedation in comparison with clinically equivalent doses of other benzodiazepines (Dawson et al. 1984; Subhan et al. 1986; Greenblatt et al. 1988).

In a previous study we have shown the usefulness of the Stroop Color Word Test (CWT) as a psychological performance task that is capable of inducing psychic distress and sympathetic adrenomedullary activation as shown by increased cardiovascular activity and plasma catecholamine secretion (Tulen et al. 1989). In a sequel study, we have shown that lorazepam had no specific effects on these responses to the CWT (Tulen et al. 1991, 1994).

The present study aimed to investigate whether oral administration of alprazolam influences catecholaminergic and cardiovascular activity during periods of rest and mental load (CWT), different from lorazepam and in comparison with placebo, in healthy volunteers. The responses to mental load were compared with responses to a physical task that is known to increase sympathetic nervous system activity (orthostatic challenge). Special attention was paid to plasma adrenaline concentrations, because several studies suggest that alprazolam specifically attenuates adrenomedullary activity (Stratton and Halter 1985; Breier et al. 1992). This has so far not been studied during mental challenge tasks in humans. In addition, the sedative properties of alprazolam were studied.

Because effects on catecholaminergic and cardiovascular responses and subjective sedation may be dose dependent, the effects of a relatively high (1 mg) and a moderate (0.5 mg) oral dose of alprazolam were evaluated and compared in a double-blind placebo-controlled design. Furthermore, responses to the high dose of alprazolam (1 mg) were compared with responses to the (approximately) clinically equivalent oral dose of 2 mg lorazepam, utilizing lorazepam as an active control for the responses to alprazolam. Both alprazolam and lorazepam are reported to be moderately rapidly absorbed, with peak plasma concentrations occurring between 0.7 and 2.1 h after oral administration, and both benzodiazepines can be regarded as intermediate half-life benzodiazepines (elimination half-life of lorazepam: 12–13 h; alprazolam: 9–19 h), whereas no active metabolites of interest are formed (Kyriakopoulos et al. 1978; Ellinwood et al. 1985; Higgitt et al. 1988; Huybrechts 1991).

Materials and methods

Subjects

Twelve healthy male volunteers with a mean (±SD) age of 22 (±2) years participated in a double-blind, randomized, placebo-controlled, cross-over study. Only male subjects were included because the phase of the menstrual cycle in females can have an effect on plasma catecholamine concentrations and autonomic nervous system responses to stress. The subjects underwent medical and psychiatric screening prior to inclusion into the study. All subjects had negative personal and family histories for psychiatric illness and substance abuse and had been medication free for at least 2 months prior to the study. The subjects were instructed to keep a regular sleep-wake pattern and to avoid physical or psychic exertions starting 3 days before the experimental sessions. During these days, alcohol consumption had to be limited to a maximum of one consumption per day. The subjects did not smoke more than five cigarettes per day. The study was approved by the Medical Ethical Review Committee of the University Hospital Rotterdam Dijkzigt. All subjects gave written consent prior to inclusion into the study.

Procedures

All subjects received, in a randomized and double blind order, either an oral dose of 0.5 mg alprazolam (ALP0.5), 1 mg alprazolam (ALP1), 2 mg lorazepam (LOR), or a placebo (PLA), on 4 different days which were separated by at least 5 days. All medications consisted of the commercially available oral dosage form, which was placed in an opaque capsule with a rapid disintegration rate. The four medications looked identical.

On the experimental day, the subjects had breakfast at home; coffee and smoking were not allowed before or during the session. Each session lasted from 8.15 a.m. until 12.15 a.m. At 8.15 a.m., the subjects received the oral dose of ALP0.5, ALP1, LOR or PLA; 30 min hereafter the experiment started. Subjects were studied during three periods of supine rest (15 min each) with 60 min between the periods. Between first and second supine periods, the subjects performed two tasks: the Color Word Test (CWT) as a mental effort task and the Orthostatic Challenge Test (OCT) as a physical task. Following the first supine rest period, the volunteers were subjected to the CWT (10 min) after a stabilization period in the sitting position (10 min). Details of the CWT have been described before (Tulen et al. 1989, 1991). Hereafter, the OCT was performed: the subjects stood for 10 min at ease in the upright position (active standing). After the second supine rest period, the test procedures were repeated in reversed order. In this paper, we will report the effects of alprazolam and lorazepam on the three consecutive periods of supine rest, as well as the effects of the drugs on the responses to the first CWT and OCT.

Measurements and analyses

Forty-five minutes prior to the start of the measurements, a catheter (Venflon, 18G, Viggo AB, Helsenborg, Sweden) was inserted into an antecubital vein of the non-dominant forearm, for serial blood sampling. For determination of the plasma concentrations of ALP0.5, ALP1 and LOR, blood (10 ml) was collected after each resting period in EDTA tubes. Blood was centrifuged (10 min, 4000 *g*) and plasma was stored at −70°C until it was assayed. Alprazolam and lorazepam plasma concentrations were assayed by means of high performance liquid chromatography with UV detection, after isolation from plasma by an extraction with heptane:isoamylalcohol (90:10). For determination of plasma adrenaline and noradrenaline concentrations, blood (10 ml) had been collected in chilled heparinized tubes containing 12 mg

gluthathione, after each supine or sitting rest period, after 5 min during performance of the CWT and after 10 min of standing. The blood samples were centrifuged at 4°C (15 min, 3000 *g*); plasma was subsequently stored at −70°C until assay. Catecholamines were assayed by means of high performance liquid chromatography with fluorimetric detection after isolation from plasma by a specific liquid-liquid extraction method and derivatization with the selective fluorogenic agent 1,2-diphenylethylenediamine (van der Hoorn et al. 1989).

ECG and blood pressure were recorded continuously during the session on a multichannel FM-type analogue recorder (Racal Store 14 DS, Sarasota, Flo. USA). Signals were on-line digitized at a sample frequency of 102.4 Hz on a personal computer (Dell optiplex 466/L) connected to an Analogue/Digital converter (Advantech PC-LabCard model PCL-718). The ECG was derived using a precordial lead, amplified by means of a polygraph (Nihon Kohden, Tokyo, Japan). R-R intervals in the ECG were detected with an accuracy of 10 ms and transposed to heart rate (HR) series. Blood pressure was recorded using a servo-plethysmomanometer for continuous non-invasive measurements of finger arterial blood pressure, employing the volume clamp technique of Penaz (Penaz et al. 1976; Settels and Wesseling 1985) (Finapres 2300 NIBP monitor, Ohmeda, Englewood, Col. USA). Mean (MBP) blood pressure was defined as the mean of the individual blood pressure values between two consecutive R-waves of the ECG. Cardiovascular data were analyzed per 5-min period for the rest and OCT situations, and per 2.5 min for the CWT. Responses to the CWT and active standing were defined as changes in absolute levels. For the CWT, differences were computed between the stabilized part of the test (last 2.5 min) and the preceding 5-min period of sitting. For the OCT, the response was defined as the difference between the stabilized part of the active standing (last 5 min) and the preceding period of supine rest (last 5 min).

Changes in sleepiness were assessed by means of the Dutch translation of the Stanford Sleepiness Scale (Hoddes et al. 1973). Changes in subjective mood were assessed by means of a shortened version of the vigor and fatigue subscales of the Profile Of Mood States (POMS) (McNair et al. 1978; validated Dutch version: Wald and Mellenbergh 1990) and a shortened state-version of the State-Trait Anxiety Inventory (STAI) (validated Dutch version: van der Ploeg et al. 1980; shortened version: Knippenberg et al. 1990). Sleepiness, mood and anxiety scores were obtained after each rest period. In this report, only sleepiness data will be presented.

Statistical analysis

Statistical analyses were performed using SPSS for Windows Release 6.0 (SPSS Inc.). Multivariate analyses of variance (MANOVA) for repeated measurements were performed to explore the effects of ALP0.5 and ALP1, in comparison to PLA and LOR, on catecholaminergic, cardiovascular and psychological parameters ($n = 12$ unless otherwise specified). Two primary hypotheses were tested:

1. H_0: the catecholaminergic, cardiovascular and sleepiness variables are not influenced by alprazolam, as compared to placebo.
   H_1: Alprazolam affects the catecholaminergic, cardiovascular and sleepiness variables differently then placebo.
2. H_0: the catecholaminergic, cardiovascular and sleepiness variables are not differently affected by alprazolam (1 mg), as compared to lorazepam (2 mg).
   H_1: Alprazolam (1 mg) affects the catecholaminergic, cardiovascular and sleepiness variables differently, as compared to lorazepam (2 mg).

Supine rest

To test hypothesis 1, two-factor MANOVAs for repeated measurements with Helmert contrasts were performed: factor DRUG (PLA, ALP0.5 and ALP1) and factor TIME (three supine rest periods). The averaged tests of significance were used to explore drug, time and interaction effects, when Mauchly's test of sphericity revealed no deviations from the symmetry assumptions. The Huyn-Feldt epsilon was used to adjust the degrees of freedom for the averaged results. To test hypothesis 2, the same strategy was used as described above, but with the factors: Drug (ALP1 and LOR) and TIME (three supine rest periods).

CWT and OCT

To test hypothesis 1, the same strategy was used as described above, but without the factor Time. To test hypothesis 2, paired *t*-tests were performed. In all cases, a *P*-value of <0.05 was considered significant.

Results

Benzodiazepine concentrations

The maximum plasma concentrations for ALP0.5 (8.1 ± 2.0 ng/ml), ALP1 (15.3 ± 3.4 ng/ml) and LOR (13.6 ± 2.1 ng/ml) were reached approximately 2 h (ALP0.5 and ALP1) and 1.5 h (LOR) after administration (Fig. 1). The individual peak concentrations, ranging from 6.7 to 13.3 ng/ml for ALP0.5, from 12.8 to 21.6 ng/ml for ALP1, and from 10.9 to 20.5 ng/ml for LOR, were reached between 0.8 and 3 h after administration. The changes over time with the different drugs were not significantly different.

Supine rest (Tables 1, 3)

Plasma catecholamines

Plasma adrenaline concentrations (Fig. 2) were reduced after administration of ALP0.5 and ALP1, as shown by a trend drug effect ($P = 0.06$). However, no dose effect was found and plasma adrenaline concentrations after ALP1 and LOR administration were not significantly different. Plasma noradrenaline concentrations were significantly altered ($P < 0.05$); inspection of the plasma concentrations showed a reduction of plasma noradrenaline concentrations after ALP1 administration, but not after ALP0.5 administration (Fig. 2). During all sessions, plasma adrenaline and noradrenaline levels showed a time-dependent increase ($P < 0.01$).

Blood pressure

The mean blood pressure (MBP) was significantly reduced after the administration of ALP0.5 and ALP1 ($P < 0.05$) (Fig. 2). No differences were found between the effect of ALP0.5 and ALP1. MBP after ALP1 administration was significantly reduced in comparison with MBP after LOR administration ($P < 0.05$).

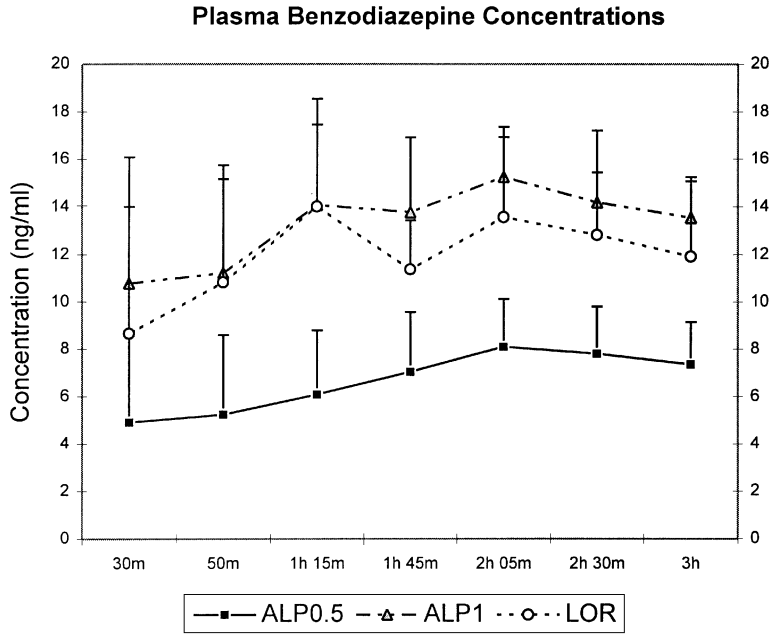

Fig. 1 Mean (+SD) plasma benzodiazepine concentrations after oral administration of alprazolam (0.5 mg and 1 mg) and lorazepam (2 mg), during a 3-h period after administration

Table 1 The mean (SD) plasma adrenaline concentrations (*Adr*), plasma noradrenaline concentrations (*Noradr*), heart rate (*HR*), mean blood pressure (*MBP*) and scores on the Stanford Sleepiness scale (*SSS*) during the three supine rest periods (*S1*,*S2*,*S3*) after placebo, alprazolam (0.5 and 1 mg) and lorazepam (2 mg) administration

	Supine rest											
	Placebo			Alprazolam 0.5 mg			Alprazolam 1 mg			Lorazepam 2 mg		
	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3
Adr (pg/ml)	10.4	8.8	13.0	6.5	7.1	7.7	6.5	6.8	9.0	6.6	10.4	12.3
	(5.2)	(3.4)	(6.4)	(4.7)	(3.7)	(4.5)	(5.4)	(4.4)	(7.3)	(3.3)	(6.2)	(7.4)
Noradr (pg/ml)	159.0	162.8	184.8	149.8	174.3	216.3	125.1	146.5	166.7	142.8	166.9	177.2
	(43.9)	(46.6)	(62.0)	(37.7)	(76.0)	(123.1)	(46.8)	(66.1)	(64.0)	(52.1)	(66.6)	(61.0)
HR (bpm)	63.3	61.2	59.2	61.7	59.4	56.2	64.5	61.2	57.8	62.0	62.4	60.9
	(8.3)	(7.0)	(6.1)	(8.3)	(7.6)	(5.3)	(10.9)	(10.1)	(7.7)	(9.3)	(10.4)	(9.2)
MBP (mm Hg)	76.6	79.1	81.6	71.5	75.0	79.0	71.9	75.6	79.9	75.2	80.6	85.8
	(9.8)	(5.4)	(7.8)	(9.1)	(7.8)	(8.3)	(9.0)	(7.9)	(10.0)	(9.9)	(10.6)	(10.6)
SSS	2.1	2.3	1.8	2.5	3.3	2.7	2.9	3.5	3.0	2.8	3.6	3.2
	(0.9)	(1.3)	(0.9)	(1.3)	(1.6)	(1.1)	(1.1)	(1.8)	(1.0)	(1.0)	(1.4)	(1.5)

Table 2 The mean (SD) response of plasma adrenaline, plasma noradrenaline, heart rate, and mean blood pressure during the CWT and OCT, as well as the number of errors to the CWT, after placebo, alprazolam (0.5 and 1 mg) and lorazepam (2 mg) administration

	CWT				OCT			
	PLA	ALP0.5	ALP1	LOR	PLA	ALP0.5	ALP1	LOR
Adr (pg/ml)	10.5	8.6	3.7	8.1	15.6	8.6	5.8	18.8
	(11.6)	(7.1)	(5.2)	(13.1)	(15.6)	(6.0)	(5.8)	(26.3)
Noradr (pg/ml)	−8.9	−6.7	5.5	2.1	259.4	253.6	294.6	220.1
	(43.7)	(36.5)	(54.8)	(39.1)	(88.5)	(75.9)	(138.7)	(71.5)
HR (bpm)	7.7	5.6	9.6	11.3	25.0	26.6	27.0	26.3
	(7.4)	(4.8)	(6.6)	(7.4)	(7.6)	(11.9)	(8.8)	(8.3)
MBP (mmHg)	13.8	9.8	12.8	10.8	12.0	11.8	13.7	15.2
	(9.3)	(4.7)	(6.6)	(7.0)	(5.8)	(3.6)	(6.9)	(8.0)
#ERR	2.4	6.2	6.0	18.1				
	(3.6)	(15.4)	(6.4)	(14.6)				

Table 3 P-Values of the drug, time and drug-by-time-interaction effects of the MANOVAs for repeated measurements and paired *t*-tests. Explicit contrasts were defined between alprazolam (0.5 and 1 mg) and placebo [factor drug: PLA, ALP0.5, ALP1, with Helmert contrasts (contr): −2 1 1]

	Supine rest						CWT			OCT		
	PLA/ALP0.5/ALP1			ALP1/LOR			PLA/ALP0.5/ALP1		ALPI/LOR	PLA/ALP0.5/ALP		ALP1/LOR
	Drug	Time	Int	Contr	Drug	Time	Int	Drug	Contr	Drug	Drug	Contr	Drug
Adr	–	0.007	–	0.061	–	0.033	–	0.062	–	–	–	0.048	–
Noradr	0.046	0.002	–	–	–	0.000	–	–	–	–	–	–	0.046
HR	–	0.005	–	–	–	0.001	0.007	–	–	–	-	–	–
MBP	–	–	–	0.036	0.027	0.000	–	–	–	–	–	–	–
SSS	0.013	0.009	–	0.003	–	0.046	–	–	–	–	–	–	–
#ERR								–	–	0.031			

During all sessions, the MBP showed a significant increase over time.

Heart rate

HR was not differently affected by ALP0.5 or ALP1, in comparison with placebo. However, ALP1 and LOR affected the HR differently, as shown by a drug-by-time interaction effect ($P < 0.01$): HR after LOR administration showed a slower reduction over time, in comparison with ALP1. HR decreased over time during all sessions ($P < 0.01$).

Sleepiness

Sleepiness increased between the first and second supine period and decreased between the second and third period. In comparison with PLA administration, sleepiness increased significantly after administration of ALP0.5 and ALP1 (Fig. 2) ($P < 0.01$), whereas no differences were found between the ALP0.5 and ALP1 sessions and the ALP1 and LOR sessions.

Mental load (CWT) (Tables 2, 3)

Performance to the CWT

The number of errors made during performance of the CWT was not significantly influenced after ALP0.5 and ALP1 administration; the number of errors after LOR administration was significantly increased in comparison to the number of errors after ALP1 administration ($P < 0.05$) (Fig. 3).

Plasma catecholamines

After PLA administration, plasma adrenaline concentrations increased with 10.5 ± 11.6 (pg/ml) during performance of the CWT (Fig. 3). CWT responses of plasma adrenaline concentrations after ALP0.5 and ALP1 administration were reduced, as shown by a trend multivariate effect ($P = 0.06$). This reduction by ALP was less during the ALP0.5 session than during the ALP1 session. No significant differences were found regarding plasma adrenaline response magnitudes between the ALP1 and LOR sessions. Plasma noradrenaline concentration during performance of the CWT was not influenced by either benzodiazepine.

Blood pressure

After PLA administration, MBP increased with 13.8 ± 9.3 mmHg during performance of the CWT. MBP response magnitudes were not affected by either drug or dose, in comparison with PLA administration.

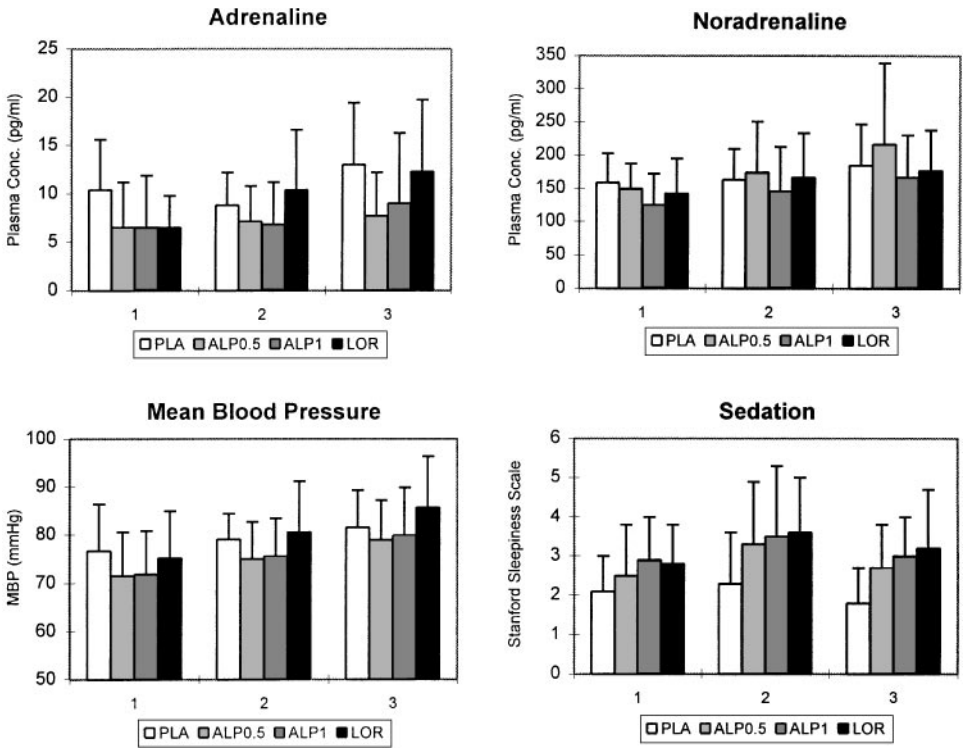

Fig. 2 Mean (+SD) plasma adrenaline concentrations, plasma noradrenaline concentrations, mean blood pressure and sleepiness scores during the three consecutive supine rest periods (1,2,3), for the PLA, ALP0.5, ALP1 and LOR sessions separately

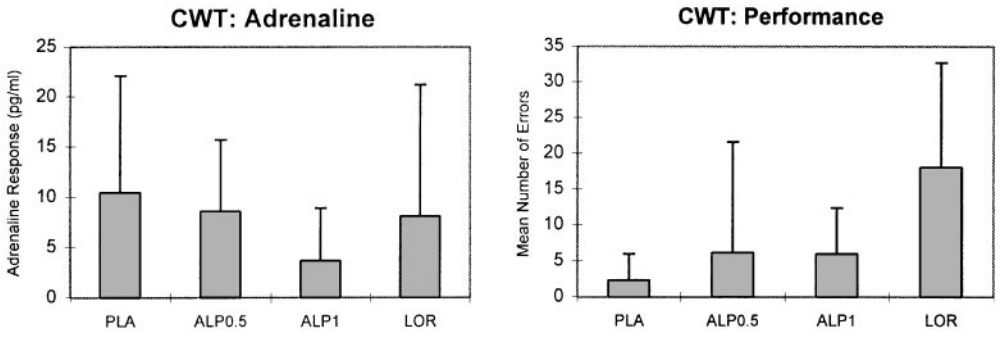

Fig. 3 Mean (+SD) plasma adrenaline response and the performance to the CWT, for the PLA, ALP0.5, ALP1 and LOR sessions separately

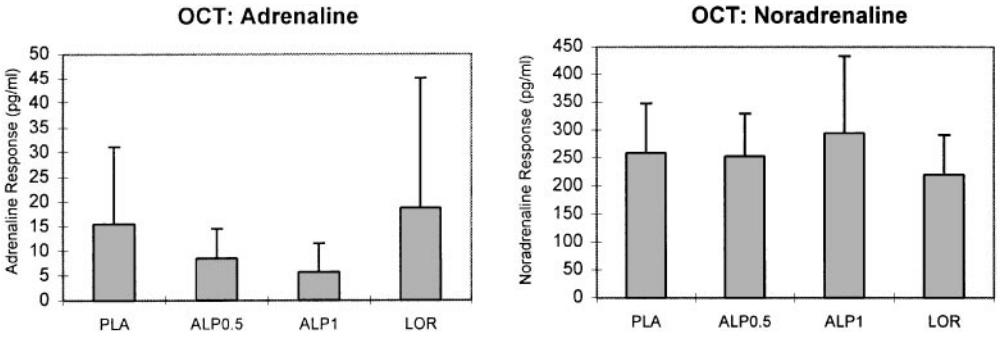

Fig. 4 Mean (+SD) plasma adrenaline and noradrenaline response to the OCT, for the PLA, ALP0.5, ALP1 and LOR sessions separately

Heart rate

The mean HR response to the CWT was 7.7 ± 7.4 bpm during the PLA session. HR response after ALP0.5 and ALP1 administration was not significantly different from PLA administration, and the HR response to the CWT after ALP1 administration was not significantly different from HR response after LOR administration.

Active standing (OCT) (Tables 2,3)

Plasma catecholamines

During the PLA session, the plasma adrenaline concentrations increased during performance of the OCT with 15.6 ± 15.6 (pg/ml); the plasma noradrenaline concentrations increased with 259 ± 88 (pg/ml). The adrenaline response (Fig. 4) to the OCT was significantly reduced during the ALP0.5 and ALP1 sessions, as compared to the PLAC session ($P < 0.05$). After administration of ALP1, the OCT response was less than after administration of ALP0.5. The adrenaline response to the OCT after ALP1 administration was not significantly different as compared to LOR. The noradrenaline response to the OCT was not influenced by ALP0.5 and ALP1, but the noradrenaline response after LOR administration was significantly reduced in comparison with ALP1 ($P < 0.05$) (Fig. 4).

Blood pressure

After PLA administration, MBP increased with 12.0 ± 5.8 mmHg during performance of the OCT. Administration of ALP0.5, ALP1 or LOR did not alter the MBP response to the OCT.

Heart rate

The HR increased with 25.0 ± 7.6 bpm during the OCT of the PLA session. HR response was not altered by either drug or dose.

Discussion

The aim of this study was to evaluate the effects of alprazolam on sympathetic nervous system activity during rest, mental load, and active standing. Two oral dosages of alprazolam (0.5 mg and 1 mg) were compared to placebo and lorazepam (2 mg). Compared with placebo administration, alprazolam induced a trend towards a reduction of plasma adrenaline concentrations during supine rest and mental load, and significantly suppressed adrenaline concentrations during orthostatic challenge; the effects during the CWT and the OCT appeared to be dose-dependent. In addition, alprazolam significantly suppressed MBP and plasma noradrenaline concentrations, but only during supine rest. At both dose levels, alprazolam significantly increased subjective sedation. When comparing responses to alprazolam (1 mg) and lorazepam (2 mg), alprazolam showed reduced MBP levels during supine rest, whereas lorazepam showed a higher HR level during supine rest, a reduced plasma noradrenaline response to the OCT and a performance deterioration to the CWT. There were no differences between alprazolam (1 mg) and lorazepam (2 mg) regarding subjective sedation.

Alprazolam versus Placebo

Plasma catecholamines

As indicators of sympathetic nervous system activity, plasma adrenaline (adrenomedullary activity) and noradrenaline (sympathoneural activity) concentrations were used. ALP tended to reduce the plasma adrenaline concentrations during supine rest, attenuated the adrenaline response to active standing, and tended to decrease the adrenaline response to mental load. These data indicate a suppressing effect of ALP on the adrenomedullary system, as well as a dose dependent attenuation of the stress induced activation. Although these effects were obtained under standardized conditions, the effects were nevertheless small. However, these effects of ALP on the plasma adrenaline concentrations are consistent with the findings reported by Stratton and Halter (1985). They described reduced plasma adrenaline concentrations during supine rest and reduced plasma adrenaline responses during physical stress (treadmill exercise) after administration of ALP (0.5 mg 3 times daily, orally, for 3 days). McLeod et al. (1990) also reported reduced adrenaline concentrations after ALP administration (0.5 mg, 1–12 times daily, orally, for 6 weeks) during a resting period in the sitting position in patients with generalized anxiety disorder. In addition, Breier et al. (1992) described an attenuation of the plasma adrenaline response to glucoprivic stress (2-deoxyglucose administration) by ALP (1.5 mg, orally). Our data are the first to show that alprazolam also attenuates the relatively small adrenomedullary responses during mental load and active standing.

In our study, plasma noradrenaline concentrations during supine rest were reduced by the higher dose of ALP (1 mg), but the responses to the CWT and OCT were not affected. The reduction of plasma noradrenaline concentrations after ALP administration during supine rest is consistent with the findings reported by McLeod et al. (1990) and Risby et al. (1989). Risby et al. described reduced plasma noradrenaline concentrations during supine rest after intravenous administration of ALP (0.02 mg/kg). However, others found no effect of ALP on plasma noradrenaline concentrations during supine rest [Stratton and Halter 1985; Linnoila et al. 1990 (alprazolam: 0.5 mg or 2 mg, orally)]. In contrast to our results, Stratton and Halter (1985) described a reduction of the noradrenaline response by ALP during the performance of a treadmill exercise, but Breier et al. (1992) found no effect of ALP on the response to glucoprivic stress (2-deoxyglucose administration).

The inconsistent findings about the influence of ALP on plasma noradrenaline concentrations can perhaps be explained by methodological differences. During rest, different methods were used with regard to posture (supine and sitting) and drug administration (oral and intravenous; single and multiple administration). Also, different stressors were used (mental, physical, exercise, and metabolic stress). Furthermore, interpretation of concentrations of venous noradrenaline is hampered by the fact that these concentrations are influenced by local sympathetic nervous system activity at the site of sample collection and concentrations are also highly dependent on the rate at which noradrenaline is removed from the circulation and not only its release into plasma (Floras et al. 1986; Esler et al. 1988; Tulen 1993). This may explain some of the differential effects of mental stressors versus physical stressors and exercise.

Cardiovascular effects

ALP reduced the MBP during supine rest, but did not influence the stress induced MBP responses. Reduced BP after ALP administration is consistent with other reports in the literature [Risby et al. 1989; Linnoila et al. 1990; Rohrer et al. 1994 (alprazolam: 0.5 mg); McLeod et al. 1990], although some studies observed no effect [Stratton and Halter 1985; Osman et al. 1993 (alprazolam: 0.003, 0.007, 0.02 mg/kg, intravenously)]. The unaffected MBP responses to mental and physical stress are in accordance with other studies, where no or a very modest influence of ALP on the MBP response was described [Stratton and Halter 1985; Breier et al. 1991; Crowe McCann et al. 1992 (0.5 mg alprazolam, orally); Rohrer et al. 1994]. HR during supine rest and the HR response during the mental and physical tasks were not affected by ALP. Comparable findings for HR during supine rest have been observed in several studies (Stratton and Halter 1985; Linnoila et al. 1990; Osman et al. 1993), although Risby et al. (1989) described a slight increase. HR, obtained while subjects were in a sitting position, was reported to decrease after ALP administration (McLeod et al. 1990; Rohrer et al. 1994). The findings regarding the influences of ALP on task induced HR increases are divergent. Some studies describe no influence of ALP administration on the HR response [Breier et al. 1991 (1.5 mg alprazolam, orally); Crowe McCann et al. 1992], others observed a reduced response after ALP (Stratton and Halter 1985; Rohrer et al. 1994), whereas Linnoila et al. (1990) described a marginal increase after ALP.

Sedation

Sleepiness increased after both dose levels of alprazolam, although this did not influence performance to the CWT. Our results are in line with previous studies reporting increases in subjective sedation after 0.5 or 1.0 mg alprazolam (Dawson et al. 1984; Subhan et al. 1986; Greenblatt et al. 1988; Risby et al. 1989).

Alprazolam (1 mg) versus Lorazepam (2 mg)

Plasma adrenaline concentrations during supine rest and adrenaline responses to the CWT and OCT were not differently affected by ALP1 or LOR. However, versus placebo, the plasma concentrations during supine rest and the adrenaline responses to the CWT and OCT indicated a suppressing effect of ALP1 (Figs 2, 3, 4). These observations make the specificity of a suppressing effect of ALP on the adrenomedullary system questionable. The mean values of plasma adrenaline concentrations during CWT and OCT were evidently lower after ALP1 than after LOR administration (Tables 1, 2). However, we could not ascertain a significant difference, possibly due to the relatively high standard deviations of the adrenaline concentrations after LOR administration. Further studies are required to elucidate the reasons for this adrenergic response variability after LOR administration.

The plasma noradrenaline response during active standing was not affected by ALP1, but was reduced by LOR. Collomp et al. (1994) described no changes in resting plasma noradrenaline concentrations after a dose of 1.5 mg LOR. In accordance with our previous findings [Tulen et al. 1991 (intravenous, increasing 0.0, 0.06, 0.13, 0.25 and 0.5 mg; cumulative dose 0.94 mg)], we observed no effects of LOR on resting catecholaminergic concentrations and responses to the CWT.

The influences of ALP1 and LOR on cardiovascular variables were also different with regard to the MBP and the HR levels, but only during supine rest. Administration of LOR did not affect the MBP during supine rest, while ALP1 did suppress the MBP. The decrease in HR over time was less during the LOR session in comparison to the ALP1 session. Both effects accentuate the suppressing effect of ALP on sympathetic adrenomedullary activity.

Both ALP1 and LOR equally increased subjective sedation. Since there were no differences regarding subjective sedation, it is remarkable that performance to the CWT was deteriorated only after LOR administration. Memory impairment and performance deterioration to psychological tasks after a dose of 2 mg lorazepam are well documented (Subhan et al. 1986; Greenblatt et al. 1988; Preston et al. 1989; Tulen et al. 1991). Similar effects have been reported after alprazolam (Subhan et al. 1986; Greenblatt et al. 1988; Linnoila et al. 1990). However, at the present dose levels of alprazolam, subjective sedation was not accompanied by performance impairment to the CWT.

The plasma concentrations, peak concentrations and peak latency of both alprazolam and lorazepam were

comparable with previous studies (Kyriakopoulos et al. 1978; Dawson et al. 1984; Greenblatt et al. 1988; Huybrechts 1991). The plasma concentration curves after 1 mg ALP and 2 mg LOR were very similar with respect to the time course during the experiment and with respect to absolute values. Radioreceptor assays have shown lorazepam to be about three times as potent as alprazolam at the central benzodiazepine receptor, but alprazolam's free fraction in serum is 2–3 times higher than lorazepam's (Arendt et al. 1987). This does not make it easy to estimate the concentrations and activity of both compounds at the central benzodiazepine receptor when serum concentrations are similar. Some experiments on memory and psychomotor functions have shown 0.5 mg alprazolam and 1 mg lorazepam to be equivalent (Block and Berchou 1984; Subhan et al. 1986; Kumar et al. 1987). In view of these data and the parallel time course of the plasma concentration curves in this experiment, it would appear that the differences observed in this study cannot be ascribed to differences in potency of alprazolam and lorazepam at the doses investigated.

The mechanisms by which benzodiazepines (BZD) change sympathetic nervous system activity during rest or attenuate stress induced sympathoneural and adrenomedullary activation are not well understood. In human brains, interaction with specific BZD-receptors facilitates the inhibitory neurotransmission of the neurotransmitter γ-aminobutyric acid (GABA). The $GABA_a$/Bz receptor complex mediates the principal actions of the BZDs (Breier and Paul 1990). The receptor was found to be localized at multiple brain sites, in particular the medial hypothalamus, the hippocampus, cortex, amygdala and brain stem sites such as the locus coeruleus. $GABA_a$/Bz receptor agonists (such as ALP) have potent suppressive effects on CRH release, an effect that is blocked by $GABA_a$/Bz receptor antagonists (Owens et al. 1989; Kalogeras et al. 1990). CRH plays a significant role in stress and affective behaviour. Beside other functions, it enhances autonomic nervous system activity (Brown et al. 1985; Kreutz et al. 1992). In this study, both alprazolam and lorazepam affected autonomic nervous system activity, although the effects were small. We observed differential effects of alprazolam and lorazepam on sympathoneural and cardiovascular activity, whereby suppression of adrenomedullary activity occurred only after alprazolam administration. The acute effects as observed in this study need to be further explored in studies with (sub)chronic drug administration. Nevertheless, our data indicate that in the treatment of anxiety symptoms in patients with cardiovascular disorders, suppression of adrenomedullary activity by alprazolam may be an advantage over the use of other benzodiazepines.

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