Br. J. clin. Pharmac. (1985), **19**, 445–451

A comparison of the effects of lorazepam with those of propranolol on experimentally-induced anxiety and performance

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1 In a double-blind cross-over study the effects of propranolol (80 mg) and of lorazepam (1 or 2.5 mg) were assessed in normal student volunteers using a number of performance tests and mood-rating and bodily symptom questionnaires. Drug effects on experimentally-induced anxiety were also studied.

2 The high dose of lorazepam impaired performance in digit-symbol substitution, symbol copying and verbal learning tests, and increased subjects' ratings of dizziness. Both lorazepam and propranolol increased simple reaction time. Lorazepam but not propranolol increased ratings of sedation.

3 Although the stressor increased subjects' ratings of anxiety, neither drug altered anxiety ratings.

4 Propranolol decreased and lorazepam increased subjects' pulse. These changes were not reflected in subjects' self-ratings - lorazepam caused a reduction in ratings of palpitations.

5 The results suggest that if administered acutely, neither drug is beneficial in the treatment of short-term anxiety associated with intellectual stress.

Keywords lorazepam propranolol anxiety performance

Introduction

The two classes of drug used most frequently in the treatment of anxiety are the benzodiazepines and the β-adrenoceptor antagonists (Greenblatt & Shader, 1974; Noyes, 1982). It has been suggested that β-adrenoceptor blockers are of greatest benefit when a patient's anxiety is secondary to a somatic complaint arising from enhanced sympathetic activity. In contrast, the benzodiazepines seem to have their greatest benefit when the source of the complaint is psychological (Tyrer & Lader, 1974a). There have been a number of studies comparing the effects of β-adrenoceptor blockers with placebo; few studies have compared the effects of a β-adrenoceptor blocker with those of a benzodiazepine (Wheatley, 1969; Tyrer & Lader, 1974b; Burrows *et al.*, 1976). The present study therefore compared the effects of propranolol with those of lorazepam in a number of performance tests and examined the effect of each compound on experimentally-induced anxiety.

The doses of lorazepam (1.0 and 2.5 mg) selected are within the clinical range and the dose of propranolol was one that would produce significant β-adrenoceptor blockade in all subjects (Brewer, 1972).

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Methods

Subjects
The subjects (mean age 22 years) were selected from 17 student volunteers (11 females and six males) from the School of Pharmacy. One (female) subject suffered from occasional asthmatic attacks and was therefore not included in the study.

Drugs
Lorazepam (1 mg (blue) or 2.5 mg (yellow), Ativan, Wyeth) or matching placebo tablets were administered orally. Propranolol (80 mg, ICI) or matching placebo tablets were also administered orally. The tablets were administered by the same person who did not know which were active and which were placebo and who took no further part in the experiment. Subjects took the tablets with their eyes closed and were unaware of the colour of the tablets they received. The experiment was double-blind, therefore, in that neither the subjects nor the experimenters knew the treatment the subjects received. On each day of testing all subjects received two tablets: either lorazepam or its placebo, and propranolol or its placebo, according to the design described below.

Procedure
The subjects were divided into two groups. Group A received a 1 mg dose of lorazepam, Group B received a 2.5 mg dose of lorazepam. Each subject was tested under three conditions: placebo, propranolol (80 mg), and lorazepam (1.0 or 2.5 mg). The experiment took place on the Mondays of 3 successive weeks. Subjects refrained from drinking alcohol-containing beverages on the day before each test day and on the test day itself. They were randomly assigned to the order in which they received their drug treatments. At 11.30 h lorazepam or its placebo was administered and at 12.30 h propranolol or its placebo was administered after which subjects were given a standard lunch. Testing started at 14.30 h (corresponding to the time of peak effect for each drug) and lasted approximately an hour. The test order was randomized amongst subjects and test days, with the exception of the verbal learning and stress tests which were performed at the end of the test session.

Simple reaction time Subjects were asked to press a key in response to a sound stimulus. The reaction time was measured using a Control Universal System 20 computer. Thirty trials were given with a randomized intertrial interval of 0.5 to 4.0 s.

Digit-symbol substitution Subjects were given 90 s to perform a digit-symbol substitution test taken from the Wechsler Adult Intelligence Scale (Wechsler, 1955). The number of digits correctly substituted was scored.

Symbol copying Subjects were asked to copy as many symbols as they could in 90 s. The symbols used in this task were the same as those used in the digit-symbol substitution test. The number of symbols correctly copied was scored.

Self-rating scales The subjects completed a mood-rating scale of 16 items from which three factors have been isolated (Bond & Lader, 1974). Factor 1 is an index of sedation and is obtained from nine of the scales (alert/drowsy, strong/feeble, muzzy/clear-headed, well co-ordinated/clumsy, lethargic/energetic, mentally-slow/quick-witted, attentive/dreamy, incompetent/proficient, interested/bored). Factor 2 is a measure of contentedness and is obtained from 5 scales (contented/discontented, troubled/tranquil, happy/sad, antagonistic/amicable, withdrawn/gregarious). Factor 3, calmness, has been used as an index of anxiety and is obtained from two scales (calm-excited, tense/relaxed).

Subjects also completed a bodily symptom scale which has been described previously (File & Lister, 1983) and a modified version of the Spielberger State Anxiety Inventory (Spielberger *et al.*, 1970; Lister & File, 1983).

Pulse The pulse of each subject was measured.

Verbal learning Subjects were shown a list of 10 words, one word at a time for 5 s, at 1 s intervals. After the final word was presented, a 6-digit number was shown (to eliminate a recency effect). The subjects were asked to write down this number and as many words as they could remember in 60 s. The test was repeated with a second list of 10 words. The total number of words correctly recalled was scored.

Stress Subjects were asked to stand and were given 9 min to attempt 20 questions from the AH5 IQ test (Heim, 1968). During this period subjects were further stressed by sounding a loud, high-frequency noise from a signal generator and audio amplifier. At the end of the test subjects were asked to complete a Spielberger State-Anxiety Inventory and a bodily symptom questionnaire while the noise was still sounding. Immediately after completing the test, the pulse of each subject was measured for a second time.

Statistics The effect of lorazepam in each test was assessed using analysis of variance with the dose of lorazepam as the independent factor. The effects of propranolol were assessed using Student's *t*-tests, or, where appropriate, analysis of variance. In the analysis of the pulse and Spielberger state anxiety scores, stress was a related measure. Bodily symptom scores were not normally distributed and so were analysed using Wilcoxon T tests.

Results

Reaction time Both lorazepam ($F(1,14) = 7.5$, $P < 0.02$) and propranolol ($t(15) = 2.8$, $P < 0.02$) significantly increased simple reaction time (Table 1).

Digit-symbol substitution Lorazepam reduced the number of symbols substituted, a result due almost entirely to the effect of the 2.5 mg dose, lorazepam x dose interaction ($F(1,14) = 10.1$, $P < 0.01$). Propranolol was without effect in this test (Table 1).

Symbol copying In this test, the low dose of lorazepam was without significant effect, but the high dose significantly reduced the number of symbols copied (lorazepam x dose interaction, $F(1,14) = 31.5$, $P < 0.0001$). Propranolol had no effect on performance in this test (Table 1).

Verbal learning Propranolol did not affect, but the high dose of lorazepam significantly impaired performance in the verbal learning test (lorazepam x dose interaction $F(1,14) = 5.5$, $P < 0.05$), (Table 1)

Self-ratings
There were no significant drug effects on Factors 2 (contentedness) and 3 (calmness). Propranolol also had no effect on Factor 1 (sedation). The higher dose of lorazepam produced a greater degree of sedation as measured by Factor 1 than the lower dose (lorazepam x dose interaction, $F(1, 14) = 7.8$, $P < 0.02$). When this interaction was taken into account there was still a significant overall lorazepam effect on Factor 1, ($F(1,14) = 8.2$, $P < 0.02$), (Table 2).

In the unstressed conditions lorazepam significantly reduced subjects' ratings of palpitations ($t = 13$, $P < 0.005$), and the high dose of lorazepam increased subjects ratings of dizziness ($t = 1$, $P < 0.02$). There were no other drug effects on bodily symptoms.

The stress test significantly increased subjects' ratings of anxiety as measured by the modified

Table 1 The effects of placebo, of lorazepam and of propranolol on performance in a number of tests. Scores are means ± s.e. mean

	Placebo	*Group A Propranolol (80 mg)*	*Lorazepam (1 mg)*	*Placebo*	*Group B Propranolol (80 mg)*	*Lorazepam (2.5 mg)*
Reaction*+ time (ms)	171 ± 16	187 ± 9	183 ± 7	183 ± 8	203 ± 10	214 ± 16
Digit-symbol# substitution	78 ± 3	76 ± 3	74 ± 4	75 ± 3	79 ± 2	59 ± 3
Symbol# copying	158 ± 6	158 ± 9	154 ± 8	162 ± 9	164 ± 7	130 ± 8
Verbal# learning	17.4 ± 1.5	16.4 ± 1.6	17.0 ± 1.4	16.6 ± 1.6	16.4 ± 1.6	11.8 ± 1.7

*significant lorazepam effect
+significant propranolol effect
#significant lorazepam x dose interaction, see text.

Table 2 The effects of placebo, of propranolol, of lorazepam and of stress on subjects' self-ratings. Scores are means ± s.e. mean or medians (range). Group A received 1 mg lorazepam and Group B received 2.5 mg lorazepam.

	Placebo		*Propranolol*		*Lorazepam*	
	Unstressed	*Stressed*	*Unstressed*	*Stressed*	*Unstressed*	*Stressed*
Factor 1 (Sedation)*#						
Group A	15.8 ± 2.0	—	18.4 ± 2.7	—	21.8 ± 1.5	—
Group B	14.1 ± 2.1	—	14.3 ± 2.2	—	26.5 ± 0.5	—
Factor 2 (Contentedness)						
Group A	7.8 ± 0.5	—	8.9 ± 1.3	—	9.6 ± 1.1	—
Group B	9.2 ± 1.2	—	7.2 ± 1.2	—	11.3 ± 0.7	—
Factor 3 (Calmness)						
Group A	4.0 ± 0.6	—	3.5 ± 0.7	—	4.1 ± 0.6	—
Group B	3.8 ± 0.6	—	4.1 ± 0.7	—	4.0 ± 0.2	—
Spielberger State Anxiety +						
Group A	493 ± 57	907 ± 110	547 ± 99	927 ± 189	579 ± 88	838 ± 113
Group B	798 ± 134	1303 ± 160	629 ± 58	1111 ± 138	802 ± 81	1273 ± 157
Bodily symptoms						
Anxiety +						
Group A	8 (0–23)	13.5 (2-37)	1 (0–50)	16.5 (2–80)	7 (1–21)	12 (1–60)
Group B	8 (0–64)	49 (0–85)	12.5 (0–51)	22.5 (0–96)	1.5 (0–16)	49 (0–86)
Dizziness						
Group A	1 (0–64)	2.5 (0–62)	4.5 (0–83)	3 (0–64)	7.0 (1–63)	7.5 (4–73)
Group B*	4 (0–77)	8.5 (0–69)	3 (0–65)	2.5 (0–43)	76.5 (23–91)	46 (0–72)
*Palpitations**						
Group A	15.5 (0–89)	3 (0–15)	3 (1–62)	4.5 (1–64)	2 (0–8)	3.5 (0–11)
Group B	8 (0–58)	14.5 (0–70)	14.5 (0–65)	19.5 (0–81)	3.5 (0–12)	4 (0–42)

*significant lorazepam effect (see text)
#significant lorazepam x dose interaction (see text)
+significant stress effect (see text)

Spielberger State-Anxiety Inventory ($F(1,14) = 39.9$, $P < 0.0001$) and neither lorazepam nor propranolol modified this effect. There was a significant group effect ($F(1,14) = 7.2$, $P < 0.02$), the subjects that received the higher dose of lorazepam rating their anxiety slightly higher under all drug conditions. The stress test also increased ratings of anxiety on the bodily symptom questionnaire regardless of whether subjects had received placebo ($t = 6$, $P < 0.005$), propranolol ($t = 13$, $P < 0.005$) or lorazepam ($t = 10$, $P < 0.005$) (Table 2).

Pulse

Lorazepam caused a significant increase in heart-rate ($F(1,14) = 30.6$, $P < 0.0002$). The stress also increased heart-rate ($F(1,14) = 6.0$, $P < 0.05$). There was no lorazepam x stress interaction. As expected, propranolol significantly reduced subjects' heart-rate ($F(1,15) = 41.6$, $P < 0.0001$). There was also a significant propranolol x stress interaction, ($F(1, 15) = 4.8$, $P < 0.05$), stress causing an increase in heart-rate when subjects received placebo, but not when they received propranolol (Figure 1).

Discussion

The performance impairment associated with acute benzodiazepine administration is well documented (e.g. Clarke *et al.*, 1970; File & Bond, 1979). In this study 2.5 mg lorazepam produced marked impairments in all performance tests. Both doses of lorazepam, in contrast to propranolol, caused increases in self-ratings of sedation reflecting an undesirable side-effect typical of many if not all anxiolytic agents acting at central benzodiazepine receptors. Although benzodiazepines have been shown to increase simple reaction time (Vogel, 1979), the effects of propranolol have been less clear. Tyrer & Lader (1974b) found 120 mg to be without effect, whereas Bryan *et al.* (1974) reported a dose-related increase in reaction time following 40–80 mg. The increase in reaction time observed in the present experiment following 80 mg propranolol presumably results from a central action, although the other performance tests and the self-rating scales gave no further indication of CNS depression.

Lorazepam and propranolol had opposite

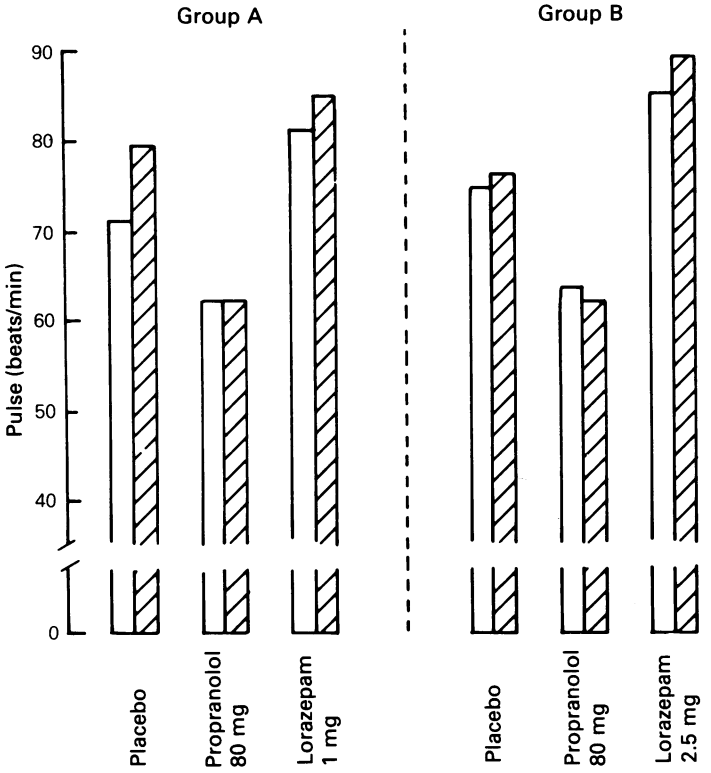

Figure 1 Mean pulse rate of subjects before (□) and after stress (▨), after administration of placebo, propranolol (80 mg) or lorazepam (Group A, 1 mg; Group B, 2.5 mg).

effects on subjects' pulse (Figure 1). Interestingly these effects were not reflected in the subjects' ratings of palpitations. Indeed the lorazepam-treated subjects had a significantly lower rating of palpitations than placebo-treated subjects although their heart-rate was higher. A poor relationship between observed physiological changes and subjects' self-ratings was also observed in the study of Tyrer & Lader (1974b), and emphasizes the importance of obtaining both measures.

Neither lorazepam nor propranolol in the doses used had an anxiolytic action as measured by subjects' self-ratings. The drugs were not only without effect on baseline anxiety levels as measured by the Spielberger State Anxiety Inventory, Factor 3 or the anxiety rating on the bodily symptom questionnaire, but also failed to reduce experimentally-induced anxiety. The doses used had clear effects in other tests so it cannot be argued that these doses were totally inactive. This raises the question of whether the anxiety induced in the present experiment is related to pathological anxiety. Results from previous work have shown drug effects on anxiety to vary according to whether the anxiety was clinical or induced experimentally (Stone *et al.*, 1973). The method used in this experiment was chosen so as to resemble examination anxiety in a student population. In a previous study alcohol, another agent with documented anxiolytic activity (see Pohorecky, 1981), was able to reduce anxiety induced in this manner (Lister & File, 1983).

Earlier studies have demonstrated the efficacy of β-adrenoceptor blockade in improving the musical performance of subjects impaired by stage fright (James *et al.*, 1977; Brantigan *et al.*, 1978). James *et al.* (1977) also found this treatment to ameliorate the subjects' self-ratings. It is clear that enhanced sympathetic activity will be detrimental to performance in tests requiring a steady hand and complex motor coordination (as in a musical performance). It is therefore not surprising that a subject aware of such excessive sympathetic activity will be anxious about it, and that a subject whose sympathetic activity has been reduced by β-adrenoceptor blockade will be less anxious. In contrast, whether sympathetic activity has a detrimental effect on performance in an IQ test is not clear. Furthermore in this study the stressor did not increase subjects' ratings of shaking or palpitations, although it did increase heart-rate. It is possible that had the subjects been required to play the piano instead of perform the IQ test they would have been aware of their tachycardia and this would have in turn increased their anxiety. We suggest that the difference in test requirements may account for the difference in the effect of β-adrenoceptor blockade on self-ratings in the present study and in that of James *et al.* (1977).

That lorazepam was without effect on ratings of anxiety is perhaps surprising. Tyrer & Lader (1974b) found that diazepam significantly reduced anxiety induced by three different methods. There are, however, at least two factors that contribute to lorazepam's overall effect on ratings of anxiety. Not only does the drug have an anxiolytic effect, but when taken acutely it causes profound impairments in performance, seen in the present experiment most clearly following the 2.5 mg dose. This impairment is likely to be anxiogenic in subjects wishing to perform well (just as enhanced sympathetic activity is anxiogenic in musical performers). Such an effect has been seen in student volunteers taking a combination of lorazepam (1 mg) and alcohol (Lister & File, 1983) and may account for the lack of anxiolysis seen in this experiment.

In conclusion, although β-adrenoceptor blockade and benzodiazepine treatment are clearly beneficial in the treatment of some anxiety disorders (Granville-Grossman & Turner, 1966; Tyrer & Lader, 1974a; Burrows *et al.*, 1976; James *et al.*, 1977; Noyes, 1982), their usefulness in the alleviation of short-term anxiety associated with intellectual stress remains to be demonstrated.

We are grateful to Wyeth for the gift of lorazepam and to ICI for the gift of propranolol. SEF is a Wellcome Trust senior lecturer. RGL is supported by a School of Pharmacy postgraduate award.

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(Received September 6, 1984, accepted November 16, 1984)