A double-blind comparison of alprazolam, diazepam and placebo in the treatment of anxious out-patients

K. DAVISON¹, R. G. FARQUHARSON¹, M. C. KHAN² & A. MAJID³

¹Department of Psychological Medicine, Newcastle General Hospital, Newcastle-upon-Tyne NE4 6BE,

²Department of Psychiatry, Hartlepool General Hospital, Cleveland and ³ St Luke's Hospital, Middlesbrough, Cleveland

1 In a double-blind 28-day comparison of alprazolam, diazepam and placebo, alprazolam 1.5–3 mg/day was of equivalent anxiolytic effect to 15–30 mg diazepam/day and there was some evidence of antidepressant activity by alprazolam, but not diazepam, in neurotic depression. No serious side-effects or laboratory abnormalities were encountered.

Keywords alprazolam diazepam anxiety out-patients

Introduction

This paper reports a double-blind trial comparing alprazolam (Xanax—Upjohn), diazepam and placebo in the treatment of anxious out-patients with anxiety states.

Methods

Patients were attending out-patient psychiatric clinics at three centres.

Selection criteria

1. Age 18–60 years.
2. Male or female, but female patients must not be pregnant and those of child-bearing age must be taking adequate contraceptive measures.
3. A diagnosis of anxiety state with a score of at least 18 on the Hamilton Anxiety Rating Scale (HARS) present for at least 1 month and not expected to remit spontaneously during the trial period.

Exclusion criteria

The presence of primary depression, schizophrenia, serious physical illness, mental subnormality, behaviour disorder, benzodiazepine sensitivity and alcohol or drug abuse.

Experimental procedure

The trial design was a double-blind between-patient comparison of randomly allocated capsules of identical appearance containing alprazolam 0.5 mg, diazepam 5 mg or placebo over a 28 day period.

The definitive trial was preceded by a 4 day wash-out period during which all psychotropic medication was withdrawn and replaced by one placebo capsule twice daily. The initial dosage of the trial drugs was one capsule three times daily increasing to up to two capsules three times daily from day 4, according to response. Dose reduction was also allowed at this stage.

Physical and laboratory screening

Before entering the trial all patients were examined physically and urine specimens were tested for the presence of albumin, sugar, red and white blood cells and renal casts. Blood samples were taken for full blood count, ESR, serum creatinine, bilirubin, urea, alkaline phosphatase and SGOT and were repeated at the end of the trial. BP, pulse rate and body temperature were recorded at the end of weeks 1 and 2 and a full physical examination was repeated at the end of the trial.

Clinical assessment

Anxiety was assessed by means of the Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959) and a self-rating scale of 35 items measured on a four-point scale (Cohn, 1981), before entering the trial and at the end of weeks 1, 2 and 4. Midway through the trial, when evidence of alprazolam's possible anti-depressant action emerged (Fabre & McLendon, 1980) the Hamilton Depression Rating Scale (HRS) (Hamilton, 1960) was included in the assessment of the last 24 patients.

The investigators also rated the severity of each patient's disorder on a seven-point scale initially and at weeks 1, 2 and 4 and the patients rated the therapeutic effect of the drug on a five-point scale at the end of the trial.

Side-effects

Side-effects were recorded by the investigators on a symptom check-list and rated as mild, moderate or severe. At the end of the trial they also recorded their overall impression for side-effects on a four-point scale.

Results

Fifty patients entered the trial but four were excluded from further evaluation leaving 46 acceptable entrants. Reasons for exclusion were:

1. Failure to return after initial assessment (two patients on diazepam).
2. Overdose of alprazolam after 5 days treatment.
3. Concomitant ingestion of nitrazepam as a hypnotic (one patient on alprazolam).

Demographic and clinical data

The age and sex composition of the three treatment groups is shown in Table 1. None of the differences was statistically significant, nor were there any statistically significant differences between groups with respect to a previous history of psychiatric disorder or duration of symptoms before entering the trial.

Twelve patients failed to complete the trial, two from both the alprazolam and diazepam groups and eight from the placebo group. Reasons for dropping out were side-effects (alprazolam 1, placebo 1), and lack of efficacy (alprazolam 1, diazepam 2 and placebo 7). These differences were not statistically significant.

The mean daily numbers of capsules consumed per patient by the end of the trial were alprazolam 4.5, diazepam 4.8 and placebo 4.2.

Table 1 Demographic data

	<i>Alprazolam</i> n = 12	<i>Diazepam</i> n = 14	<i>Placebo</i> n = 20
<i>Gender</i>			
Male	8	5	10
Female	4	9	10
<i>Age (years)</i>			
Mean $\pm$ s.d.	41.7 $\pm$ 13.7	38.6 $\pm$ 11.6	32.9 $\pm$ 11.8
Range	18-60	24-60	18-57

Efficacy

In order to minimise bias end-point scores were used in the statistical calculations i.e. when a patient dropped out of the trial the last score recorded beforehand was regarded as the final score for computation purposes.

Scores on the Hamilton Anxiety Rating Scale (HARS) are shown in Table 2. All groups achieved statistically significant improvement between their initial and end-point HARS scores, greatest for alprazolam and least for placebo. Although the per cent reduction in scores was of the same order the differences between groups did not reach the 5% probability level.

Comparison of scores on the depression component of the HARS (Table 3) showed statistically significant improvement only in the alprazolam group and the difference between the alprazolam and the other groups reached the 10% probability level.

Scores on the Hamilton Rating Scale for Depression (HRS) on 24 patients only (Table 4) also showed statistically significant improvement only in the alprazolam group but the small numbers involved resulted in quite large differences between groups being statistically non-significant.

The investigators' overall assessment of illness severity (Table 5) paralleled closely the HARS scores in that all three groups showed statistically significant improvement, maximal for the alprazolam group but differences between groups were not statistically significant. Their overall evaluation of therapeutic effect on a five-point scale (1 = marked improvement to 5 = worse) showed, however, a statistically significant superiority of alprazolam over placebo which was not achieved by the diazepam group (Table 6). The difference between the alprazolam and diazepam groups was not significant.

On the patients' self-rating symptom scale (35 items, 0 = absent to 3 = extremely severe) both the alprazolam and diazepam groups, but not the placebo group showed statistically

Table 2 Comparison of HARS scores

Total score	Alprazolam			Diazepam			Placebo		
	n	Mean	s.d.	n	Mean	s.d.	n	Mean	s.d.
Initial	12	26.5	6.6	14	30.0	6.2	20	26.6	6.2
Week 1	12	14.5	8.7	14	19.5	8.1	20	20.1	10.0
Week 2	12	13.0	10.1	14	19.1	11.9	17	15.1	11.1
Week 4	10	9.8	7.3	12	13.7	10.5	12	13.5	11.1
End-point	12	12.0	10.0	14	17.6	13.9	20	18.9	12.5
Mean difference									
Initial vs end-point scores		-14.5			-12.4			-7.7	
Statistical significance		$P < 0.001$			$P < 0.01$			$P < 0.05$	
(<i>t</i> -test)									
% change in score		-54.7%			-41.3%			-28.9%	
Difference between groups		all NS							

Table 3 Comparison of depression component of HARS scores

Depression component score	Alprazolam			Diazepam			Placebo		
	n	Mean	s.d.	n	Mean	s.d.	n	Mean	s.d.
Initial	12	1.75	0.75	14	1.86	0.86	20	1.30	0.8
Week 1	12	0.92	0.90	14	1.00	0.96	20	1.11	0.99
Week 2	12	0.92	0.79	14	1.21	1.18	17	0.63	0.89
Week 4	10	0.64	0.67	12	1.17	1.11	12	0.75	1.29
End-point	12	0.75	0.75	14	1.43	1.22	20	0.95	1.1
Mean difference									
Initial vs end-point scores		-1.0			-0.43			-0.35	
Statistical significance		$P < 0.001$			NS			NS	
(<i>t</i> -test)									
% change in score		-57.14%			-23.12%			-26.92%	
Differences between groups									
Alprazolam vs placebo		$0.05 < P < 0.10$							
Alprazolam vs diazepam		$0.05 < P < 0.10$							
Diazepam vs placebo		NS							

Table 4 Comparison of HRS scores in 24 patients

HRS total score	Alprazolam		Diazepam		Placebo	
	n	Mean	s.d.	n	Mean	s.d.
Initial	6	15.7	6.8	7	17.1	7.5
Week 1	6	6.3	3.3	7	9.9	6.2
Week 2	6	5.8	4.9	7	12.0	8.6
Week 4	6	5.3	6.0	5	7.4	11.0
End-point	6	5.3	6.0	7	11.6	12.0
Mean difference						
Initial vs end-point scores			-10.4			-4.1
Statistical significance			$P < 0.01$			NS
(<i>t</i> -test)						
% change in score			-65.6%			-27.0%
Differences between groups			all NS			

Table 5 Psychiatrists' global assessment of illness severity (Scale 1 = normal to 7 = extremely ill)

Score	Alprazolam		Diazepam		Placebo	
	n	Mean	s.d.	n	Mean	s.d.
Initial	12	4.5	0.52	14	4.57	0.51
End-point	12	2.58	1.0	14	2.79	1.43
Mean difference						
			-1.92			
			-1.78			
			-1.1			
Statistical significance			$P < 0.001$			$P < 0.01$
(<i>t</i> -test)						
% improvement			-42.7%			-25.6%
Differences between groups			all NS			

Table 6 Psychiatrists' evaluation of therapeutic effect (1 = marked improvement to 5 = worse)

	<i>Alprazolam</i>	<i>Diazepam</i>	<i>Placebo</i>
<i>n</i>	12	14	20
Mean score $\pm$ s.d.	1.75 $\pm$ 1.22	2.21 $\pm$ 1.58	3.25 $\pm$ 1.65
<i>Statistical significance</i> (analysis of variance)			
A vs D vs P	$P = 0.025$		
A vs P	$P = 0.012$		
A vs D	NS		
D vs P	NS		

significant improvement (Table 7). This was the only scale on which the diazepam group scored marginally better than the alprazolam group, possibly because two good responders to alprazolam completed their scale forms incorrectly and these had to be excluded from the analysis.

On the patients' overall evaluation of therapeutic effect (1 = helped very much to 5 = no effect) alprazolam, but not diazepam, was rated significantly better than placebo (Table 8).

Adverse effects

The investigators' overall assessment of the incidence and severity of side-effects is shown in Table 9. Although the majority of the more severe side-effects occurred in the placebo group the differences were not statistically significant. Specific symptoms in the check-list which appeared or increased in severity during the trial were recorded on 34 occasions in the alprazolam group, mean 0.77 per patient evaluation, on 48 occasions in the diazepam group, mean 0.92 per patient evaluation and 63 occasions in the placebo group, mean 1.05 per patient evaluation. Drowsiness was reported on four occasions in the alprazolam group, seven in the diazepam and five in the placebo group. One patient receiving alprazolam developed an allergic skin rash affecting the arms during the fourth week which caused her to leave the trial. No other significant side-effects were noted.

Physical and laboratory data

Apart from the skin rash in one patient no changes were observed on physical examination nor were any abnormalities attributable to alprazolam noted in Hb, WBC, platelets, ESR, blood chemistry and urine.

Safety

One male patient aged 54 years swallowed 15 capsules of alprazolam (7.5 mg) on the fifth day of treatment after his wife deserted him. He reported that he went to bed, slept soundly all night and woke as usual next morning feeling none the worse. Physical examination and laboratory investigations carried out 36 h later were entirely normal. He was withdrawn from the trial.

Discussion

In this trial all forms of assessment, except the self-rating scale showed greatest improvement in the alprazolam group. The size of the group was such, however, that quite marked inter-group differences sometimes failed to reach the 5% significance level e.g. the HARS scores. On the other hand both patients' and investigators' evaluations of therapeutic effect showed a statistically highly significant superiority of alprazolam over placebo but the differences

Table 7 Self-rating symptom scale (35 items, 0-3)

<i>Score</i>	<i>n</i>	<i>Alprazolam</i> <i>Mean</i>	<i>s.d.</i>	<i>n</i>	<i>Diazepam</i> <i>Mean</i>	<i>s.d.</i>	<i>n</i>	<i>Placebo</i> <i>Mean</i>	<i>s.d.</i>
Initial	10	51.8	16.5	14	54.5	15.1	20	42.2	16.7
End-point	10	33.0	23.2	14	33.0	29.4	20	32.6	26.9
Mean difference		18.8			21.5			9.6	
Statistical significance (<i>t</i> -test)		$P < 0.05$			$P < 0.01$			NS	
% improvement		36.7%			39.5%			22.7%	
Difference between groups		all NS							

Table 8 Patients' evaluation of therapeutic effect (1 = helped very much to 5 = not at all)

	Alprazolam	Diazepam	Placebo
n	12	14	20
Mean score ± s.d.	1.92 ± 1.24	2.36 ± 1.82	3.60 ± 1.73
Statistical significance (analysis of variance)			
A vs D vs P	P = 0.02		
A vs P	P = 0.008		
D vs P	NS		
A vs D	NS		

between alprazolam and diazepam and diazepam and placebo were not significant.

The improvement in the scores on the depression component of the HARS and, in 24 patients, the HDRS, were statistically significant in the alprazolam group only. In the former the differences between alprazolam and the other groups reached the 10% probability level. The patients in this trial were, however, not selected for the presence of depression hence the type of depression involved was the milder form of neurotic depression often associated with anxiety symptoms.

Nevertheless no anti-depressant effect was recorded in the diazepam group and it is an unusual property for a benzodiazepine (Committee on the Review of Medicines, 1980).

No serious side-effects were encountered. One patient in the alprazolam group developed an allergic skin rash but other side-effects in this group were fewer than those found in the diazepam and placebo groups. No effects on renal, hepatic and haematopoietic systems

attributable to alprazolam were detected, even after overdose.

Conclusion

This investigation has confirmed that alprazolam is at least as effective as diazepam in relieving anxiety and strongly suggests that it also possesses anti-depressant activity. Alprazolam also induced few side-effects and no significant metabolic changes, even in overdose.

A larger sample would probably have produced more clear-cut results but this study supports others in finding that alprazolam is a safe and effective anxiolytic (Fabre & McLendon, 1979; Aden & Thein, 1980; Maletzky, 1980; Cohn, 1981) with some beneficial effect on neurotic depression (Fabre, 1976; Fabre & McLendon, 1980).

Thanks are due to Upjohn Ltd for providing the capsules and other assistance in the organisation of the trial.

Table 9 Psychiatrists' assessment of side-effects

Side-effects	Alprazolam	Diazepam	Placebo
Absent	8	8	13
Not interfering with patients' functioning	3	6	2
Interfering with patients' functioning	0	0	2
Outweighing therapeutic effect	1	0	3

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