Bromazepam, a new anxiolytic: a comparative study with diazepam in general practice

ROYAL COLLEGE OF GENERAL PRACTITIONERS
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SUMMARY. In a double-blind randomized trial, 120 patients suffering from acute anxiety states received treatment for two weeks with bromazepam 3 mg, bromazepam 6 mg or diazepam 5 mg, each given three times daily. A shortened Hamilton anxiety rating scale showed similar and significant improvement with all three regimens. However, a global rating scale showed that, in the physicians' opinion, the lower dose of bromazepam was preferred. Its use was associated with the lowest incidence of adverse reactions and best dosage compliance. A twice daily administration of bromazepam may offer further advantage, as may a lower unit dose.

Introduction

BROMAZEPAM, a 1,4-benzodiazepine, has been shown in clinical trials to be a highly effective anxiolytic. In one large-scale study of 301 patients the response rate was 96 per cent[1] and tolerance was excellent. Compared with diazepam, the pharmacokinetic profile of bromazepam is uncomplicated. Absorption from the gastrointestinal tract is rapid and the mean terminal half-life is 12-16 hours; the metabolites do not possess significant clinical activity and are cleared at least as fast as the parent compound.[2-4]

Several comparative studies have suggested that bromazepam may be preferable to diazepam.[5-8] However, these studies have not provided definitive information on the dosage equivalents of the two preparations and nor have they investigated the response to varying doses of bromazepam.

The present study was designed primarily to compare the efficacy and tolerance of a 3 mg dose of bromazepam with a 6 mg dose. It was also important to confirm that bromazepam had a higher milligram potency than diazepam; diazepam in a 5 mg dose was therefore included in the study.

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Patients and methods

The trial was conducted in the UK by members of the Royal College of General Practitioners who had responded to a postal invitation from the Medicines Surveillance Organisation. Each general practitioner was asked to recruit three subjects of either sex in the age range 18-65 years. In the opinion of the general practitioner the subjects were suffering from a mild to moderate anxiety state for which treatment with a benzodiazepine was appropriate. Of each doctor's three subjects: one was randomly allocated to receive bromazepam 3 mg; one, bromazepam 6 mg; and one, diazepam 5 mg. Each dose was to be taken three times a day for 14 days. All tablets were identical in appearance. Patients in whom depression was the dominant symptom were excluded, as were pregnant or lactating women, alcoholics or drug addicts, patients with a history of epilepsy or fits, and patients experiencing anxiety secondarily to a treatable organic illness.

Patients were seen three times: on entry to the trial, after seven days treatment and after the full 14 days treatment. On each occasion, the severity of the anxiety state was measured using the short Hamilton anxiety rating scale. The patient's general condition at each follow-up visit was assessed by the physician using a global rating scale as follows:

'Completely recovered': no signs or symptoms of anxiety

'Much improved': residual psychological symptoms but lessened physical signs and symptoms

'No change': symptoms and signs unchanged

'Worse': increased symptoms and/or signs

Adverse reactions were recorded on the second and final visits, initially by noting the patient's answer to the question, 'Have you had any problems since taking the tablets?', and then by specifically soliciting information on drowsiness, ataxia and dizziness, the three important adverse reactions to benzodiazepines. It was recognized that by soliciting these data, over-reporting of problems would be introduced, but it was considered that this was preferable to under-reporting and would make comparisons more powerful.

At the start of the study, each patient was given 52 tablets—that is, 10 more than was required for the 14 days treatment. Compliance with the proposed treatment regimen was checked at the final visit by counting unused tablets.

If a patient left the study before completing the 14 days treatment, the reasons were noted wherever possible.

Results

A total of 120 patients were included in the analyses. Some doctors were unable to recruit three subjects; as a result, it was necessary to exclude 44 patients from the analyses in order to maintain the balanced design of the trial. By mistake, four patients over the age of 65 years were entered into the trial, but it was thought reasonable to include them in the analyses. There were no material differences in the characteristics between the patients in the three treatment groups (Table 1).

Table 1. Demographic characteristics of the three groups of patients.

	Bromazepam 3 mg tds	Bromazepam 6 mg tds	Diazepam 5 mg tds
Sex			
Male	14	9	11
Female	26	31	28
All	40	40	40[a]
Age			
Median	38 years	39.5 years	44 years
(Range)	(18-65 years)	(19-73 years)	(20-70 years)
History of anxiety			
Yes	24	25	31
No	16	15	9
Duration of present anxiety			
Median	6 weeks	1 month	2 months
(Range)	(2 days-18 months)	(3 days-12 months)	(4 days-24 months)

[a] One patient's sex not stated.
tds = three times daily.

Withdrawals

Twenty-six patients withdrew before completing the 14-day course, 16 of them because their toleration of the treatment was poor. Four patients receiving the 3 mg dose of bromazepam withdrew because of adverse reactions, compared with five receiving diazepam and seven receiving the 6 mg dose of bromazepam (Table 2). The overall withdrawal rates are not significantly different (χ^2 test) but only one of the four patients who withdrew because of adverse reactions while on the low dose bromazepam regimen did so during the first week, compared with first week withdrawals by all seven on the high dose bromazepam and four out of five taking diazepam.

Wherever possible, data on these patients were included up to the time of their withdrawal; these data included their reported side-effects.

Table 2. Reasons why patients withdrew from trial.

	Number of patients		
	Bromazepam 3 mg tds	Bromazepam 6 mg tds	Diazepam 5 mg tds
Adverse reactions	4	7	5
Felt better	0	1	0
Felt no better	1	0	2
Left district	0	1	0
Not known	2	2	1
Total	7	11	8

Therapeutic effect

Hamilton anxiety rating scores were completed for 98 patients only. These data indicated that all three treatment regimens significantly decreased the anxiety state ($P<0.005$, Friedman test on each group) and did so to a similar degree (Kruskal-Wallis test comparing initial scores and changes from initial), as shown in Table 3.

Table 3. Results from shortened Hamilton anxiety rating scale at start of trial, after one week and after two weeks.

	Median score on rating scale		
	Bromazepam 3 mg tds ($n=36$)	Bromazepam 6 mg tds ($n=29$)	Diazepam 5 mg tds ($n=33$)
Initial visit	15.5	17.0	16.0
Day 7	6.0	7.0	7.0
Day 14	4.0	6.0	6.0

n = number of subjects with complete results.

On the basis of the physicians' global assessment, the outcome of treatment was classified as a success (patient completely recovered or much improved) or a failure (no change, worse or patient withdrew from trial). Treatment was successful for most patients in each regimen group, but the lower dose of bromazepam was successful for significantly more patients than the higher dose at day 7 ($P < 0.05$, χ^2 tests) and for more patients than both the higher doses of bromazepam and the diazepam at day 14 ($P < 0.01$) (Table 4).

Table 4. Results of physicians' global assessment after one week and after two weeks (40 patients per group).

	Number of patients		
	Bromazepam 3 mg tds	Bromazepam 6 mg tds	Diazepam 5 mg tds
Day 7			
Success	33	21*	29
Failure	7	19	11
Day 14			
Success	35	22**	22**
Failure	5	18	18

* $P < 0.05$ versus 3 mg bromazepam.
** $P < 0.01$ versus 3 mg bromazepam.

Adverse reactions

The number of patients reporting side-effects in each treatment group in response to the question 'Have you had any problems since taking the tablets?' was lower in the low dose bromazepam group than in the other two groups, but the differences were not statistically significant (χ^2 test). The commonest adverse reaction volunteered was drowsiness (Table 5).

Table 5. Number of patients with unprompted reports of adverse reactions.

	Bromazepam 3 mg tds	Bromazepam 6 mg tds	Diazepam 5 mg tds
Drowsiness	12	22	18
Any adverse reaction	20	26	23

The occurrence of drowsiness, ataxia and dizziness, when unprompted and solicited reports were combined, was lower in the low dose bromazepam group than in either of the other groups. For ataxia and dizziness the differences between the low dose and high dose bromazepam were statistically significant (χ^2 tests) (Table 6).

Table 6. Number of patients with unprompted and prompted reports of adverse reactions.

	Bromazepam 3 mg tds	Bromazepam 6 mg tds	Diazepam 5 mg tds
Drowsiness	20	30	26
Ataxia	5	16*	12
Dizziness	5	18**	13

* $P < 0.05$ versus 3 mg bromazepam.
** $P < 0.01$ versus 3 mg bromazepam.

Compliance

Compliance was clearly affected by withdrawals from the trial and is, therefore, another reliable 'global' estimate of satisfactory treatment. Whether or not the patients who withdrew early were included in the analysis, compliance estimated by returned tablet count differed between the three groups (Table 7). The results suggest that the low dose bromazepam regimen was most successful in terms of compliance though the differences were not statistically significant.

Table 7. Compliance: percentage of patients adhering to treatment regimens (total number of patients in each group in parentheses).

	Bromazepam 3 mg tds	Bromazepam 6 mg tds	Diazepam 5 mg tds
All patients	*72.5* (40)	*55.0* (40)	*50.0* (40)
Excluding withdrawals	*88.0* (33)	*76.0* (29)	*62.5* (32)

Discussion

The number of subjects included in the analysis was less than had been planned and some material differences between the treatment groups failed to reach statistical significance. The planned 130 patients per group would have given an 80 per cent power of detecting clinically significant differences in efficacy from diazepam; usually four patients out of five respond favourably to this drug. Such a group size would also have had a similar power to detect a doubling of spontaneously reported adverse reactions which occur typically in about 10 per cent of diazepam takers. Recruitment rate was much slower than had been anticipated, possibly owing to the strict criteria for entry and perhaps also reflecting the reduction in the use of tranquillizers in the UK since 1978.

Nevertheless, although there were no major differences in the success rates between the three treatment regimens, several minor differences emerged which, taken together, favourably distinguished the low dose bromazepam. When the results of patients with complete Hamilton anxiety rating scores were considered all three groups showed significant and consistent improvement within the first week of starting therapy and maintained, or increased, their response during the second week. However, the physicians' global assessment showed that after seven days the group receiving the lower bromazepam dose contained significantly more successful cases than the group taking the higher dose. Furthermore, after 14 days, the low dose of bromazepam showed a significant advantage over each of the other two treatments. These differences most likely reflect the 'global' assessment as an indication of the balance between improvement and side-effects and this procedure closely matches the way in which a general practitioner reviews the response of a particular patient to treatment.

We believe that Table 4 expresses the fairest way of assessing treatment; that is, 'success' or 'failure' with no intermediate levels of benefit. The protocol was designed to allow the global score at day 14 to shown changes since day 7. Thus some failures at day 7 became successes during the second week.

Withdrawals from the trial owing to adverse reactions reflect the adverse reaction rate in each group, whether these reports were solicited or unprompted. Adverse reactions in patients taking bromazepam were clearly dose-dependent, with significantly fewer reports of ataxia and dizziness on the lower dose, together with an important though non-significant reduction in the reports of drowsiness.

As expected, the soliciting of information about adverse reactions leads to a higher rate of reporting. Tables 5 and 6 show that reports of drowsiness, for example, were materially increased when specific enquiries were made about the symptom. In the study as

a whole, 52 patients reported the symptom voluntarily, but an additional 24 patients admitted the side-effect at some time or other when the doctor asked about it.

It is worth noting, however, that only four subjects in the low dose bromazepam group left the study because of adverse drug reactions, even though dose titration was not permitted. A fixed dose regimen with an anxiolytic is 'artificial' and the normal use of this type of drug is, of course, to commence treatment with a low dose and to increase the dose to obtain the best balance between response and adverse reactions. Had this been permitted for all the groups then withdrawals may have been reduced, but dose-dependent data on comparative tolerability may not have been generated.

Using the accepted criterion of balancing the anxiolytic benefit against the risk of adverse reactions, and including comparisons with diazepam 5 mg tds, it can be concluded that bromazepam 3 mg tds is an effective and well-tolerated anxiolytic for the short-term management of anxiety states in general practice. The higher dose of bromazepam was no more efficacious at this level of anxiety. The level of reporting of adverse reactions associated with the 6 mg dose regimen suggests that this is too high a dose of bromazepam for patients with mild to moderate anxiety. Bromazepam has been reported to be at least twice as potent as diazepam and this study strongly suggests that doses even lower than 3 mg tds may be effective. A twice daily dosage regimen may be adequate and there is likely to be a place for a lower unit dose of bromazepam.

References

1. Podiwinsky F, Jellinger K. Bromazepam in der Behandlung psychogener Stoerungen mit Somatisierungstendenz. (Bromazepam in the treatment of somatized psychogenic disorders.) *Wien Klin Wochenschr* 1979; **91:** 240-244.
2. Raaflaub J, Speiser-Courvoisier J. On the pharmacokinetcs of bromazepam in man. *Arzneimittelforsch* 1974; **24:** 1841-1844.
3. Kaplan SA, *et al.* Biopharmaceutical and clinical pharmacokinetic profile of bromazepam. *J Pharmacokinet Biopharm* 1976; **4:** 1-16.
4. Schwartz MA, *et al.* Metabolites of bromazepam, a benzodiazepine, in the human, dog, rat and mouse. *J Pharm Sci* 1973; **62:** 1776-1779.
5. Lapierre YD, *et al.* A placebo-controlled study of bromazepam and diazepam in anxiety neurosis. *Curr Ther Res* 1978; **23(4):** 475-484.
6. Cherpillod C, Hitz F. Clinical trial in double blind at different dosing with Valium. *Praxis* 1976; **65:** 693-698.
7. Lens F. Une Nouvelle Benzodiazepine, passee au crible d'un test double aveugle parallele. *Acta Psychiatr Belg* 1974; **74:** 327-337.
8. Sonne LM, Holm P. A comparison between bromazepam (Ro 5-3350 Lexotan) and diazepam (Valium) in anxiety neurosis—A controlled, double blind clinical trial. *Int Pharmacopsychiatry* 1975; **10(2):** 125-128.

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