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ORIGINAL INVESTIGATION

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A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder

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Abstract The efficacy of hydroxyzine and buspirone, controlled by placebo, was investigated in a double-blind, parallel group, multicentre study conducted in France and the UK. A total of 244 patients with generalised anxiety disorder in primary care was allocated randomly to treatments with hydroxyzine (12.5 mg morning and mid-day, 25 mg evening), buspirone (5 mg morning and mid-day, 10 mg evening) or placebo (three capsules/day) for 4 weeks, preceded by a 1-week single-blind placebo run-in and followed by 1-week single-blind placebo administration. Rating scales were applied on days -7, 0, 7, 14, 12, 28 and 35. Seventy percent of the patients were female; the average age was 41 ± 11 years, and the mean Hamilton Anxiety Score at day 0 was 26.5 ± 4.2. Only 31 of the 244 patients dropped out, but equally in the three groups. Intention-to-treat LOCF analyses on the primary variable showed a significant difference only between hydroxyzine and placebo with respect to improvement on the Hamilton Anxiety Scale (10.75 versus 7.23 points, respectively). Secondary variables such as CGI and self-ratings (HAD scale) showed both hydroxyzine and buspirone to be more efficacious than placebo. Thus, hydroxyzine is a useful treatment for GAD.

Key words Hydroxyzine · Buspirone · Generalized anxiety disorder

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Introduction

Hydroxyzine acts as an antagonist at H_1 receptors and to a lesser extent at muscarinic receptors and 5-HT_2 receptors and with even less binding to alpha$_1$ and dopamine$_2$ receptors (Kubo et al. 1987; Snyder and Snowman 1987). It has anxiety-allaying properties in doses of 50 mg/day and was introduced to the French market as long ago as 1955. It is licenced throughout most countries in the world to treat patients with anxiety, often in conjuction with bodily symptoms such as pruritus (Cambazard and Chambefort 1987), dyspepsia and irritable bowel (Grimaldi 1987) and brochospasm (Ramon 1987). Over its many years of usage, there have been no documented reports of dependency, abuse, or memory disturbances. The commonest unwanted effect is sedation, which is clinically expressed by somnolence, but this usually wanes with continuing treatment.

In the treatment of anxiety, the benzodiazepines have been extensively used, often on a long-term basis. Concern has been mounting in many countries with regard to such wide usage as the adverse effects of these drugs have emerged (Hallström 1993). Normal dose dependence, abuse potential, neuropsychiatric reactions and effects on memory have led to calls to restrict the use of the benzodiazepines (British Committee on Safety of Medicines 1988). In many countries, prescriptions of benzodiazepines have fallen markedly and a switch has been made to using non-benzodiazepines without these disadvantages. Among the newer compounds are buspirone, a 5-HT_{1A} partial agonist (Gelenberg 1994) and its congeners.

Hydroxyzine has a favourable risk/benefit and its role in the management of patients with GAD has been re-examined. In a recent study of 110 GAD patients, hydroxyzine (50 mg/day for 4 weeks) was significantly better than placebo in ameliorating anxiety (Darcis et al. 1995). No rebound and no withdrawal syndrome were detected following discontinuation of the drug;

somnolence, although reported in 28% of patients on hydroxyzine versus 14% of those on placebo (NS), led to drop-out in only one.

In this publication, we report a large-scale double-blind, randomised study comparing hydroxyzine with placebo and buspirone in the treatment of patients with GAD according to DSM-IV criteria. Many of the instruments used were the same as those in the previous study, thus facilitating comparison.

Materials and methods

The study was multi-centre (62 centres, 48 in France, 14 in the UK); the patients were seen by primary care doctors with a particular interest in psychiatric disorders under the coordination of hospital psychiatrists. The participating doctors were trained in the use of the various rating instruments. The study was approved by the appropriate ethics committees and all participants gave informed consent. This study was carried out following the GCP-ICH guidelines.

Patient selection

Out patients of either sex aged between 18 and 65 years presenting with GAD according to DSM-IV criteria were eligible for inclusion, providing their initial Hamilton Anxiety Rating Score was 20 or more. Depressive disorders according to DSM-IV criteria were excluded, but low levels of depressive symptoms did not exclude patients who met GAD criteria. Exclusion criteria included pregnancy or inadequate contraceptive precautions, major depressive disorder or alcohol abuse, organic or psychotic disorders, undergoing long-term psychotherapy, or intake of psychotropic medication during the previous 4 weeks.

Patients gave a urine sample and were placed single-blind on placebo for 1 week (day -7 to day 0). On day, 0 they were reassessed and placebo responders (more than 7-point improvement on the Hamilton) or anyone proving positive for urinary benzodiazepines were excluded.

Power calculations showed that 180 evaluable patients were needed to allow the detection with a 90% probability of a drug-placebo difference of 5 points on the Hamilton scale. To allow for 20% withdrawals, a target of at least 228 patients was aimed at.

Drugs and dosages

Patients were allocated randomly to receive over 4 weeks (days 0–28) fixed doses of: hydroxyzine 50 mg/day (12.5 morning, 12.5 mid-day, 25 evening), buspirone 20 mg/day (5, 5, 10) or placebo three capsules (1, 1, 1).

The dose of hydroxyzine is that usually used to treat anxiety (Darcis et al. 1995). That for buspirone is in the mid-range of the recommended dosage schedule. Compliance was estimated by a capsule count every visit. There were no differences between the groups with respect to compliance. No concomitant psychotropic medication was allowed; beta-blockers and clonidine were also excluded.

Following the active treatment phase, patients were placed on placebo single-blind for 7 days (days 28–35) to investigate possible discontinuation effects.

Clinical assessments

The investigator carried out the following assessments:

Hamilton Anxiety Rating Scale (Hamilton 1959) (main outcome variable);
Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg 1979);
Clinical Global Impression (Ecdeu 1976);
Ferreri Anxiety Rating Diagram (Ferreri et al. 1988) (France only).

These ratings were carried out on days 0, 7, 28 and 35. The patients rated themselves on:

Echelle Dyscontrole Comportemental (EDC) (Hantouche et al. 1992) (France only);
Hospital Anxiety and Depression Scale (Zigmund and Snaith 1983);
Tyrer Withdrawal Symptom Scale (Tyrer et al. 1990).

The first two were carried out weekly, the last on days 28 and 35. Urinary benzodiazepine screening was performed on days -7, 28 and 35.

Clinical examinations were carried out weekly (except days 14 and 21).

Adverse events were recorded whether or not attributed to the medication.

Statistical analysis

This followed standard procedures with analysis of intent-to-treat population with last observation carried forward (LOCF) to deal with premature discontinuations. All tests were two-tailed and the 0.05 probability was accepted as the significance level. Analysis of variance was used for parametric data, Kruskal-Wallis for non-parametric quantitative data, and chi-square for qualitative data. The double-blind was not broken until after data analysis was completed.

The primary outcome variable was pre-set as change in Ham-A from day 0 to day 28.

Results

Patient characteristics

Patients were recruited from November, 1995 until April 1996 by 62 general practitioners organised into six groups, each coordinated by a psychiatrist. A total of 266 patients was recruited, of whom 20 failed to meet inclusion criteria after the placebo run-in (day -7 to day 0). Thus, 246 patients meeting DSM-IV GAD criteria were allocated randomly to hydroxyzine, buspirone or placebo (82 in each group). However, two patients (one hydroxyzine; one placebo) dropped out before taking any medication.

Demographic and baseline data are presented in Table 1. There were no statistically significant differences between the groups for any of the variables.

Efficacy

The primary outcome variable is shown in Fig. 1. Null hypothesis of equal efficacy between treatments was rejected ($P = 0.015$); from pairwise comparisons (Buspirone-Placebo, Hydroxyzine-Placebo, Hydroxyzine-Buspirone), only the difference in improvement between placebo and hydroxyzine was

Table 1 Demographic and baseline data (ITT). Means (SD)

Variable	Hydroxyzine $n = 81$	Buspirone $n = 82$	Placebo $n = 81$
Sex F/M	56/25	62/20	51/30
Mean age	42 (11)	41 (12)	40 (11)
Number of previous episodes of anxiety	4.3 (3.6)	5.7 (11.8)	4.7 (5.0)
Hamilton Anxiety Rating Scale	26.6 (4.3)	26.7 (4.1)	26.2 (4.2)
Montgomery - Åsberg Depression Rating Scale	17.0 (7.4)	17.7 (7.1)	15.7 (7.0)
Clinical Global Impression	4.4 (0.7)	4.4 (0.7)	4.3 (0.7)
Hospital Anxiety and Depression Scale			
Anxiety	8.7 (3.5)	8.8 (3.6)	8.5 (3.1)
Depression	13.2 (2.8)	12.9 (2.9)	12.5 (2.9)
Echelle Dyscontrole	35.2 (10.6)	31.4 (10.8)	34.2 (10.5)
Comportemental	($n = 53$)	($n = 53$)	($n = 52$)
Ferreri Anxiety Rating	31.1 (7.8)	30.3 (7.4)	29.5 (7.1)
Diagram	($n = 60$)	($n = 59$)	($n = 60$)

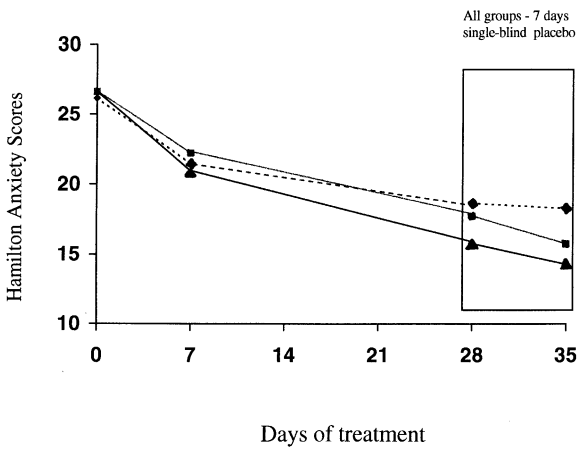

Fig. 1 Mean effects of hydroxyzine, buspirone and placebo on Hamilton Anxiety Rating Scale over 28 days of treatment. This was followed by 7 days placebo substitution to day 35. ◆ Placebo, ■ buspirone, ▲ hydroxyzine

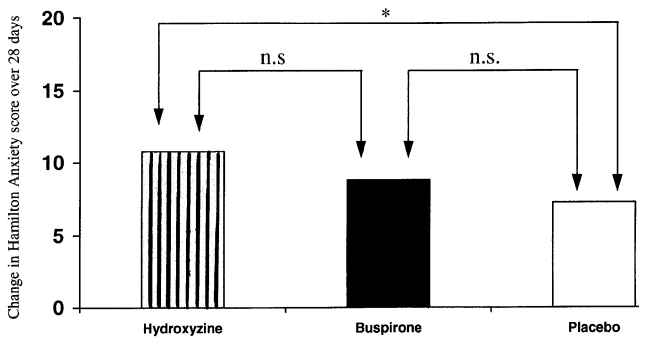

Fig. 2 Significance of drug effects on change in Hamilton. Score over 28 days. HO, $P = 0.015$. * Statistically significant; ns not significant

statistically significant (Fig. 2). The somatic and psychic subscales showed similar patterns. Because hydroxyzine might have shown efficacy predominantly because of sedative effects on sleep, the data were re-analysed omitting the sleep item: the patterns of significance were unchanged. Another way of judging efficacy is to count the number of patients whose total HAM-A score halved with treatment. These were 42% with hydroxyzine, 36% for buspirone, and 29% for placebo (NS).

The Clinical Global Severity Scale showed an improvement over the 28 days of treatment of 1.53 points in the hydroxyzine patients, 1.27 in the buspirone patients and 0.95 in the placebo-treated patients ($P < 0.02$; hydroxyzine significantly different from placebo) (Table 2). On the Clinical Global Improvement Scale, significantly ($P < 0.005$) more patients were improved on hydroxyzine (50%) than on placebo (30%).

With respect to the MADRS Scale, both hydroxyzine and buspirone patients were significantly better than placebo ($P < 0.001$) (Table 2). Similarly, in the self-rating of depression (HAD-Dep scale), both active drugs were significantly superior to placebo ($P < 0.01$); differences were also found on the anxiety scale ($P < 0.001$) (Table 2).

The EDC scores continued this latter pattern with both hydroxyzine and buspirone effecting greater improvements than placebo. This was repeated for the FARD total score (Table 2).

Effects of symptomatic depression

Only one-quarter of the patients were judged to have "pure" GAD, the rest suffering an admixture of symptomatic depression, as is typical in general practice. This is shown by the appreciable initial MADRS scores (Table 1). The mixed group were significantly more anxious and impulsive than the uncomplicated group but there were no other baseline differences. Some differential drug effects were detected: hydroxyzine tended to be just as effective in the "pure" as in the mixed group, whereas buspirone appeared more effective than placebo only in the mixed group (trend only).

Effects of discontinuation

As Fig. 1 shows, there was no rebound with respect to HAM-scores following placebo substitution at day 28.

Table 2 Effects of treatments on some secondary efficacy variables: change over 28 days (ITT)

Variable	Hydroxyzine	Buspirone	Placebo
Hamilton Anxiety Rating Scale	10.8 (7.5)*	8.8 (7.8)	7.2 (7.7)
Clinical Global Impression	1.53(1.3)*	1.27 (1.2)	0.95 (1.1)
Montgomery-Åsberg Rating Depression Rating Scale	6.64 (6.9)***	6.35 (7.5)***	2.97 (6.0)
Hospital Anxiety and Depression Scale			
Depression	2.05(3.8)*	1.89(4.2)**	0.11 (3.1)
Anxiety	4.01 (3.9)***	3.31 (4.0)***	1.41 (3.0)
Echelle Dyscontrole Comportemental	12.8 (12.5)*	10.0 (15.5)*	4.0 (8.4)
Ferreri Anxiety Rating Diagram - Total	14.3 (11.5)***	12.1 (11.1)***	6.8 (7.7)

*vs placebo $P < 0.02$; **vs placebo $P < 0.01$; ***vs placebo $P < 0.001$

Indeed, both the hydroxyzine and the buspirone patients continue to improve. Similar patterns were seen with the other efficacy variables. No significant withdrawal symptoms for either active drug were detected on the Tyrer Scale.

Adverse events

Of the 244 patients given medication, 10/81 hydroxyzine, 10/82 buspirone and 11/81 placebo dropped out prematurely, a total of only 31 (12.7%). The commonest reason (six, seven, six respectively) was protocol violation, the second (two, two, two) lack of efficacy. No serious ADRs were recorded.

In the three groups, 32/81 hydroxyzine-treated patients (39.5%) reported one or more side effects, as compared with 31/82 buspirone (38%) and 23/81 placebo (28%) patients. The only side effects affecting more than 5% of the exposed patients were somnolence in the hydroxyzine group (9.9%) as compared with 4.9% in the buspirone and none in the placebo group; headache and migraine (6.1%) in the buspirone group (4.9% and 1.2% in hydroxyzine and placebo groups); dizziness (6.1%) in buspirone-treated patients (cf. 0 in hydroxyzine and 2.5% in placebo patients). No changes in cardiovascular measures (pulse, BP) or in weight were detected. The somnolence associated with hydroxyzine was transient and had largely disappeared by day 10 except for one patient.

Thus, both active treatments were very well tolerated.

Discussion

This study was designed to confirm the results of an earlier study (Darcis et al. 1995) that hydroxyzine was an effective drug in the treatment of patients with the carefully defined primary diagnosis of generalised anxiety disorder. The main difference between the two studies was the incorporation of an active comparator, buspirone, in the present study. The study followed the usual format with placebo control, random allocation to treatment, double-blind procedures, and moreover, the following points are worthy of note.

The patients studied were fairly typical of those participating in GAD trials (e.g. Power et al. 1990; Ansseau et al. 1991), with a 2:1 ratio of females/males and a mean age in the early 40s. The condition was generally a chronic or relapsing one with about five previous episodes, during which a wide range of treatments had been used. The typical patient had anxiety of moderate secerity. The groups were well matched (see Table 1).

Recruitment for the study was rapid, few responded to initial placebo, the running of the study was uneventful and the drop-out rate was gratifyingly low (less than 15%). This reflects the interest and experience of the investigators, and careful training by the psychiatrists of their groups of general practitioners. Many of these GPs had a particular interest in psychiatric problems. In view of the consistently positive results for hydroxyzine, less so for buspirone, it must be assumed that the rating procedures were both reliable and valid.

The primary efficacy variable, the Hamilton Anxiety Score showed differences between hydroxyzine and placebo but not between buspirone and placebo. However, hydroxyzine was not significantly different from buspirone. The efficacy of hydroxyzine was not due to sedative actions on sleep. Some sub-analyses suggested that buspirone showed better efficacy in patients with an admixture of depression than in those with "pure" anxiety. By contrast, hydroxyzine was equally effective in both groups. The secondary variables mostly showed both hydroxyzine and buspirone to be superior to placebo (Table 2). Some apparent efficacy was seen on measures of depressive symptoms. However, these results should be interpreted with caution, as these rating scales have not been validated in patients other than those suffering from primary depressive disorders. Thus, hydroxyzine is confirmed as having efficacy in GAD, across a fairly wide spectrum of assessment instruments, both investigator- and self-rated. In terms of numbers improved (CGI rating), about half of those treated showed major improvement as compared with 30% on placebo.

Comparison with the Darcis et al. (1995) study shows that efficacy was a little less in the present study. For example, difference in number of responders on the HAM-A on hydroxyzine (41%) versus placebo (18%) was significant ($P < 0.01$) in the earlier study but not in the present one (42% versus 29%).

Despite the known sedative effects of centrally acting antihistaminic compounds, adverse effects were not a major problem with hydroxyzine. Somnolence was reported in about 10% of patients, but this was a fixed dose study and dosage adjustment would be expected to lessen this figure. A study is currently in progress to evaluate the effects of hydroxyzine on psychological performance. The side-effect profile with buspirone was as expected with headache and dizziness at fairly low rates.

One of the main reasons for re-evaluating the risk/benefits of hydroxyzine in GAD is the concern over the dependence potential of the benzodiazepines (Hallström 1993). Although 4 weeks is a relatively short term for the induction of dependence, no discontinuation phenomena were noted with hydroxyzine (or with buspirone). There are no reports in the literature of any such problems with hydroxyzine, even in longer-term use (Shalowitz 1961), and it is highly probable that this drug has a low or absent dependence potential (Barrance and Bridger 1977). A study is ongoing to address this question. The present study confirms previous open-label and controlled studies (Garber 1958; Breslow 1968; Lipton 1961; Goldberg and Finnerty 1974). It also very closely replicates the data in the Ferreri et al. (1995) study with respect to baseline characteristics of the patients studied, improvements attained and significance levels achieved. Like them, we conclude that hydroxyzine "offers the possibility of effective relief of generalised anxiety" and is a useful and safer alternative to the benzodiazepines.

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