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A Multicentre Double-Blind Placebo-Controlled Study Investigating the Anxiolytic Efficacy of Hydroxyzine in Patients with Generalized Anxiety

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The efficacy of hydroxyzine was investigated in 110 patients suffering from generalized anxiety, in a double-blind placebo controlled multicentre study. Oral hydroxyzine 50mg/day for four weeks significantly improved standard measurements of anxiety compared with placebo control. These improvements were seen from the end of the first week of treatment and were maintained throughout the study; there was no rebound effect after cessation of therapy. The most commonly reported adverse effect in both active and placebo treatment groups was a transient sleepiness. We conclude that hydroxyzine is an effective and well-tolerated treatment for generalized anxiety.

KEY WORDS—hydroxyzine; anxiety; efficacy; tolerability; double-blind; placebo-controlled

INTRODUCTION

Hydroxyzine is an anxiolytic of the H, antihistamine group which is of particular interest because, in more than 30 years, there have been no documented reports of abuse, dependency or adverse effects on memory (Natens, 1992). Hydroxyzine is unrelated to other minor tranquillisers, and is believed to act by reducing activity in certain key subcortical regions such as the reticular formation and limbic system (Barranco, 1977).

As the use of benzodiazepines is becoming more restricted, it is appropriate to review the use of alternative anxiolytic therapies which could fill the important niche previously occupied by this group of drugs. Hydroxyzine appears to combine anxiolytic efficacy with a favourable side-effects profile (Natens, 1992), and may prove suitable for patients with generalized anxiety. We therefore investigated the efficacy and tolerability of hydroxyzine in the treatment of anxiety.

METHODS

The study was a double-blind placebo-controlled trial with a two-group parallel design, carried out in three geographic areas (North Paris, South France, Dijon). Patients with a diagnosis of generalized anxiety (according to DSM-IIIR, rej.) were referred and assessed as outpatients by participating physicians who were trained in the use of a semi-structured interview and the various rating instruments used in this study.

Patient selection

Outpatients of either sex aged between 18 and 65 years who had suffered from generalized anxiety (DSM-IIIR) for not less than six months and who had a score of at least 20 on the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) were eligible for the study.

Patients with a history of major depression or with a rating of 10 or more on the 17-item Hamilton Depression Rating Scale (HAM-D), (Hamilton, 1960) at the start of the study were excluded. Also excluded were patients suffering from panic attacks, obsessive-compulsive disorder or any psychotic condition. Other exclusion factors included pregnancy, physical ill-health due to significant cerebral, cardiovascular, hepatic or renal disease, and a history of alcohol abuse or recent use of neuroleptics, antidepressants, antihistamines or opiates. Benzodiazepines taken for more than 2 days per week in the 4 weeks preceding the study or at any time during the last week before the trail prevented inclusion. No other psychotropic medication was allowed during the 5-week study period, and the

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doses of any other essential non-psychotropic drugs were kept consistent.

Randomization, assessment and follow-up

Patients were assessed on four occasions; at the start of the study (visit 1, week 0); after one week of treatment (visit 2, week 1); after four weeks of treatment (visit 3, week 4), and one week after stopping therapy (visit 4, week 5).

Patients were randomly allocated to receive either 50 mg hydroxyzine or matching placebo daily for a period of four weeks, followed by a treatment-free period of one week. Daily medication was taken in three doses: 1/2 tablet at breakfast and lunch, and one tablet at bedtime. Each tablet consisted of 25 mg hydroxyzine hydrochloride or placebo of identical appearance.

At visit 1, it was verified that subjects fulfilled the inclusion and exclusion criteria of the study. Subjects' generalized anxiety was confirmed through the DSM-IIIR criteria. Psychometric evaluations were carried out using the HAM-A and HAM-D, the 10-item Brief Scale for Anxiety (BSA) (Tyrer *et al.*, 1984), and the 12-item Ferreri Anxiety Rating Diagram (FARD) (von Frenckell *et al.*, 1987; Ferreri *et al.*, 1988). Subjects were also rated on an 8-point Global Clinical Impression Scale (GCI) (Ecdeu, 1976).

At visits 2 and 3, all the psychometric evaluations were repeated as well as the GCI. Adverse events were evaluated by open and direct questioning. Compliance with study medication was checked by a count of returned tablets. Urine samples were collected and tested to detect possible use of benzodiazepines.

At visit 4, the assessments were repeated and a general physical examination was performed. Moreover, each week, from week 1 to week 5, patients were asked to complete a 58-item questionnaire of anxiety-related problems and symptoms.

Power of the study (sample size calculation)

A total 88 subjects (44 subjects in each group) was used, which, it was calculated, was able to detect with a power of 80 per cent, at the 5 per cent level of significance, a 15 per cent difference between active and placebo treatments in HAM-A scores.

Statistical analysis

After the last patient had finished the 5-week study period, data management was completed and a statistical analysis was carried out. At this stage, the code was partly broken to allow the separation of patients into groups A and B. It was only when the statistical analysis was finally completed that the groups A and B were identified as hydroxyzine and placebo.

Data were analysed on a valid patient basis. Valid patients correspond to randomized patients for whom: (1) HAM-D scores at visit 1 were equal to or below 10, (2) urine samples were collected, (3) there was no evidence of benzodiazepine use (BZ) at visit 1, (4) there was no concomitant use of BZ during the study. The last value carried forward method was used to handle the problem of drop-outs and withdrawals. All tests were two-tailed and performed at the 5 per cent level of significance.

Mean age was compared using Student's *t*-test. Distribution of sex was analysed using the Fisher exact test. Global scores (the sum of scores of all items in a scale) were computed, at each visit, for HAM-A, HAM-D, BSA, FARD, GCI and the 58-item questionnaire.

These global scores were analysed by means of the Mann-Whitney's *U*-test. Furthermore, for the HAM-A scale, the percentage of items scored as 'absence of' and/or 'mild' (scores 0 and/or 1) was computed at each visit. This percentage was analysed using the Mann-Whitney *U*-test.

All adverse events in the final analysis were reported and analysed for all subjects included.

RESULTS

Recruitment and baseline characteristics

Recruitment began in April 1991 and was completed in July 1992. Of the 133 patients assessed, 124 (93 per cent) were allocated to a treatment group (hydroxyzine: 60; placebo: 64). A further 14 (11 per cent) patients were excluded from the efficacy evaluation because they did not satisfy the definition of valid patient (four patients had a HAM-D score above 10, four patients were using BZ at inclusion, five patients did not supply a urine sample and one subject used BZ concomitantly).

Demographic data are shown in Table 1. No

Table 1. Patient details (mean values ± SD)

Criteria	Hydroxyzine ($N=54$)	Placebo ($N=56$)	p
Age (years) (mean value ± SD)	44·7 ± 11·3	42·8 ± 12·6	0·40*
Sex (% male)	43	38	0·73†

*Student's *t*-test.
†χ^2.

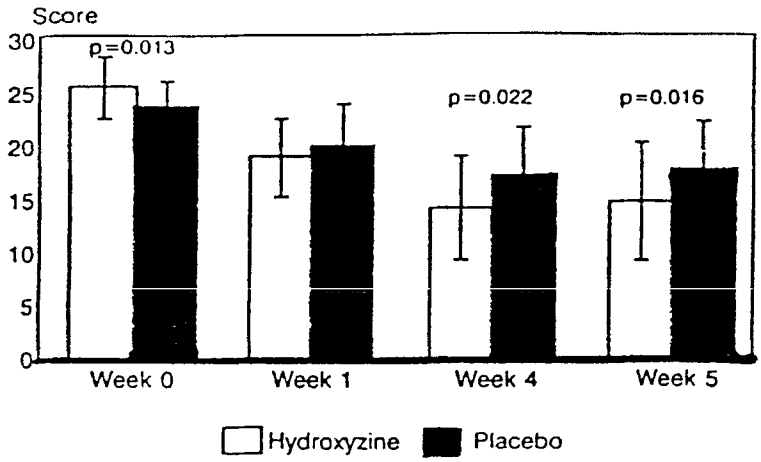

Figure 1. Hamilton Anxiety Rating Scale total mean scores

significant age or sex differences were noted between the hydroxyzine and placebo groups. Baseline scores for depression and anxiety scales are shown in Table 2.

Table 2. Baseline score—depression and anxiety scales (mean values ± SD)

Scale	Hydroxyzine ($N=54$)	Placebo ($N=56$)	p
HAM-A	25·9 (±4·2)	24·1 (±3·9)	0·01
HAM-D	8·0 (±1·3)	8·0 (±1·4)	0·66
BSA	19·6 (±5·6)	18·4 (±4·8)	0·28
FARD	25·0 (±7)	22·5 (±7·7)	0·07
Auto-evaluation	55·1 (±22)	57·9 (±24·1)	0·59

*Mann Whitney U-test.

Hydroxyzine and placebo groups were comparable at baseline for all scales except for HAM-A where hydroxyzine patients by chance scored significantly higher (more anxious) than placebo patients.

Assessment of efficacy

It is worth noting that the mean HAM-D scores at baseline for both groups were below the predefined limit of depression: HAM-D = 10.

The primary end-point of the study was to evaluate the efficacy of hydroxyzine, against placebo, in reducing the generalized anxiety evaluated through the HAM-A scale (Figure 1).

The mean change scores (±SD), from week 0 are presented in Table 3. At weeks 1, 4 and 5, it is shown that generalized anxiety is significantly more reduced under hydroxyzine than under placebo.

Table 3. Hamilton Anxiety Rating Scale (HAM-A): mean change scores from week 10

Week	Hydroxyzine ($N=54$)	Placebo ($N=56$)	p
Week 1	−6·7 (±4·9)	−3·8 (±5·2)	$p < 0·001$
Week 4 (end of treatment)	−4·5 (±7·1)	−6·6 (±7·4)	$p < 0·001$
Week 5 (after 1 week untreated)	−11 (7·7)	−5·9 (± 7·3)	$p = 0·001$

*Mann Whitney U-test.

The percentage of items scored as 0 (absence) or 1 (mild) was also computed at weeks 0, 1, 4 and 5. Results are presented in Figure 2. The percentage of items scored as 0 or 1 at weeks 4 and 5 are significantly greater under hydroxyzine than under placebo.

BSA and FARD global scores are presented in Figures 3 and 4. Generalized anxiety evaluated on the BSA score appeared to be significantly more reduced at weeks 4 and 5 under hydroxyzine. Generalized anxiety evaluated on the FARD score appeared to be significantly more reduced at week 4 under hydroxyzine. The results of the investigators'

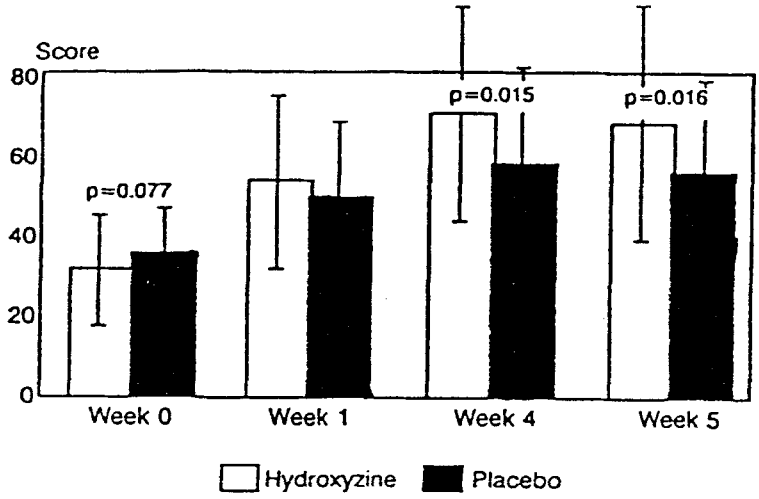

Figure 2. Hamilton Anxiety Scale percentage of items scoring 0 or 1

clinical global impression are shown in Table 4. There was a significantly greater percentage of ratings of improvement found following hydroxyzine at all visits (week 1, 4 and 5). From the table it also appears that under hydroxyzine the modal score of 'penetrable improvement' occurs at weeks 1, 4 and 5, while under placebo the most frequent scored categories are 'no change' (week 1) and 'slight improvement' (week 4).

The 58-item self-evaluation questionnaire results are presented in Figure 5. From week 2 to week 5, patients in the hydroxyzine group are significantly less anxious than patients treated with placebo.

Evaluation of adverse effects (tolerability)

Of the 124 patients included in the study, 121 were evaluated for tolerability; three patients (two hydroxyzine and one placebo) were lost for follow-up after the inclusion visit. Treatment-related adverse effects were reported by 52 patients (30 in the hydroxyzine group (52 per cent) and 22 in the placebo group (35 per cent)). There was no statistical difference between these reporting frequencies. The most frequent reported adverse effects are shown in Table 5. Only three patients discontinued the study explicitly because of adverse effects; two in the hydroxyzine group (one with nephritic colic with

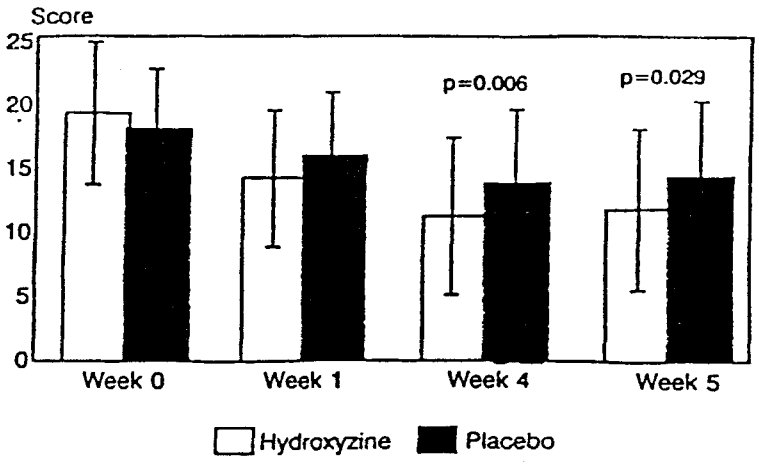

Figure 3. Brief scale for anxiety (Tyrer, 1984) total mean scores

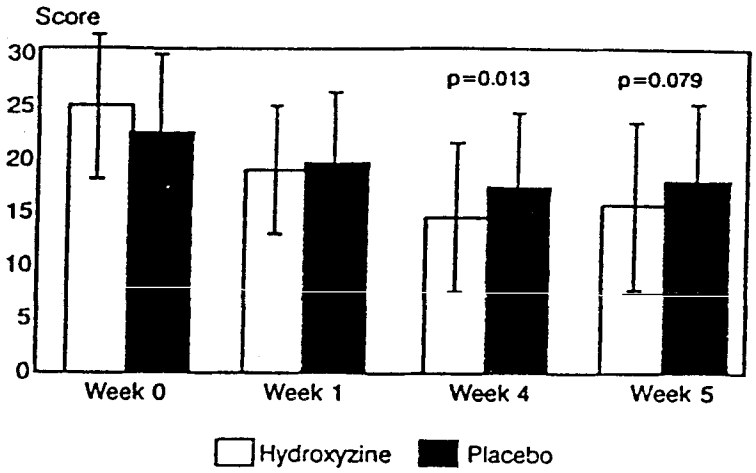

Figure 4. FARD Anxiety scale total mean scores

Table 4. Investigators' clinical global impression of changes in anxiety status (Following data to be plotted as a bar chart) (improvement from baseline)

	Hydroxyzine ($N=54$)	Placebo ($N=56$)	p
Week 1			< 0·001
Remarkable improvement	51%	20%	
Slight improvement	33%	25%	
No change	16%	53%	
Slight worsening	0%	2%	
Remarkable worsening	0%	0%	
Week 4			< 0·001
Remarkable improvement	73%	18%	
Slight improvement	18%	39%	
No change	8%	31%	
Slight worsening	0%	12%	
Remarkable worsening	0%	0%	
Week 5			< 0·001
Remarkable improvement	57%	22%	
Slight improvement	29%	25%	
No change	12%	39%	
Slight worsening	2%	10%	
Remarkable worsening	0%	4%	

*χ^2 test.

superinfection and the other complaining of sleepiness and vertigo) and one in the placebo group (nervousness, depression, vertigo and tachycardia).

The most commonly reported adverse effect was sleepiness. This occurred more frequently in the hydroxyzine group than with placebo controls, but this difference did not reach statistical significance ($p = 0·114$). There were no significant differences in the incidence of other reported adverse effects.

DISCUSSION

This double-blind randomized placebo controlled study was designed to investigate the clinical efficacy of hydroxyzine in treating generalized anxiety. Our findings have adequately confirmed studies published over the past 30 years in demonstrating that hydroxyzine is significantly more effective than placebo for the short-term control of generalized anxiety. Garber (1958) carried out an open study on hydroxyzine in 143 patients with psychoneuroses and anxiety, and 89·5 per cent of these had good to excellent response to therapy.

Table 5. Most frequently reported adverse effects

	Hydroxyzine ($N=58$)	Placebo ($N=63$)
Sleepiness	16 (28%)	9 (14%)
Dry mouth	8 (14%)	9 (15%)
Weight gain	7 (12%)	6 (10%)
Insomnia	5 (9%)	4 (6%)
Nervousness	4 (7%)	3 (5%)

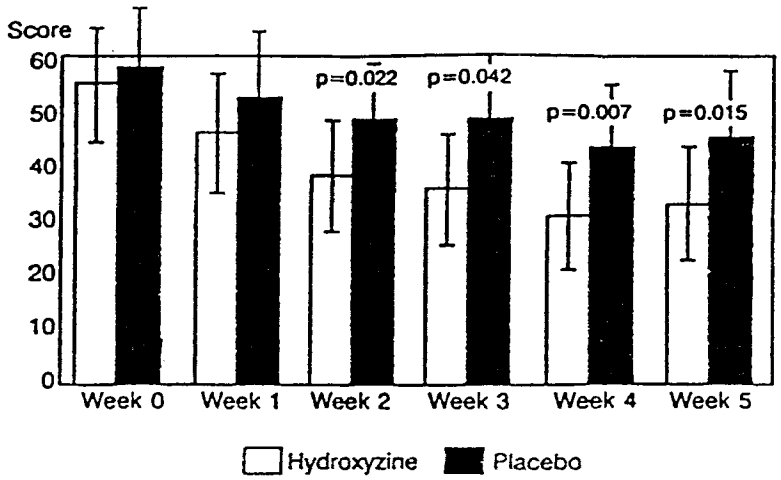

Figure 5. Auto-evaluation scale total mean scores

Breslow (1968), in a double-blind cross-over study, showed hydroxyzine to be superior to placebo in controlling anxiety, agitation and insomnia, in addition to other neurotic symptoms. A long-term (4½ year) open study by Shalowitz (1961) demonstrated good to excellent symptomatic relief from tension and anxiety in 89 per cent of 401 patients. Another open study by Lipton (1961) on 51 outpatients showed that hydroxyzine was most effective in neuroses where anxiety or depression predominated. A double-blind study, by Goldberg (1973) concluded that hydroxyzine was effective but slow-acting in the treatment of psychoneurotic symptoms including anxiety, but it did not demonstrate any improvements in depression.

Most previous studies on hydroxyzine have suffered from methodological deficiencies, and this study has been to our knowledge the first to comply with the standards of Good Clinical Practice.

Throughout the study, all efficacy variables (except perhaps the FARD scores at week 5) showed significantly greater improvement in the hydroxyzine group compared to the placebo control. As none of the subjects were clinically depressed, the slight improvement in the HAM-D scores from the initially low baseline levels would be expected to reflect the several items of this rating instrument which measure aspects of psychic and/or somatic anxiety.

The mean HAM-A scores of the hydroxyzine group at baseline were slightly and significantly higher than those of the placebo group; however, within 1 week from the start of therapy, significant differences were recorded between the two groups, in favour of hydroxyzine. These persisted until the end of treatment, and were still apparent one week later in contrast to the study by Goldberg *et al.* (1961), in which a significant improvement was not achieved until week 4.

The small difference between the groups in initial scores is very unlikely to account for the much greater (44 per cent versus 27 per cent at four weeks) average reduction in HAM-A scores seen with hydroxyzine treatment compared to placebo, because absolute scores were also lower in the active than in the placebo group at the end of treatment. Although it remains a remote possibility that hydroxyzine treatment was randomized to a more anxious and treatment-responsive group of patients, this is unlikely as the other rating scales showed a similarly greater anxiolytic effect of hydroxyzine over placebo.

Although the most common adverse effect reported with hydroxyzine was sleepiness, this only occurred in about one-quarter of the subjects, and the increased incidence over the placebo group was not statistically significant. An increase in sleepiness due to hydroxyzine might appear as an anxiolytic effect by improving the insomnia item of the HAM-A, and thereby reducing the total score compared to the placebo group. However, the greater reduction in the HAM-A total score due to hydroxyzine was such that it could not be accounted for by a differential effect over placebo on just one

item. Even after omitting the HAM-A insomnia item, the significantly greater reduction in the total HAM-A score due to hydroxyzine was preserved.

There was a tendency for reports of sleepiness to decrease between weeks 1 and 4 in both treatment groups. However, this might be partly explained by the fact that five subject (three hydroxyzine, two placebo) who complained of sleepiness at week 1 were withdrawn from the study before the next visit. Only in one case was the explicitly due to somnolence, although this may have contributed indirectly to the non-compliance with medication and other protocol violations reported in the remainder of the patients.

This study confirmed the short-term anxiolytic efficacy of hydroxyzine under general practice conditions which are likely to be applicable to the majority of patients who present with generalized anxiety. There was no measurable tolerance to the anxiolytic effect of hydroxyzine over the short duration of the study, and the anxiolytic effect was maintained for at least one week after the end of treatment.

Although more detailed and longer term studies with hydroxyzine are needed, during 30 years of clinical experience with the drug, there have been no confirmed cases of dependency or other deleterious adverse effects of the type associated with prolonged benzodiazepine use. (Owen and Tyrer, 1983; Csernansky and Hollister, 1983; Subhan and Hindmarch, 1984; Böning, 1985; Curan, 1986; Cantophar, 1990). We conclude that hydroxyzine offers the possibility of effective relief of generalized anxiety.

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