

Efficacy and Safety of Hydroxyzine in the Treatment of Generalized Anxiety Disorder: A 3-Month Double-Blind Study

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Background: The prevalence of generalized anxiety disorder (GAD) represents an important public health issue. Hydroxyzine, an antagonist of histamine receptors, showed both efficacy and safety in previous short-term double-blind studies over placebo in this pathology. The aim of the current study was to confirm those positive results over a 3-month period in adult outpatients.

Method: This multicenter, parallel (hydroxyzine [50 mg/day]; bromazepam [6 mg/day]), randomized, double-blind, placebo-controlled trial included 2 weeks of single-blind run-in placebo, 12 weeks of double-blind randomized treatment, and 4 weeks of single-blind run-out placebo. Three hundred thirty-four of 369 selected outpatients with a diagnosis of GAD according to DSM-IV criteria and a Hamilton Rating Scale for Anxiety (HAM-A) total score ≥ 20 were randomized before entering the double-blind period. The primary outcome criterion was the change in the HAM-A score from baseline to 12 weeks of double-blind treatment with hydroxyzine compared with placebo.

Results: In the intent-to-treat analysis, the mean \pm SD change in HAM-A scores from baseline to endpoint was -12.16 ± 7.74 for hydroxyzine and -9.64 ± 7.74 for placebo ($p = .019$). Results at endpoint for percentage of responders ($p = .003$) and remission rates ($p = .028$), Clinical Global Impressions-Severity scale score ($p = .001$), maintenance of efficacy ($p = .022$), and Hospital Anxiety and Depression scale score on day 84 ($p = .008$) also confirmed the efficacy of hydroxyzine over placebo. The study showed no statistically significant difference between hydroxyzine and bromazepam. Except for drowsiness, which was more frequent with bromazepam, safety results were comparable in the 3 groups.

Conclusion: Hydroxyzine showed both efficacy and safety in the treatment of GAD and appears to be an effective alternative treatment to benzodiazepine prescription.

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Generalized anxiety disorder (GAD) is one of the most common anxiety disorders and currently represents an important public health issue. The prevalence of the disease, which often presents a chronic course, ranges from 4% to 6% in the general population.¹ This disorder is a recent nosographic concept, whose clinical definition in both DSM-III and DSM-IV² focused on the psychic dimension of anxiety more than on somatic aspects.

Pharmacologic treatment of GAD usually depends on benzodiazepine prescription, whose well-known potential for dependency appears to be a relevant concern. Furthermore, benzodiazepines affect memory capacities and require precautions for use.³ The new generation of antidepressants also has a specific action on anxiety, especially venlafaxine in GAD, but by means of a different mechanism of action and a different profile of side effects and tolerance.⁴ Hydroxyzine treatment presents an interesting benefit-risk ratio, due to its pharmacologic and efficacy profile. Chemically, hydroxyzine is a derivative of piperazine that is not related to phenothiazines. The main pharmacologic action of hydroxyzine is an antagonism of histamine (H₁) receptors. Moreover, hydroxyzine has less affinity for muscarinic, serotonergic (5-HT₂), dopa-

minergic, and α_1 -adrenergic receptors than other first-generation H_1 receptor antagonists.⁵

Several previous short-term studies demonstrated anxiolytic effects of hydroxyzine in the treatment of GAD.⁶ A 4-week, double-blind, placebo-controlled study conducted in 110 patients suffering from GAD showed a significant efficacy of hydroxyzine over placebo at the daily dose of 50 mg.⁷ Another 4-week, double-blind, controlled study comparing the efficacy of hydroxyzine (50 mg/day), buspirone, and placebo in 244 patients with GAD also demonstrated the efficacy of hydroxyzine over placebo.⁸ In this study, the anxiolytic effect of the drug was maintained after abrupt treatment discontinuation, without any rebound or withdrawal symptoms.

The aim of the current double-blind study with parallel groups (hydroxyzine, 50 mg/day; bromazepam, 6 mg/day; and placebo) was to confirm these previous efficacy results over a 3-month period in outpatients with GAD, according to DSM-IV criteria. Bromazepam was used as an internal reference control since it is commonly prescribed in the treatment of GAD. The main objective was to assess the change in the Hamilton Rating Scale for Anxiety (HAM-A)⁹ total score in the hydroxyzine group compared with placebo from baseline to 12 weeks of double-blind treatment. Secondary efficacy objectives were evaluating, in each treatment group, the change in HAM-A, Clinical Global Impressions-Severity scale (CGI-S),¹⁰ and Hospital Anxiety and Depression (HAD) scale¹¹ scores, the responder and remission rates, and the maintenance of treatment efficacy. Evaluation of rebound and withdrawal symptoms was also described. Safety results were determined by recording adverse events throughout the study.

METHOD

This study was conducted by 89 French general practitioners under the supervision of psychiatrists from January 1998 to March 1999. Before starting the study, general practitioners were specifically trained in order to set a homogeneous practice for GAD diagnosis and assessment scales during specific investigators' meetings. Each physician viewed videotapes of patients suffering from GAD and performed an individual evaluation using the HAM-A. Results were then collectively discussed, and corrective explanations were given by the coordinating psychiatrist in case of deviations. Ratings on the other assessment scales were also reviewed during the training. This study was conducted according to International Conference on Harmonization guidelines on Good Clinical Practice (ICH GCP) and received favorable approval from the Ethics Committee of Boucicaut's Hospital in Paris. Each patient was properly informed about the aim of the trial and about its potential benefits and risks before giving his/her written informed consent.

Patients

Subjects who were allowed to enter the run-in period of the study on day -14 had to fulfill the following inclusion criteria: male or female adult outpatients (age = 18-65 years), diagnosis of GAD according to DSM-IV criteria, and HAM-A total score ≥ 20 . Inclusion criteria before entering the double-blind period on day 0 were as follows: difference in HAM-A total score ≤ 7 between day -14 and day 0, HAM-A total score ≥ 20 ; satisfactory treatment compliance during the run-in period; and presence of the other inclusion criteria met on day -14. Exclusion criteria on day -14 were as follows: pregnant or breast-feeding and absence of contraception method for women; known alcohol or drug dependence; major depressive episode within the preceding 6 months and/or a score ≥ 7 on the Raskin Severity of Depression and Mania scale¹²; psychotic or delusional disorders within the preceding 3 years; concomitant chronic diseases; closed-angle glaucoma or prostatic adenoma; intolerance or allergy to hydroxyzine, bromazepam, lactose, or cellulose; inability to use self-assessment scales; treatment with antidepressants, neuroleptics, mood regulators, morphine or derivatives, hydroxyzine, or bromazepam within the preceding 4 weeks; treatment with benzodiazepines > 2 days per week during the previous 30 days or benzodiazepine intake during the previous 2 weeks; central nervous system-active treatment within the last week preceding inclusion; and need for psychotherapy, unless psychotherapy was conducted on a continuous basis for at least 6 months prior to entry in the trial. Exclusion criteria on day 0 were a positive urinalysis for benzodiazepine screening and the same criteria that were previously described for day -14. Psychotropic drugs or other treatments likely to impact the central nervous system or non-pharmacologic treatments, such as psychotherapy or acupuncture, were not allowed throughout the study.

Study Design

This was a 12-week, multicenter, parallel, randomized, double-blind, placebo-controlled study of hydroxyzine that also included a bromazepam arm. Its total duration of 18 weeks was divided into 3 successive periods as follows: 2 weeks of single-blind run-in placebo (day -14 to day 0), 12 weeks of double-blind treatment (day 0 to day 84), and 4 weeks of single-blind run-out placebo (day 84 to day 112). Patients' visits occurred on days -14, 0, 21, 42, 63, 84, 91, and 112. Patients were assigned to double-blind treatment in 1 of the 3 treatment groups. Daily medication was always given as oral capsules in 3 divided doses (t.i.d.) during each period of the study. During the double-blind period, the daily dose of hydroxyzine was 50 mg (12.5 mg in the morning and at noon, 25 mg in the evening). This dose has previously been used in the treatment of GAD.^{7,8} The daily dose of bromazepam was 6 mg (1.5 mg in the morning and at noon, 3 mg in the evening).

Placebo was also given in a t.i.d. manner in order to ensure blinding. These doses remained unchanged throughout the double-blind period. Patients received placebo in a single-blind manner in both run-in and run-out periods. Patients who entered the run-out period were also allowed to take the trial medication they received during the preceding period at any time, on request, and in a double-blind manner, but not exceeding the total daily dose given during the double-blind period. Treatment compliance was assessed by counting the remaining capsules returned at each visit.

Clinical Assessments

HAM-A scoring⁹ and clinical examination were performed at each visit. The CGI-S¹⁰ score, evaluating the severity of the disease, was recorded at each visit from day 0 onward. Patient's self-assessment for anxiety and depression severity was performed using the HAD scale¹¹ at each visit from day 0 onward. The Raskin scale¹² was used to prevent the inclusion of severely depressed patients on day -14 and day 0. A scale that was intended to rate the impact of anxiety on a patient's behavior¹³ and GAD severity scoring were performed on day 0. The Petursson and Lader scale¹⁴ and patient's self-assessment scale by Tyrer et al.¹⁵ were used at each visit of the run-out phase to evaluate the effects of drug withdrawal. Patients considered to be responders were defined as achieving at least a 50% reduction in the HAM-A score compared with day 0. Remission was defined as a HAM-A total score ≤ 10 during the course of the study. Maintenance of efficacy was first defined as a very strict narrow range of maintenance among patients considered as responders on day 42 whose HAM-A score did not deteriorate by more than 2 points between day 42 and day 84. Considering that the fluctuation of the HAM-A score may sometimes spread over this interval, an additional analysis was similarly performed on responders using a HAM-A cutoff score of 3 points. Adverse events were recorded at each visit, whether or not they were related to trial medication.

Statistical Analysis

The primary efficacy criterion and other secondary criteria were analyzed by using an intent-to-treat analysis including all patients who were randomized on day 0 and for whom at least 1 postbaseline datum was available. Where applicable, a missing score was replaced by the last available score under treatment in case of withdrawal from the study, according to the last-observation-carried-forward (LOCF) method. A per-protocol analysis was also performed to assess the primary efficacy criterion. A covariance analysis was performed on the main objective to compare the change in the HAM-A score in the hydroxyzine group with that in the placebo group, on the basis of changes in HAM-A total scores between day 84 and day 0. Baseline scores were used as covariates. The following analyses were used to assess the secondary objectives:

(1) a covariance analysis was performed with pairwise comparisons between each treatment group, on the changes in HAM-A total scores and HAD scale scores; (2) chi-square tests were used for comparisons of remission and responder proportions between each treatment group, and also for maintenance of efficacy; (3) semiquantitative criteria of the CGI-S were assessed with the nonparametric Mann-Whitney test since the data on the change from baseline were not normally distributed; and (4) comparisons between groups were performed in patients experiencing at least 1 adverse event whether or not related to study medication, after patients were randomized, by using a chi-square test. Analyses were tested at a 2-sided α level of .05. Other safety information was considered on a descriptive basis. A chi-square test compared both the appearance and worsening of each symptom indicated in the Petursson and Lader scale between each treatment group in order to evaluate the withdrawal effects during the run-out period. Only descriptive data were displayed for the Tyrer et al. scale. All statistical analyses were performed using the Statistical Analysis Software (SAS version 6.12, SAS Institute, Cary, N.C.).

RESULTS

Population Characteristics

Three hundred sixty-nine patients, all suffering from GAD according to DSM-IV, entered the study during the recruitment period. No patient with a history of psychosis was included in the study. Three hundred thirty-four were randomized to 1 of the 3 treatment groups on day 0. The randomized population was composed of 105 patients receiving hydroxyzine, 116 patients receiving bromazepam, and 113 patients receiving placebo. Patients' characteristics were comparable in each group of the randomized population. The mean \pm SD age of patients was 41.5 ± 11.9 years in the placebo group, 43.6 ± 11.7 years in the hydroxyzine group, and 44.9 ± 11.5 years in the bromazepam group. As expected, women were predominantly represented in each group, with sex ratios (male:female) being 38:75 for placebo, 31:74 for hydroxyzine, and 37:79 for bromazepam. Data regarding GAD history, which were collected by specific questioning of patients at the time of inclusion, and psychometric assessments for the randomized population are presented in Table 1.

Treatment Compliance

In the 3 groups, compliance with treatment was considered excellent since drug intake represented more than 85% of the total theoretical number of capsules throughout the study. Results were comparable between groups.

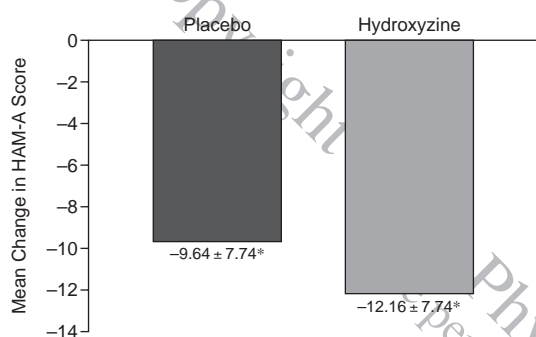
Study Withdrawals

A total of 56 of 334 patients discontinued prematurely after being randomized (22 in the placebo group, 17 each

Table 1. GAD History and Psychometric Assessments on Day 0^a

Variable	Placebo (N = 113)	Hydroxyzine (N = 105)	Bromazepam (N = 116)	Total (N = 334)
Personal history of GAD (not including the current episode), N (%)	92 (81.4)	81 (77.1)	96 (82.8)	269 (80.5)
Family history of GAD, N (%)	76 (67.3)	67 (63.8)	81 (69.8)	224 (67.1)
HAM-A total score, mean (SD)	25.73 (4.14)	25.49 (3.61)	25.32 (3.44)	25.51 (3.74)
HAM-A psychic subscore, mean (SD)	14.32 (2.55)	14.23 (2.46)	14.28 (2.25)	14.28 (2.42)
HAM-A somatic subscore, mean (SD)	11.41 (3.19)	11.26 (2.90)	11.04 (3.01)	11.23 (3.03)
Raskin scale score, mean (SD)	3.41 (1.81)	3.30 (1.87)	3.36 (1.82)	3.36 (1.83)

^aAbbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety.

Figure 1. Main Efficacy Criterion: Mean Change in the HAM-A Total Score (endpoint to day 0) in GAD Patients^a

^aAbbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety. Number of patients included in the covariance analysis: hydroxyzine (N = 102), placebo (N = 108). In the randomized population, 5 patients from the placebo group and 3 patients from the hydroxyzine group had only baseline data and were not included in this analysis.

*p = .019; 95% CI = 0.42 to 4.62.

in the hydroxyzine and bromazepam groups). The main reasons for discontinuation were withdrawal of consent (N = 23), lost to follow-up (N = 9), adverse events (N = 13), and drug inefficacy (N = 6).

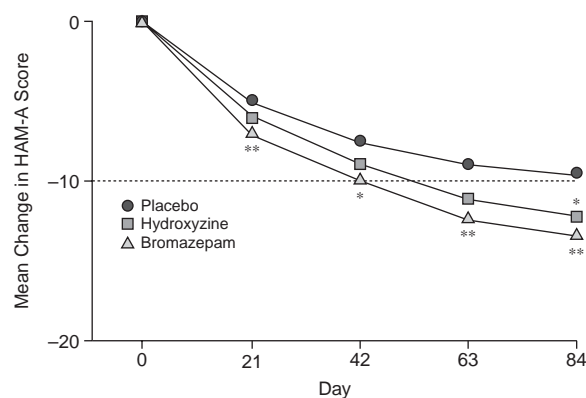
EFFICACY

Primary Efficacy Criterion

In the randomized population, the primary efficacy criterion defined by the adjusted mean changes in HAM-A scores between endpoint and day 0 was statistically significant for hydroxyzine compared with placebo (Figure 1). The per-protocol analysis also confirmed the efficacy of hydroxyzine over placebo with a difference in HAM-A scores between endpoint and day 0 being equal to -12.54 ± 7.69 for hydroxyzine (N = 96) and -9.73 ± 7.69 for placebo (N = 100) (p = .011; 95% CI = 0.64 to 4.96).

Secondary Efficacy Criteria

Secondary efficacy criteria were assessed in the randomized population. For each criterion, no statistically significant difference was shown between hydroxyzine and bromazepam groups regardless of the evaluation

Figure 2. Change of HAM-A Score Compared With Day 0 (baseline adjusted means)^a

^aAbbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

*p ≤ .03 vs. placebo.

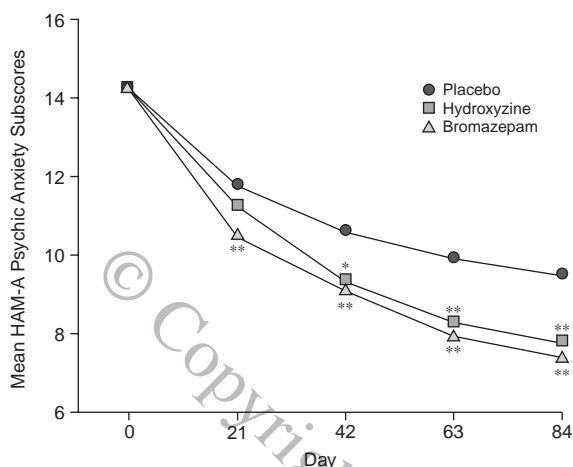
**p ≤ .01 vs. placebo.

time, even though hydroxyzine efficacy over placebo was delayed compared with bromazepam efficacy for some secondary criteria. It should be considered that this study was not intended to compare these 2 drugs and thus was not sufficiently powered to detect a possible difference between them. Figure 2 shows the mean changes in HAM-A scores in the 3 groups.

Moreover, the HAM-A contains some specific items related to psychic anxiety; those subscores are displayed for each treatment group (Figure 3).

Responders

The percentages of responders in the randomized population are displayed in Figure 4. An analysis of maintenance of efficacy (HAM-A cutoff score = 2 points; i.e., score that did not deteriorate by more than 2 points) was also performed in the population of patients considered as responders on day 42. Efficacy was significantly maintained versus placebo in 32 (86.5%) of 37 patients in the hydroxyzine group (p = .022) and in 37 (88.1%) of 42 patients in the bromazepam group (p = .010) until day 84. The second analysis that was performed in the same way by using a HAM-A cutoff score of 3 points confirmed the

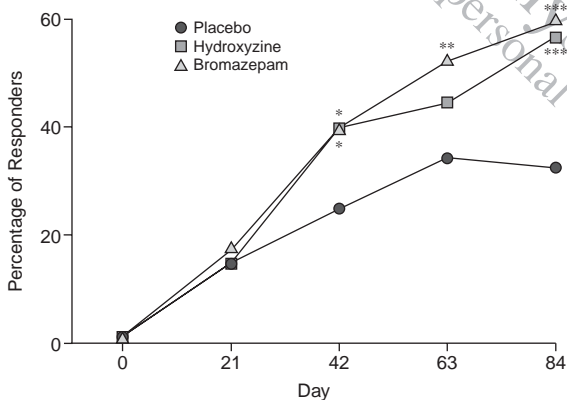
Figure 3. Mean HAM-A Psychic Anxiety Subscores^a

^aAbbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

* $p \leq .03$ vs. placebo.

** $p \leq .01$ vs. placebo.

Figure 4. Percentage of Responders (randomized population)



* $p \leq .05$ vs. placebo.

** $p \leq .03$ vs. placebo.

*** $p \leq .01$ vs. placebo.

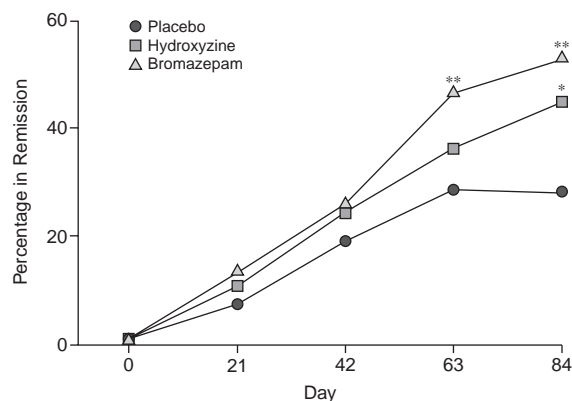
significant maintenance of efficacy of hydroxyzine over placebo in 35 (94.6%) of 37 patients ($p = .012$), but not for bromazepam (37/42 [88.1%]; $p = .066$ versus placebo).

Patients in Remission

The percentages of patients in remission in the randomized population are displayed for each assessment point and in each group in Figure 5.

HAD Scale

The HAD scale is a self-administered questionnaire containing 14 items with possible scores ranging from 0 to 42. The change in the HAD total scores (mean \pm SD) from baseline to day 84 was -4.51 ± 6.82 for placebo,

Figure 5. Percentage of GAD Patients in Remission^a

^aAbbreviation: GAD = generalized anxiety disorder.

* $p \leq .03$ vs. placebo.

** $p \leq .01$ vs. placebo.

-7.08 ± 6.82 for hydroxyzine ($p = .008$), and -7.03 ± 6.82 for bromazepam ($p = .007$). HAD results in the hydroxyzine group became significantly different from placebo from day 42 onward. Bromazepam also showed statistical significance versus placebo from day 21 onward, except on day 42 ($p = .059$).

CGI-S

The CGI-S provides a rating of disease severity in patients with scores ranging, when evaluation is available, from 1 (normal, not at all ill) to 7 (among the most seriously ill). CGI-S median scores of the change from baseline were improved by 1 point in the placebo group compared with 2 points in the 2 other active treatment groups ($p \leq .001$). During the course of the study, changes became statistically different from placebo in both the hydroxyzine and bromazepam groups from day 42 onward.

SAFETY

The evaluation of safety was performed on 325 patients for whom at least 1 safety recording was available after randomization. One hundred forty-two randomized patients (43.7%) experienced at least 1 adverse event, both in double-blind and run-out periods, as follows: 49/109 patients (45.0%) in the placebo group, 42/102 (41.2%) in the hydroxyzine group, and 51/114 (44.7%) in the bromazepam group. In the placebo, hydroxyzine, and bromazepam groups, only 10.1%, 14.7%, and 14.0% of patients, respectively, experienced at least 1 adverse event considered to be possibly, probably, or very likely related to treatment, according to the investigators. Comparisons of results showed no statistically significant difference between each treatment group. Only 1 serious adverse event (appendicitis) unrelated to treatment occurred in the hydroxyzine group during the study. Drowsiness was

Table 2. Change in HAM-A Total Score During the Run-Out Period^a

Treatment Type	N ^b	HAM-A Total Score			Final N ^d	Patients With a Worsening of at Least 4 Points on Day 112 Compared With Day 84, N (%)
		Day 0	Day 84	Endpoint During Run-Out Period ^c		
No on-demand treatment						
Placebo	40	25.43	14.25	13.93	40	8 (20.0)
Hydroxyzine	49	25.06	11.08	10.39	48	8 (16.7)
Bromazepam	46	25.15	9.43	9.83	44	9 (20.5)
On-demand treatment						
Placebo	40	25.63	16.10	14.43	39	3 (7.7)
Hydroxyzine	33	26.42	14.91	15.03	31	6 (19.4)
Bromazepam	48	25.50	12.27	12.75	48	9 (18.8)

^aAbbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

^bNumber of patients with information of on-demand treatment, HAM-A data at baseline, HAM-A data on day 84, and HAM-A data at least once during the run-out (day 91 or day 112) period.

^cLast data collected day 91 or day 112.

^dNumber of patients with information of on-demand treatment and HAM-A data on day 84 and on day 112.

the treatment-related adverse event most frequently reported in the hydroxyzine group (3.9%). Incidences of drowsiness were, however, twice as high in the bromazepam group (7.9%) and lower in the placebo group (1.8%). Overall, descriptive adverse events, whether or not related to treatment and occurring with an incidence of at least 5% during the study, were headache (5.5%), pharyngitis (6.4%), rhinitis (8.3%), and bronchitis (5.5%) in the placebo group; pharyngitis (5.9%) in the hydroxyzine group; and drowsiness (7.9%), pharyngitis (8.8%), and rhinitis (6.1%) in the bromazepam group. No weight gain compared with baseline was observed in any of the 3 groups. Thirteen patients withdrew from the study prematurely due to adverse events that were not considered as serious (4 in the placebo group, 5 in the hydroxyzine group, and 4 in the bromazepam group). Adverse events included depression, nausea, upper respiratory infection, and disorder of visual accommodation in the placebo group; colitis, depression, drowsiness, and agitation associated with anguish in the hydroxyzine group; and depression, headaches associated with epigastralgia and palpitations, rebound of anxiety, and drowsiness in the bromazepam group. Pregnancy, leading to premature study discontinuation, was also reported in the hydroxyzine group.

EFFECT OF TREATMENT DISCONTINUATION

A total of 295 patients, 98 taking placebo, 93 taking hydroxyzine, and 104 taking bromazepam, entered the run-out period from day 84 onward.

Rebound Effect

The detection of a possible rebound effect was evaluated by measuring the use of on-demand treatment (treatment requested by patients) that was taken in addition to placebo treatment during the run-out period in case of

reappearance of anxiety disorders. Rebound effect was also based on the change in HAM-A score following treatment discontinuation from day 84 onward. On-demand treatment was more frequent in the placebo and bromazepam groups (50.0% and 51.1% of patients, respectively) than in the hydroxyzine group (40.2%), but not statistically significant between groups. Two hundred seventy-eight patients (86 taking hydroxyzine, 100 taking bromazepam, and 92 taking placebo) provided data regarding the change in HAM-A

score from day 84 to the end of the run-out period. Regarding the population of patients having provided on-demand medication information, and HAM-A data on day 84 and on day 112 during the run-out period, 11/79 (13.9%) of patients in the placebo group showed a worsening by at least 4 points on day 112 compared with day 84, compared with 14/79 (17.7%) in the hydroxyzine group, and 18/92 (19.6%) in the bromazepam group. There was no statistically significant difference between each treatment group.

The evaluable population during the run-out period was further split into 2 subgroups: those patients who had taken on-demand medication at least once and those who had not. As shown in Table 2, the anxiety level measured on day 84 was higher in each of the 3 treatment groups in patients who took on-demand medication during this period. The change in HAM-A total score between day 84 and endpoint was relatively stable in each subgroup, as was also the case for the percentages of patients undergoing a worsening of at least 4 points in HAM-A score, except for placebo (see Table 2).

Withdrawal Symptoms

A possible appearance of withdrawal syndrome was considered by using both the Petursson and Lader scale and the Tyrer et al. scale to collect data on clinical symptoms during the run-out period (i.e., worse score between day 91 and day 112), compared with day 84. Among the items on the Petursson and Lader scale, only the following 3 differed unfavorably compared with placebo in both appearance and worsening of symptoms (difference from placebo > 5%): (1) headaches (14/94 [14.9%] of patients taking placebo, 15/88 [17.0%] taking hydroxyzine, and 24/102 [23.5%] taking bromazepam); (2) sweating (11/94 [11.7%] taking placebo, 20/88 [22.7%] taking hydroxyzine, and 17/102 [16.7%] taking bromazepam); and (3) sleep disturbances (18/93 [19.4%] taking placebo,

26/88 [29.5%] taking hydroxyzine, and 40/102 [39.2%] taking bromazepam). Results showed that bromazepam induced significantly more sleep disturbances than placebo ($p = .002$). Other comparisons between groups did not reach statistical significance, with the exception of sweating in the hydroxyzine group compared with the placebo group ($p = .048$). Results on the Tyrer scale showed no specific important descriptive difference between the 3 arms.



DISCUSSION

This randomized, parallel-group, double-blind, placebo-controlled study was designed to confirm the efficacy of hydroxyzine in comparison with placebo in the treatment of GAD as previously shown in the studies by Ferreri and Hantouche⁶ and Lader and Scotto.⁸ Unlike the time span in those studies, treatment was assessed during 12 weeks to confirm that the anxiolytic activity of hydroxyzine is maintained over this period. We also used the benzodiazepine bromazepam as an internal reference because it is frequently prescribed in this pathology in daily practice. The population studied was representative of patients suffering from GAD since sex ratio (female:male) was about 2:1. Mean \pm SD age was 43.3 ± 11.8 years. This disorder usually has a chronic course with generally more than 5 relapses on average. In the current study, hydroxyzine efficacy was statistically significant over placebo for all of the primary and secondary criteria. Its efficacy appeared progressively over time and was maintained up to day 84.

Regarding the global evolution of the curves displayed in each figure, it can be expected that the efficacy of hydroxyzine will probably extend beyond a treatment period of 3 months. Although the efficacy of bromazepam over placebo appeared earlier than that of hydroxyzine for some efficacy criteria, this study, which was not specifically designed to compare hydroxyzine to bromazepam, showed no statistically significant difference between these 2 drugs.

In the context of a chronic pathology like GAD, maintenance of efficacy and safety should be considered as the main 2 suitable criteria to take into account for the long-term therapeutic evaluation. Thus, the anxiolytic activity of hydroxyzine appeared globally comparable with that of benzodiazepines, which confirms the data from the studies of Tornetta¹⁶ and Herr and colleagues.¹⁷ Those 2 studies compared the anxiolytic efficacy of hydroxyzine with that of diazepam in premedication administration. The respective dosages of hydroxyzine were 50 mg and 100 mg administered in intramuscular injections. In these studies, hydroxyzine demonstrated an anxiolytic efficacy comparable with that of diazepam.

Hydroxyzine appears to act more specifically on the psychic component of anxiety that would be most specific

in GAD, according to Barlow.¹⁸ The results of our study are consistent with the data of Ferreri and Hantouche,⁶ who also found that the molecule had a more specific activity on psychic symptoms as measured with the FARD scale for anxiety.¹⁹ This 12-item scale is intended to evaluate the repercussion of anxiety on relational, somatic, vigilance, and cognitive dimensions. Rather than a comparison with benzodiazepines, it would be interesting to compare the clinical efficacy of hydroxyzine with the impact of venlafaxine in GAD, which seems to have a delayed action on the psychic component of anxiety.^{20,21}

The demonstration of hydroxyzine anxiolytic activity during the course of this study appears to be relevant since the treatment of GAD is often maintained for several weeks in clinical practice. Safety of the study medications was good in each treatment group; however, drowsiness was more frequent in the bromazepam group than in the hydroxyzine and placebo groups. Furthermore, 2 studies, one in individuals with GAD and the other in a population of healthy volunteers, showed that hydroxyzine induces less cognitive impairment than lorazepam.^{22,23}

All of this information confirms that hydroxyzine is relevant in the treatment of GAD. Treatment discontinuation after 12 weeks led to no significant symptoms of rebound anxiety. Patients treated with bromazepam presented a significant number of sleep disturbances over placebo after treatment withdrawal. This observation, which was not encountered with hydroxyzine, should be considered as an important topic in the long-term management of medical care of such patients. Although 12 weeks may seem to be a limited period of time, hydroxyzine appears to have no potential for dependency in the studied population. This finding confirms the first observations on the clinical use of hydroxyzine that showed good safety and the absence of dependency symptoms in the treated patients. Those observations were extracted from open-label trials with a limited methodology but gave further information on the use of the molecule in daily clinical practice.²⁴

As Ferreri and Hantouche⁶ emphasized, patients with GAD often require successive intermittent treatments and may remain without drug therapies for protracted periods of time. Hydroxyzine could also be suitable in this situation since this drug seems to lack particular risk of rebound anxiety or withdrawal symptoms. This study confirms that hydroxyzine is both effective and safe in the treatment of patients suffering from GAD over a longer period of time than previously demonstrated in other studies. Therefore, hydroxyzine appears to be an interesting alternative treatment to benzodiazepines in the treatment of GAD.

Drug names: buspirone (BuSpar and others), diazepam (Valium and others), hydroxyzine (Vistaril and others), lorazepam (Ativan and others), piperazine (Multifuge and other), venlafaxine (Effexor).

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