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Controlled Comparison of Buspirone and Oxazepam in Generalized Anxiety

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Abstract. The anxiolytic activity, the tolerance, and the withdrawal symptoms of buspirone and oxazepam were compared in two groups of 14 and 12 outpatients, respectively, suffering from generalized anxiety in a double-blind study with random allocation of patients. The 6-week active period was preceded and followed by 1 and 2 weeks on placebo, respectively. Clinical assessments were performed before and after the predrug placebo period and every 2 weeks thereafter and included Hamilton anxiety and depression scales and AMDP anxiety subscale. The initial daily dose was 15 mg buspirone or 45 mg oxazepam in 3 intakes and the mean final daily doses were 22.2 and 55.8 mg, respectively. Results showed a slower anxiolytic activity of buspirone compared to oxazepam with less improvement after 2 weeks of treatment. The rebound anxiety following abrupt discontinuation of the drug and the level of side effects did not significantly differ between the two compounds.

Introduction

Buspirone is a new anxiolytic drug that is chemically and pharmacologically distinct from the benzodiazepines [review in Goa and Ward, 1986]. Most controlled studies indicated efficacy comparable to classical benzodiazepines such as diazepam, clorazepate, lorazepam, bromazepam, and clobazam, with considerably less unwanted sedation, psychomotor impairment, alcohol potentiation, and addiction/abuse potential [review in Goa and Ward, 1986, and in Napoliello and Domantay, 1988].

Until now, however, no study has compared buspirone with oxazepam, a benzodiazepine derivative characterized by an excellent profile of efficacy and tolerance and a low abuse potential [Vaisanen and Jalkanen, 1987; Bond and Lader, 1988; Tyrer, 1988]. Therefore, the purpose of the present study was to compare the anxiolytic activity and the tolerance of buspirone and oxazepam, with special attention to the rebound phenomena following abrupt discontinuation of the drug.

Methods

Subjects

The study included a total of 26 psychiatric outpatients who fulfilled DSM-III criteria for generalized anxiety disorder [American Psychiatric Association, 1980] and exhibited a score of at least 18 on the Hamilton [1959] anxiety scale at the end of a 1-week placebo period. The sample comprised 14 male and 12 female patients, with age ranging from 19 to 54 years and a mean (SD) age of 40.2 (10.8) years. Patients presenting any evidence of contraindication for a benzodiazepine anxiolytic, serious or uncontrolled medical illness, benzodiazepine withdrawal symptoms of any degree, or major depressive symptomatology were excluded from the study. The association of any other drug was not permitted throughout the study period. Finally, the protocol was approved by the Ethical Committee of the University of Liège Medical School and all patients gave their informed consent.

Design

The study used a double-blind design. After a 1-week washout period on placebo (one tablet 3 times a day), the patients were randomly assigned to buspirone (5 mg 3 times a day) or oxazepam (15 mg 3 times a day). The duration of the active treatment was 6 weeks, with assessments every 2 weeks. The daily dose could be adapted at each visit according to both efficacy and tolerance, with a

maximal daily dose of 60 mg buspirone or 180 mg oxazepam. The active period was followed by 2 weeks on placebo with the same daily number of tablets as at the final evaluation with the assessment of withdrawal phenomena.

Assessments

Each assessment included the Hamilton [1959] anxiety scale, the 21-item Hamilton [1960] depression scale, and the anxiety subscale extracted from the system developed by the Association for Methodology and Documentation in Psychiatry (AMDP-AT) [Bobon et al., 1985]. All side effects as well as blood pressure, pulse rate, and weight were carefully recorded. Moreover, the clinical global impressions (CGI) were completed at baseline and at the end of the treatment.

Data Analysis

The baseline homogeneity of the two treatment groups was confirmed using one-way analysis of variance (ANOVA), chi-square statistics or Fischer exact test, and contingency coefficient. The changes over time in clinical ratings were compared by multivariate ANOVA with repeated measures on the differences between the baseline scores and the following ones. This type of analysis, which takes the usually heterogeneous correlations among the repeated measurements automatically into account, is preferred over the usual univariate ANOVA with the Greenhouse-Geisser correction in the multilevel within-subjects F tests [Ekstrom et al., 1990]. A first analysis was performed during the placebo week; then, multivariate ANOVAs were performed from the baseline week to the 2nd, 4th and 6th weeks of treatment. Changes over time from baseline to the 4th and 6th weeks of treatment were also analyzed using endpoint data for patients who left the study after the 2nd week. Finally, a last analysis was performed from the 6th to the 8th week in order to compare the withdrawal phenomena. All statistical procedures used the SAS package.

Results

Dropouts

A total of 11 patients left the study before the final assessment: 8 in the buspirone group and 4 in the oxazepam group (chi square = 1.47, d.f. = 1, p = NS). The reasons for these dropouts were inefficacy in 4 patients on buspirone (2 after 2 weeks and 2 after 4 weeks) and in 1 patient on oxazepam (after 6 weeks), side effects in 2 patients on buspirone (both after 2 weeks), and unknown in 2 patients on buspirone (after 4 and 6 weeks) and 3 patients on oxazepam (after 2, 4, and 6 weeks). The number of dropouts for inefficacy was not significantly different between the two treatment groups (chi square = 1.40, d.f. = 1, p = NS).

Pretreatment Placebo Week

None of the rating scales exhibited significant changes during the placebo week.

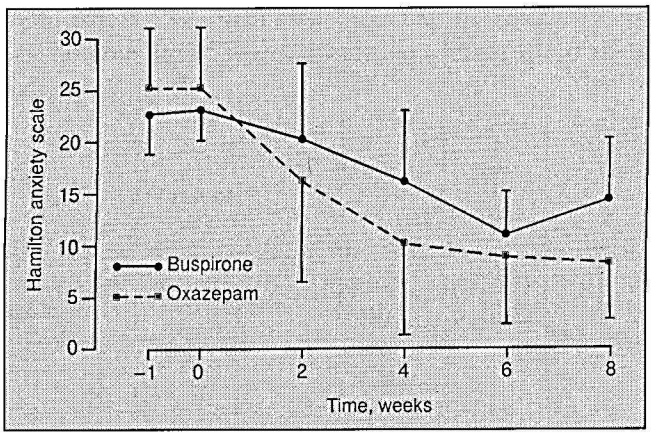

Fig. 1. Changes over time in Hamilton anxiety scores (mean and SD) in patients treated by buspirone (n = 14) or oxazepam (n = 12). The 6-week active period was preceded and followed by 1 and 2 weeks on placebo, respectively.

Baseline Homogeneity of the Treatment Groups

No significant difference existed between the two treatment groups with regard to all demographic data, medical and psychiatric history, previous use of psychotropic drugs, clinical examination, and intake of coffee and alcoholic beverages. Mean (SD) age was 38.9 (9.3) years in the buspirone group and 41.7 (12.3) years in the oxazepam group [F(1, 24) = 0.38, p = NS]. The buspirone group comprised 7 male and 7 female patients and the oxazepam group 5 male and 7 female patients (chi square = 0.18, d.f. = 1, p = NS). Baseline scores in all rating scales did not significantly differ between the two treatment groups.

Efficacy

Hamilton anxiety scores (fig. 1) exhibited significantly more improvement with oxazepam as compared to buspirone during the first 2 weeks [F(1, 24) = 6.71, p = 0.02]. During the first 4 weeks, a trend toward superiority of oxazepam over buspirone was still present [F(2, 19) = 2.95, p = 0.08], which became significant with the report of endpoint data [F(2, 23) = 4.04, p = 0.03]. Over the whole 6-week treatment period, no significant differences in changes over time were noted [F(3, 13) = 2.17, p = NS]; however, a trend toward superiority of oxazepam over buspirone reappeared with the report of endpoint data [F(3, 22) = 2.76, p = 0.07]. The superiority of oxazepam over buspirone during the first 2 weeks of treatment was noted on both the psychic and the somatic factors [F(1, 24) = 5.07, p = 0.04 and F(1, 24) = 7.03, p = 0.02].

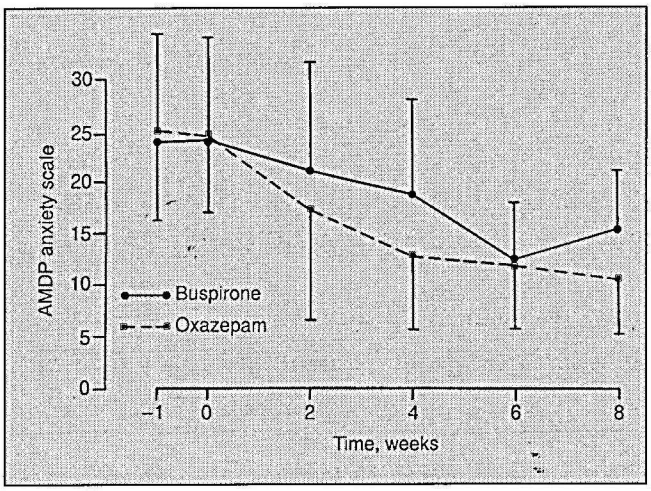

Fig. 2. Changes over time in AMDP anxiety scores (mean and SD) in patients treated by buspirone (n = 14) or oxazepam (n = 12). The 6-week active period was preceded and followed by 1 and 2 weeks on placebo, respectively.

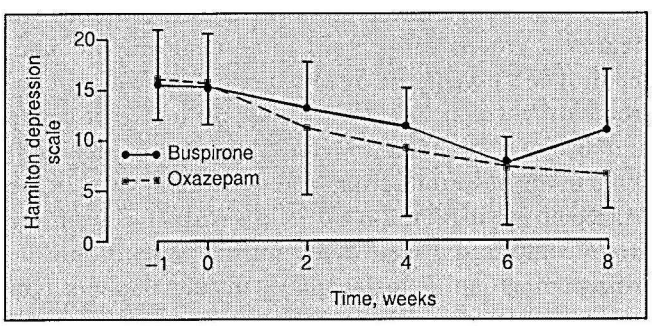

Fig. 3. Changes over time in Hamilton depression scores (mean and SD) in patients treated by buspirone (n = 14) or oxazepam (n = 12). The 6-week active period was preceded and followed by 1 and 2 weeks on placebo, respectively.

On the AMDP anxiety scale (fig. 2), a trend toward better efficacy of oxazepam over buspirone was also noted during the first 2 weeks [$F(1, 24) = 2.99$, $p = 0.09$]. There was no difference during the 4 first weeks [$F(2, 19) = 1.14$, p = NS] and no modifications were found using the report of endpoint data. For the whole 6-week treatment period, a trend toward better improvement with oxazepam as compared to buspirone was again present [$F(3, 13) = 3.28$, $p = 0.06$] but disappeared with the report of endpoint data [$F(3, 22) = 1.33$, p = NS].

The Hamilton depression scale (fig. 3) did not exhibit any significant differences between the two treatment groups [$F(3, 13) = 1.11$, p = NS]. The report of endpoint data did not change the conclusions.

The changes in illness severity, as assessed by the CGI, exhibited a trend toward superiority of oxazepam over buspirone [$F(1, 22) = 3.12$, $p = 0.09$]. The CGI rating the therapeutic effect, however, did not exhibit significant differences between the two treatment groups [$F(1, 22) = 2.85$, p = NS].

Side Effects

Three patients in the buspirone group experienced side effects which were attributed to the drug: nausea and panic attacks, dizziness and headaches, and dizziness and restlessness. Two patients in the oxazepam group experienced side effects: prurigo which was not attributed to the treatment and drowsiness which appeared to be linked to the compound. Blood pressure, pulse rate, and weight did not exhibit significant changes throughout the study period.

Withdrawal Period

The patients who underwent the 2-week withdrawal period (7 in the buspirone group and 8 in the oxazepam group) did not exhibit a significant difference in their changes in clinical ratings on the three scales despite a somewhat opposite evolution (fig. 1–3): $F(1, 12) = 0.26$, 0.04, and 0.04 for the Hamilton anxiety scale, the AMDP anxiety scale, and the Hamilton depression scale, respectively.

Doses

The daily number of tablets used between weeks 2 and 4 did not differ between the two treatment groups: 3.31 (0.48) of buspirone vs. 3.50 (0.90) of oxazepam [$F(1, 23) = 0.45$, p = NS]. Between weeks 4 and 6, however, the daily number of tablets tended to be higher in the buspirone group: 4.45 (0.93) vs. 3.72 (1.01) [$F(1, 20) = 3.08$, $p = 0.09$].

Discussion

The results of the present study suggest slower anxiolytic activity of buspirone as compared to a standard benzodiazepine such as oxazepam. Indeed, the only significant differences in clinical improvement between the two drugs are noted after 2 weeks of treatment and disappear after 4 weeks of intake. This initial difference is not simply related to sedative effects, since it is present on both psychic and somatic factors of the Hamilton anxiety scale, but does not appear on the individual item

'insomnia'. It is also not related to previous benzodiazepine therapy, as recently demonstrated in another study [Schweizer et al., 1986]: only 3 patients in the buspirone group were previously treated with benzodiazepines (2 with diazepam and 1 with bromazepam). This delayed onset of action of buspirone has previously been noted in several studies [Feighner et al., 1982; Wheatley, 1982; Tyrer and Owen, 1984; Tyrer et al., 1985; Jacobson et al., 1985; Pecknold et al., 1985; Rickels et al., 1988; Murphy et al., 1989]. The peak anxiolytic effect of buspirone may not be felt before 4–6 weeks of treatment [Tyrer et al., 1985].

Our study does not exhibit differences in antidepressant activity between buspirone and oxazepam. This contradicts preliminary trials suggesting that buspirone may exhibit antidepressant properties, at least in nonendogenous depressive patients [Schweizer et al., 1986]. It should be noted, however, that the patients included in our study fulfilled DSM-III criteria for generalized anxiety and that a severe depressive symptomatology was an exclusion criterion.

In our study, the rate of side effects does not differ between buspirone and oxazepam. This contrasts with previous comparisons with other benzodiazepines showing better tolerance of buspirone, particularly for the sedative effect [Newton et al., 1986]. A possible explanation is that oxazepam exhibits less sedative side effects than more potent benzodiazepines such as diazepam, lorazepam, or clorazepate.

This study does not show differences in withdrawal symptoms following abrupt discontinuation of buspirone and oxazepam given for 6 weeks. This contrasts with previous comparisons of the withdrawal phenomena of buspirone with other benzodiazepines such as diazepam or clorazepate [Rickels et al., 1988; Murphy et al., 1989]. These data suggest that the potential for dependence of oxazepam is low, confirming previous opinions [Tyrer, 1988]. Indeed, if oxazepam has a short half-life, it is a low-potency benzodiazepine, thus withdrawal responses could possibly not be expected to occur after only 6 weeks of therapy. The small number of patients included in our study, and particularly during the withdrawal period (7 on buspirone and 8 on oxazepam), prevents however definitive conclusions.

Finally, our study does not answer the important question related to the type of patients who will exhibit good response to buspirone. Obviously, some patients do very well on buspirone and some do not. Since the clinical improvement with buspirone may take as long as 4–6 weeks, it seems of the highest importance to define predictors for treatment response, particularly in view of the obvious advantage of buspirone with regard to abuse potential.

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