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Etizolam in the Treatment of Generalized Anxiety Disorder: a Controlled Clinical Trial

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A total of 45 patients with generalized anxiety disorder were treated twice daily for 2 weeks, on a double-blind basis, with 0.5 mg etizolam, 0.5 mg alprazolam or 3 mg bromazepam, and symptoms were assessed using Hamilton's rating scale for anxiety and Hamilton's rating scale for depression. Patients then received the same drug for a further 2 weeks, the drugs being given three times daily if a poor response was observed during the first 2 weeks. All drugs displayed equivalent anxiolytic activity after 2 weeks, but etizolam displayed a progressive increase in anxiolytic activity over 4 weeks of treatment. Etizolam also possessed a more marked antidepressant effect than did alprazolam or bromazepam. There were no differences in the tolerability of the three drugs.

KEY WORDS: Generalized anxiety disorder; etizolam; alprazolam; bromazepam.

INTRODUCTION

Generalized anxiety disorder is characterized by diffuse and persistent anxiety, motor tension, autonomic hyperactivity, a state of apprehension and increased vigilance and alertness.[1] Not infrequently the fragile emotional balance (i.e. immaturity and poorly structured personality) of patients with this syndrome becomes impaired, resulting in the subject developing symptoms of depression.[2]

The syndrome requires both psychotherapeutic and pharmacological treatment, with benzodiazepines playing an important role.[3] The large number of benzodiazepines now available may make the selection of a suitable drug difficult given that a difference among the various members of this class of compounds, as far as drug action is concerned has not been firmly established. Some bendoziazepines, however, have been shown to have unusual properties; in particular, bromazepam and alprazolam have pharmacological effects similar to those of some antidepressants.[4,5]

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Theoretically, these benzodiazepines may be useful in the treatment of generalized anxiety disorder.

Another benzodiazepine derivative with antidepressant activity – etizolam – has been recently developed. Etizolam is a thienotriazolodiazepine comprising a thiophenic ring and a thiazolic ring. The thiophenic ring makes etizolam easily oxidized and, hence, easily metabolized. Following oral administration, etizolam reaches peak plasma concentration within 3 h. Thereafter it is rapidly excreted in the urine after being metabolized; its clearance half-life is about 6 h (Shibata M, unpublished).[6 - 8] During breakdown of etizolam five intermediate metabolites have been identified, of which only one, the hydroxymethylated derivative, with a half-life of 15 h, appears to make a slight con-tribution to the therapeutic activity of etizolam (Shibata M, unpublished).

Screening has shown that etizolam has low toxicity,[9,10] but an unusual feature of the drug is its effect on monoamine metabolism. In rat brain it has been shown to reduce serotonin turnover and to antagonize stress-induced increases in serotonin, noradrenaline and dopamine turnover.[11] In mouse brain etizolam has been shown to inhibit noradrenaline uptake.[12] The pharmacological similarity of the anti-depressant activity of etizolam with that of tricyclic drugs has been confirmed by computerized electroencephalograph analysis.[12,13] The effect of etizolam has also been documented at the clinical level.[14 - 17]

Based on the above considerations, it was thought that it would be of particular interest to study, within a controlled clinical trial, the effect of etizolam in the treatment of generalized anxiety disorder and to compare it with bromazepam and alprazolam.

PATIENTS AND METHODS

Patients

A total of 45 patients of both sexes (32 female, 13 male; aged 18 – 60 years) with generalized anxiety disorder, as defined under DSM-III-R 300.02,[1] were selected to participate in the study. Patients initially chosen had a Hamilton's rating scale for anxiety (HRSA) total score of not less than 20 and a Hamilton's rating scale for depression (HRSD) total score of not less than 16. Patients finally included in the trial were those who were still presenting following a 1-week washout period and who had total scores measured using HRSD and HRSA of not less than 18 and 14, respectively.

Patients with psychotic or epileptic episodes, or mental retardation, as well as cardiac, renal, hepatic, neurological or gastro-intestinal disorders of such severity as might interfere with the effects of the drugs under study, were excluded from the trial. Pregnant women and patients with severe myasthenia and abusers of alcohol or psychoactive drugs were also excluded.

Trial design and dosages

The trial consisted of a 1-week washout phase using a placebo on a single-blind basis, followed by a 2-week phase during which 15 patients were assigned to each of the following treatment groups: 0.5 mg etizolam twice daily; 0.5 mg alprazolam twice daily; or 3 mg bromazepam twice daily. The drugs were administered at 8.00 a.m. and 8.00 p.m. each day. Patients were then submitted to a third phase of 2 weeks' duration in which the drugs used remained the same, but the dose was given three times daily in cases where the total HRSA and HRSD scores at the end of the previous 2 weeks did not show a reduction of at least 25% compared with the values recorded at the end of the washout phase. If a reduction of more than 25% occurred the dosage was not increased.

Clinical assessment

The condition of patients was rated by two independent observers – mean scores being

established in the case of disagreement – using HRSA, HRSD and Covi's anxiety scale on entry to the trial, after the washout phase, on completion of the first 2 weeks of drug treatment and at the end of the trial (i.e. after 4 weeks' treatment).

On completion of treatment patients were asked to express a global judgement on drug treatment according to a four-point scale. Any side-effects spontaneously reported by patients were also recorded. At the end of the trial, patients were also asked to assess drug tolerability on a four-point scale from 1 to 4 (from poor to excellent).

Statistical evaluation

Results were statistically evaluated using Student's *t*-test for paired and between group data. In addition, the χ^2-test and the Mann-Whitney *U*-test were performed utilizing SPSS-PC software on an IBM-AT PC.

RESULTS

Compared with baseline, alprazolam, bromazepam and etizolam significantly ($P<0.001$) reduced HRSA total score after treatment for 14 days (Table 1) by 39.1%, 37.3% and 36.8%, respectively. The values of HRSA were also significantly ($P<0.001$) reduced after treatment for a further 14 days by 48.2%, 42.7% and 47.3%, respectively, compared with baseline.

Alprazolam and etizolam significantly ($P<0.001$) reduced HRSD total score after 14 days (Table 2) by 21.2% and 17.2%, respectively, and bromazepam significantly

Table 1
Hamilton's rating scale for anxiety total score measured at different times in patients with generalized anxiety disorder receiving benzodiazepines (mean values ± SD)

Drug	After washout	Duration of treatment	
		14 days	28 days
Alprazolam	47.3 ±2.4	28.8 ±0.76[a]	24.5 ±3.0[a,b]
Bromazepam	44.0 ±1.3	27.6 ±2.1[a]	25.2 ±1.4[a,b]
Etizolam	45.7 ±1.9	28.9 ±2.3[a]	24.1 ±1.6[a,b]

[a]$P<0.001$ versus washout.
[b]$P<0.001$ versus day 14.

Table 2
Hamilton's rating scale for depression total score measured at different times in patients with generalized anxiety disorder receiving benzodiazepines (mean values ± SD)

Drug	After washout	Duration of treatment	
		14 days	28 days
Alprazolam	31.6 ±2.8	24.9 ±4.3[a]	23.5 ±5.6[a,c]
Bromazepam	33.8 ±2.0	31.4 ±2.2[b]	30.6 ±2.2[b,c]
Etizolam	34.3 ±0.6	28.4 ±1.9[a]	27.1 ±2.5[a,c]

[a]$P<0.001$ versus after washout.
[b]$P<0.01$ versus after washout.
[c]Non-significant versus day 14.

($P<0.01$) reduced HRSD total score after 14 days by 7.1%. The reduction in HRSD total score was maintained following treatment for another 14 days, but there were no further significant increases in the antidepressant effect. A summary of the comparison of the anxiolytic and antidepressant effects of alprazolam, bromazepam and etizolam assessed using Student's *t*-test applied to HRSD and HRSA is given in Table 3.

Comparison of the three drugs was also undertaken using Covi's anxiety scale. After 14 days' treatment, the three drugs produced equivalent anxiolytic effects. After 28 days, however, etizolam showed a significantly greater anxiolytic effect compared with bromazepam ($P=0.0016$) and alprazolam ($P=0.0328$), using the Mann – Whitney *U*-test; the anxiolytic effects of bromazepam and alprazolam were equivalent ($P=0.1974$). Alprazolam induced a statistically significantly greater anxiolytic effect than bromazepam when the effects of 28 days' treatment were compared to 14 days.

There was no significant difference in tolerability between the three drugs. Tolerability was rated as 'excellent' in all but two cases, both of whom had received etizolam; those patients rated etizolam as 'good' due to the development

Table 3
Comparison of the effect of alprazolam, bromazepam and etizolam in generalized anxiety disorder

Day 14 versus baseline	Day 28 versus baseline	Day 28 versus day 14
Hamilton's rating scale for anxiety		
Alprazolam = bromazepam	Alprazolam = bromazepam	Alprazolam = bromazepam
Etizolam = alprazolam	Etizolam > alprazolam[a]	Etizolam > alprazolam[c]
Etizolam = bromazepam	Etizolam = bromazepam	Etizolam > bromazepam[c]
Hamilton's rating for depression		
Alprazolam > bromazepam[a]	Alprazolam > bromazepam[a]	Alprazolam = bromazepam
Etizolam > alprazolam[b]	Etizolam > alprazolam[b]	Etizolam = aprazolam
Etizolam > bromazepam[b]	Etizolam > bromazepam[b]	Etizolam = bromazepam

[a] $P<0.001$
[b] $P<0.01$
[c] $P<0.05$

Table 4
Global effectiveness rating in the three treatment groups

	Incidence (%)		
Effectiveness	**Bromazepam**	**Alprazolam**	**Etizolam**
Excellent	33.3	13.3	40.0
Good	33.3	73.3	33.3
Fair	33.3	13.3	26.7

No significant differences between the drugs.

of asthenia.

The global effectiveness ratings of alprazolam, bromazepam and etizolam as assessed by the patients on completion of treatment were not statistically different (Table 4).

DISCUSSION

Generalized anxiety disorder, as defined by DSM-III-R,[1] consists of chronic anxiety associated, in most cases, with somatic and depressive symptoms. It is not easy to define precisely the prevalence of the syndrome, which sometimes maintains itself at the sub-clinical level. It is also difficult to establish prevalence because the syndrome is often judged differently by general practitioners and psychiatrists. A recent study showed that the prevalence of the syndrome in the general population was 2.5%.[18]

The most efficacious pharmacological treatment of the disorder is based on the use of benzodiazepine-derived compounds.[19] A wide range of benzodiazepines is available and it has been generally believed that the only difference between these compounds is at the pharmacokinetic level.[20] It would not seem to be important, therefore, which benzodiazepine is used to treat generalized anxiety disorder provided that its pharmacokinetics are satisfactory.

Recently, however, certain benzodiazepines have been developed which have different pharmacokinetic properties. Included among this new range are alprazolam and etizolam, which have been shown to possess antidepressant activity.[4,11] Owing to the antidepressant activity of these drugs they may be particularly suitable for the treatment of patients suffering from generalized anxiety disorder with its associated depression.

The results of this study confirm that bromazepam, alprazolam and etizolam have anxiolytic activity. The study also shows that etizolam and alprazolam exhibit an appreciable antidepressant effect at a clinical level. The anxiolytic effect of all three drugs was apparent after 2 weeks' treatment and was increased after a further 2 weeks. The antidepressant effect of etizolam and alprazolam was also apparent after 2 weeks, but displayed no further increase thereafter.

Tolerability appears to be quite acceptable for all three drugs tested, with no differences between etizolam, alprazolam and bromazepam.

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