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A DOUBLE-BLIND, CONTROLLED EVALUATION OF THE EFFICACY AND ADVERSE EFFECT PROFILE OF SUSTAINED-RELEASE ALPRAZOLAM

CHITTARANJAN ANDRADE, ANITHA ASWATH, S.K. CHATURVEDI, R. RAGURAM & AJIT BHIDE

ABSTRACT

In a double-blind, prospective study, 40 patients diagnosed with DSM-IV generalized anxiety disorder and stabilized on alprazolam therapy were randomized to receive the same dose of either conventional or sustained-released alprazolam for two weeks, followed by the other formulation of alprazolam in an identical dose for a further two weeks. Conventional alprazolam was administered thrice daily while the sustained-release formulation was administered once-daily, in the morning. Thirty four patients completed the study. Recruitment into the study was associated with a significant decrease in all measures of illness severity; however, no efficacy differences between the two forms of alprazolam were observed. Adverse effects, specifically insomnia, were reported more with the sustained-release formulation. It is concluded that once-daily sustained-release alprazolam is as effective as the conventional form of the drug, and may be preferable because of a wide range of advantages; in this study, the higher incidence of adverse effects with the sustained-release drug was probably an artefact of the experimental design, which fostered a (nighttime) state of partial drug withdrawal.

Key words : Alprazolam, sustained-release alprazolam, generalized anxiety disorder, drug trial

Alprazolam is a triazolobenzodiazepine which is effective in the management of several disorders, chiefly generalized anxiety, panic and depression (Andrade,2000). A disadvantage of alprazolam is that its anxiolytic efficacy wears off faster than its blood levels drop. Therefore, thrice or even 4 times daily dosing may be necessitated, despite which interdose anxiety is some times a clinical problem (Schweizer et al., 1993). Such repeated daytime dosing is associated with sedation, cognitive slowing, psychomotor slowing, and other adverse effects that accompany the dose peaks. Repeated daytime dosing is also inconvenient, can be embarrassing at the patient's places of work, and predisposes to poor compliance and the consequences thereof. Finally, repeated daytime dosing repeatedly reminds the patient about his illness. There therefore appears to be a need for a sustained-release preparation of alprazolam.

In previous research, conducted in patients with panic disorder, sustained-release alprazolam was found to be as effective as conventional alprazolam; the sustained-release formulation was also well-tolerated (Schweizer et al.,1993; Pecknold et al.,1994; Figueira,1995). Additionally, the sustained-release formulation was observed to be associated with a more favourable withdrawal profile (Schweizer et al., 1993), and with a smaller risk for relapse (Pecknold,1993).

To the best of the authors' knowledge, India is the only country in which a sustained-release preparation of alprazolam is

commercially available (since 1998). The present study therefore sought to assess the anxiolytic efficacy and the adverse effect profile of sustained-release alprazolam, in comparison with the conventional formulation of the drug.

MATERIAL AND METHOD

The sample comprised consecutive outpatients diagnosed with Generalized Anxiety Disorder (DSM-IV; American Psychiatric Association,1994), recruited from a psychiatric hospital and from the psychiatry department of a general hospital in an urban setting in South India. To be eligible for selection into the study, all patients had to have been receiving conventional alprazolam therapy for a minimum of 2 weeks, at a dose that was considered clinically appropriate by the treating psychiatrist. Only patients stabilized on their individual regimes at an alprazolam dose of either 0.75 or 1.5 mg per day were considered for recruitment. Further selection criteria included an absence of alcohol and/or substance abuse, and an absence of significant medical and/or psychiatric comorbidity that might have influenced either diagnosis of anxiety or response to alprazolam. The research protocol was approved by the Ethics Committee in the institution of the first author, and all patients provided written informed consent for participation in the study.

Recruited subjects were randomized to receive either conventional or sustained-release alprazolam, in the same dose as at intake, for two weeks. Subsequently, they received the other formulation of alprazolam, again in the same dose, for a further two weeks. No other psychotropic medication was permitted during the study.

Conventional alprazolam was administered in capsule form, in the dose of 0.25 or 0.5 mg (as applicable) thrice a day. Sustained-release alprazolam was also administered in capsule form, once in the morning. Lactose placebo was administered as capsule in the afternoon and night during the sustained-release phase of therapy. All capsules were identical in appearance, and the number of capsules at each time of day, and during each phase of therapy, was the same.

The sustained-release form of drug, as described by the manufacturers, releases about 15% of its contents during the first hour, and about 7-8% per hour thereafter. Release is substantially complete 10-14 hours after oral administration. The structure of release thus permits once daily dosing. When the dose is administered in the morning, relatively uniform blood levels are maintained during the day; levels drop at night, during sleep, when the experience of anxiety is rare.

Patients were rated at baseline, after two weeks of one form of alprazolam, and after a further two weeks on the other form of alprazolam, using the Hamilton Rating Scale for Anxiety (Bech et al.,1986), and using a Global Rating Scale. The latter was assessed by the patient and by the rater separately, with assessment points anchored as follows, and with decimal ratings encouraged : 0=no symptoms, 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms; 4=very severe symptoms. Adverse effects were assessed after each phase of alprazolam therapy using the Systematic Assessment for Treatment Emergent Effects (SAFTEE; Levine and Schooler,1986) checklist.

Neither patients nor rater were aware of the initial or final treatment assignment. The study was therefore double-blind.

Statistical methods : Means were compared between groups using the independent sample Student's 't' test. Means were compared within the same subjects across time using repeated measures multivariate analysis of variance (RMANOVA) with Pillai's trace as the statistical criterion. Means from non-normal distributions were compared within the same subjects across two time points using the Wilcoxon signed ranks test. Preference for a particular drug at endpoint, or experience of a particular adverse effect, was assessed using the Chi square test with the assumption of equal proportions. All hypotheses,

wherever applicable, were two-tailed. Alpha for significance was set at $p<0.05$.

RESULTS

The sample comprised 40 subjects aged 18-55 years, with a mean (standard deviation) [M(SD)] age of 37.8 (8.81) years. There were 22 males and 18 females. The M(SD) age of the males was 37.8 (9.4) years, while that of the females was 37.8 (8.4) years. The difference was not statistically significant (t=0.01, d.f.=38, NS).

The duration of illness in the sample ranged from 6 to 96 months, with a M(SD) of 36.5 (18.1) months. The duration of prior alprazolam exposure ranged from 2 to 36 weeks, with a M(SD) of 11.6 (8.9) weeks.

Thirty-two (80%) patients were receiving alprazolam 0.75 mg per day, while 8 (20%) were receiving alprazolam 1.5 mg/day. Eighteen (45%) patients had been randomized to receive conventional alprazolam first, while the remaining 22 (55%) had been randomized to receive sustained-release alprazolam first.

Four patients dropped out of the study during the conventional alprazolam assessment phase, while 2 dropped out during the sustained-release alprazolam phase. Data from the remaining 34 patients were available for final efficacy and adverse effect analyses.

The anxiety and global ratings at different time points of assessment are presented in table-1. There was a significant reduction in Hamilton anxiety ratings after induction into the study (Pillai's trace=0.47, f=14.00, d.f.=2,32, $p<0.001$); ratings however did not differ significantly between conventional and sustained-release formulations. There was a significant reduction in patients' global ratings of illness severity after induction into the study (Pillai's trace=0.53, f=18.39, d.f.=2,32, $p<0.001$); again, ratings did not differ significantly between conventional and sustained-release formulations. Finally, there was a significant reduction in the rater's global ratings of illness severity after induction into the study (Pillai's trace=0.20, f=3.90, d.f.=2,32, p=0.03); once again, ratings did not differ significantly between conventional and sustained-release formulations.

TABLE 1
M (SD) ANXIETY AND GLOBAL ILLNESS RATINGS AT BASELINE, AFTER CONVENTIONAL ALPRAZOLAM AND AFTER SUSTAINED-RELEASE ALPRAZOLAM

Variable	Baseline	After conventional alprazolam	After sustained-release alprazolam
Hamilton anxiety score	18.0 (5.4)	14.4 (5.7)	15.2 (6.3)
Global rating (by patient)	1.8 (0.6)	1.2 (0.6)	1.3 (0.8)
Global rating (by rater)	1.3 (0.6)	1.2 (0.4)	1.1 (0.7)

TABLE 2
ADVERSE EFFECTS REPORTED BY PATIENTS (N=34) RECEIVING CONVENTIONAL AND SUSTAINED-RELEASE ALPRAZOLAM

Adverse effect	Conventional alprazolam	Sustained-release alprazolam
Headache	8	10
Insomnia	2	16
Sedation	2	2
Anxiety	8	12
Cognitive problems	0	3
Weakness	0	2
Somatic complaints	3	2

The M(SD) number of adverse effects reported by the patients was 0.7 (1.0) with conventional alprazolam, and 1.4 (1.0) with the sustained-release formulation; the difference was statistically significant (Wilcoxon signed rank test, z=2.73, p=0.006). A qualitative analysis of adverse effects is presented in table 2. Insomnia, commoner with sustained-released alprazolam, was the only adverse effect to significantly differentiate the two formulations (X^2=10.89, d.f.=1, $p<0.001$).

Twenty (50%) subjects preferred the convention formulation of alprazolam while 12 (30%) preferred the sustained-release formulation. Two (5%) subjects offered no preference. Preference for conventional alprazolam did not differe significantly from that for the sustained-release drug (X^2=2.00, d.f.=1, NS).

DISCUSSION

This study found that anxious patients stabilized on alprazolam therapy experienced further improvement when recruited for research, although no dose changes had been effected, nor additional psychological or biological interventions instituted. It is likely that nonspecific factors or a placebo effect were responsible for the improvement; such responses are well known in both anxiety (Londborg et al.,1998; Andrade et al.,2000) and depressive (Weiss et al.1997) disorders.

There was no significant difference obtained in efficacy ratings (on any measure) between conventional (thrice daily) and sustained-release (once-daily) formulations of alprazolam. This suggests that the sustained-release drug is as effective as the conventional formulation, and can conveniently substitute for it in clinical practice because of the variety of advantages that it purveys. These advantages include a smoother onset of action, a more sustained effect due to the maintenance of uniform blood levels, less adverse effects (such as sedation, cognitive slowing and psychomotor slowing) associated with dosage peaks, less inconvenience/embarrassment at the workplace and better compliance due to once-daily administration, and lesser emphasis of illness due to once-daily administration (Andrade,1999). Regrettably, the psychosocial advantages of once-daily dosing could not be empirically studied in the present investigation because of the need for double-blindness, which necessitated afternoon and nighttime dosing (with placebo) even during the sustained-release phase of therapy.

Previous research, conducted in patients with panic disorder, showed that once-daily sustained-release alprazolam was as effective and as well-tolerated as thrice-daily conventional alprazolam (Schweizer et al.,1993; Pecknold et al.,1994). One study, conducted on patients with generalized anxiety disorder, found that once-daily sustained-release alprazolam was as affective and as well-tolerated as thrice-daily bromazepam (Figueira,1995). To the best of our knowledge, this is the first study to compare the two formulations of alprazolam in a crossover design.

In this study, treatment with sustained-release alprazolam was associated with significantly more adverse effects. Only insomnia was present significantly more commonly with the sustained-release form. This was probably an artefact of the research design. Patients had been stabilized on thrice-daily conventional alprazolam therapy prior to intake; thus, all had been receiving nighttime alprazolam, and had been conditioned to a nighttime peak in the blood level of the drug. During the sustained-release phase, alprazolam therapy was limited to a single morning dose. The pharmacokinetics of the formulation resulted in terminal absorption by evening; this would necessarily be followed by a drop in blood levels at night. As a consequence, the patient would experience a state of relative drug withdrawal at night, in contrast with his prior experience of a peak in blood levels with the nighttime dose of conventional alprazolam. The result would be insomnia with the sustained-release drug.

This experience suggests that alprazolam therapy should ideally be directly initiated with the sustained-release formulation in order to prevent prior habituation to a night time peak in blood levels of the drug; or, in patients already on conventional alprazolam, and in those already experiencing insomnia, twice-daily dosing with the sustained-release formulation may be considered. A nighttime dose of the sustained-release formulation may also be considered in patients who report anxiety or panic during the night or early morning, at which time alprazolam levels are low.

Interestingly, no patient reported early morning anxiety during the sustained-release alprazolam phase, indicating that the decrease in drug levels during the night and early morning is not associated with breathrough anxiety. This finding underlines the acceptability of once-daily dosing, which is a major advantage with the sustained-release formulation. This finding also

draws attention to the need to study psychobiological phenomena which are associated with diurnal variations in anxiogenesis.

Greater sedation with conventional alprazolam was expected but not observed in this study. One explanation is that the doses used in this study were relatively low compared to those common in panic disorder. Another explanation is that patients were stabilized on conventional alprazolam therapy before intake; this meant that their doses would have been adjusted for maximum efficacy and minimum adverse effects, and that tolerance to the sedative adverse effects would already have developed.

Although numerically more subjects favoured the use of the conventional formulation, this finding did not attain statistical significance, perhaps because of a type 2 error arising from the small sample size. The numerical preference for the conventional formulation may have due to the 'relative withdrawal' type of adverse effects referred to earlier.

In conclusion, once-daily sustained-release alprazolam was as effective as thrice-daily conventional alprazolam; the greater experience of adverse effects (particularly insomnia) with the sustained-release formulation was probably an artefact of the experimental design, which fostered a state of relative drug withdrawal at night during the sustained-release drug phase. Sustained-release alprazolam, administered once or twice daily, may be a useful therapeutic strategy for the management of anxiety disorders, in view of the pharmacokinetic and psychosocial advantages that it carries.

Future research could be directed to the study of drug-naive patients, to demonstrate the possible better tolerability and acceptance of sustained-release alprazolam. Naturalistic studies could examine issues such as long-term efficacy, compliance and withdrawal. Of particular interest in the context of discontinuation of sustained-release alprazolam therapy is the possibility of lowered risk for withdrawal symptoms, rebound, and relapse in patients with generalized anxiety disorder, as has been reported in patients with panic disorder (Schweizer et al.,1993; Pecknold,1994).

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CHITTARANJAN ANDRADE, MD, Additional Professor & Head, ANITHA ASWATH, MA, Research Assistant, Department of Psychopharmacology, S.K. CHATURVEDI, MD, Additional Professor, Department of Psychiatry, R. RAGURAM, MD, Additional Professor, National Institute of Mental Health and Neurosciences, Bangalore-560 029, AJIT BHIDE, MD, Chief Consultant, Department of Psychiatry, St. Martha's Hospital, Bangalore-560 009.*

** Correspondance*