META-ANALYSIS OF THE SAFETY AND TOLERABILITY OF TWO DOSE REGIMENS OF BUSPIRONE IN PATIENTS WITH PERSISTENT ANXIETY

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Buspirone is an azapirone with 5-HT$_{1A}$ partial agonist activity which has demonstrated efficacy in the treatment of generalized anxiety disorder, commonly referred to as persistent anxiety. In this meta-analysis report, safety results from two studies comparing buspirone 15 mg twice daily (BID) with buspirone 10 mg three times daily (TID) in patients with persistent anxiety are presented. In the study protocols, qualified patients completed a 7-day placebo lead-in phase and were randomized to receive buspirone 30 mg per day, as either a BID or TID regimen, for 6-8 weeks. A total of 289 patients received buspirone 15 mg BID (n=144) or 10 mg TID (n=145) at 15 sites. The incidence of adverse events was similar between the two treatment groups, except for a significantly greater incidence of palpitations in patients receiving buspirone BID (5%) compared to buspirone TID (1%). The most frequently reported adverse events for both buspirone BID- and TID-treated patients were dizziness, headache, and nausea. No appreciable differences between treatments were observed for vital signs, physical exam, ECG, or clinical laboratory results. A change to BID dosing for buspirone may offer convenience and possibly higher compliance in patients with persistent anxiety without compromising the excellent safety and tolerability profile of the medication. Depression and Anxiety 9:131–134, 1999.

Key words: ***anxiolytic; generalized anxiety disorder; 5-HT$_{1A}$ partial agonist; Hamilton Anxiety Scale (HAM-A); clinical trial***

INTRODUCTION

Buspirone is an azapirone with 5-HT$_{1A}$ partial agonist activity which has demonstrated efficacy in patients with generalized anxiety disorder, commonly referred to as persistent anxiety [Feighner, 1987; Feighner and Cohn, 1989]. Advantages of buspirone over the benzodiazepine class of anxiolytics include its favorable safety profile for long term use, lack of abuse and dependence potential, and lack of withdrawal reactions [Shuckit, 1984; Lader, 1991; Pecknold, 1997]. In addition, buspirone maintains cognitive functioning, psychomotor skills, and alertness, producing no more sedation than placebo [Lader, 1982; Cohn and Wilcox, 1986; Mattila et al., 1986]. The current recommended minimum effective dosage of buspirone is 30 mg/day in divided doses, with a therapeutic dose range of 30 to 60 mg/day. Due to its relatively short half-life of 2-11 hours [Gammans et al., 1986], buspirone has been administered on a three times daily (TID) dose regimen in most studies, and thus has been prescribed largely on a TID basis in clinical practice as well.

Few studies have examined the safety of buspirone on a less frequent (twice-daily; BID) dosing schedule. Two studies compared buspirone at doses of 5 mg TID and 10 mg BID and found no differences in safety; however, two different total daily doses were evaluated [Zelfelder, 1990; Fontaine and Napoliello, 1993]. More recently, a double-blind study comparing buspirone 15 mg BID and 10 mg TID reported no appreciable differences in safety or efficacy between the two treatment groups, with patients achieving significant improvement on the Hamilton Anxiety Scale (HAM-A) and Clinical Global Impressions with both regimens [Sramek et al., 1997].

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Received for publication 27 August 1998; Accepted 29 January 1999

Several studies have suggested that patient compliance may be improved with less frequent dosing schedules [Blackwell, 1973; Boyd et al., 1974; Fischer, 1990; Greenberg, 1984]. Thus, a BID dosing schedule may potentially enhance compliance in patients with persistent anxiety without compromising the excellent safety and tolerability profile of buspirone. Compliance is of particular concern in the treatment of persistent anxiety, which is typically a chronic disorder requiring long-term therapy. In this meta-analysis report, pooled safety results from a comparative study of buspirone 15 mg BID and buspirone 10 mg TID in patients with persistent anxiety [Sramek et al., 1997], and a placebo-controlled study of these two dose regimens, are presented. We hypothesized that BID buspirone dosing would have a similar safety profile to TID dosing.

METHODS

A meta-analysis of two double-blind studies (one placebo-controlled) was conducted to evaluate the safety and tolerability of two dose regimens of buspirone. One of these studies has previously been published elsewhere [Sramek et al., 1997]. Both studies were similar in design. Male and female patients with persistent anxiety, ages 18-65 years, were eligible to participate in these double-blind, single-center and multicenter randomized trials examining the safety and efficacy of two dose regimens of buspirone: 15 mg BID compared to 10 mg TID and placebo (one study). All protocols were approved by an Institutional Review Board, and all patients gave written and oral consent prior to the study.

In both of these studies, patients were required to meet DSM III-R criteria for persistent anxiety, modified to include those patients with a symptom duration of four or more weeks [American Psychiatric Association, 1987]. Patients were also required to have a HAM-A total score of at least 18 [Hamilton, 1959], an "anxious mood" item score of at least 2 and a "tension" item score of at least one on the HAM-A, a Covi Anxiety Scale score of at least 8, and a Covi score exceeding a Raskin Depression Scale score at baseline. Females of child-bearing potential were required to be on adequate birth control throughout the study.

Patients were excluded if they had a concurrent DSM III-R Axis I disorder, a history of two or more discrete panic attacks within four weeks of the beginning of screening, a Hamilton Depression Scale (HAM-D) [Hamilton, 1967] total score less than 4 points below their HAM-A score, a total HAM-D score of 18 or more, a "depression" item score of 3 or more on the HAM-D, or a Raskin Depression Scale score of 8 or more at screening. Patients were also excluded if they were unable to discontinue the use of psychotropic drugs (including fluoxetine) one month prior to randomization, had been treated with benzodiazepines or MAO inhibitors for a total of 14 days or more in the two months prior to screening, required treatment with other prohibited concomitant medications, or received an investigational drug within one month prior to screening. Patients could not have any known allergy or hypersensitivity to buspirone or other azapirones; significant cardiovascular, gastrointestinal, renal, hepatic, hematologic, neurologic, or pulmonary disease; cancer; a history of current or recent (within one year) drug abuse; a positive urine drug test for benzodiazepines at screening; ECT within three months; or a previous inadequate therapeutic response to buspirone.

Following a 7-day placebo lead-in phase, those patients who demonstrated no more than a 25% improvement or a 50% worsening in HAM-A total score from screening were randomized to receive buspirone 15 mg BID, 10 mg TID, or placebo (in one protocol) for a treatment period of 6-8 weeks. Buspirone was titrated from an initial dosage of 15 mg per day (5 mg TID) to the target treatment dose of 30 mg per day over the first week; dose titration was 5 mg per day every 2-3 days. At the beginning of the second week, patients were switched to either a BID or TID dosing regimen. No patients were started on the BID schedule because 7.5 mg tablets were not available, and we wished to initiate treatment at the same dose for all patients. Adverse events were recorded every two weeks by study personnel who asked open-ended questions about how patients were feeling. Throughout the study, including the placebo lead-in phase, all patients received medication as 3 tablets three times a day. Patients randomized to buspirone 15 mg BID received placebo tablets for the mid-day dose and patients randomized to placebo (one study) received 3 placebo tablets three times a day.

Patients were not allowed to take any investigational drugs or psychotropic medications during the study period, with the exception of infrequent p.r.n. use of chloral hydrate (0.5 to 1.5 g for insomnia) or antihistamines.

The comparative incidence of adverse events between the buspirone BID and TID treatment groups were analyzed using Fisher's Exact Test. Safety parameters were tested at $\alpha<0.05$.

RESULTS

A total of 289 patients (147 males, 142 females) received buspirone 15 mg BID (n=144) or 10 mg TID (n=145) at 15 sites. There were no significant differences between the two treatment groups in demographic characteristics (Table 1). There were no significant differences in overall discontinuation rates between the two treatment groups, although the TID treatment group had a greater number of patients discontinue treatment because of adverse events compared to the BID treatment group (13% vs 10%). Buspirone was well tolerated on both dosage regimens, with the majority of adverse events reported as mild in intensity. No serious adverse events were observed in any treatment group. The incidence of adverse events

TABLE 1. Summary of demographic information

	Buspirone BID n (%)	Buspirone TID n (%)	Placebo n (%)
Sex			
Male	71 (49.3)	76 (52.4)	27 (36.5)
Female	73 (50.7)	69 (47.6)	47 (63.5)
Ethnicity			
White	100 (69.4)	104 (71.7)	60 (81.1)
Black	14 (9.7)	17 (11.7)	7 (9.5)
Asian	3 (2.1)	5 (3.5)	0 (0)
Hispanic	26 (18.1)	16 (11.0)	6 (8.1)
Other	1 (0.7)	3 (2.1)	1 (1.3)
Age			
N	144	145	74
Mean (SE)	34.4 (0.84)	35.5 (0.85)	36.5 (1.22)
Min.	18	19	18
Max.	63	62	64

occurring in a total of 5% or more of patients in either treatment group are listed in Table 2. For all reported adverse events, only one statistically significant difference between the two treatment groups was observed: seven patients (5%) reported palpitations with BID dosing compared to one patient (1%) with TID dosing ($P<0.05$). This adverse event occurred in patients who had previously reported palpitations in relation to their anxiety; thus, this finding was not thought to be clinically significant.

Although only one of the studies in this analysis included a placebo group, data from these patients indicated that the incidence of the most commonly observed adverse events was lower in the placebo group (n=74) in comparison to either buspirone regimen (4%, 28%, 9%, 0%, 0% for dizziness, headache, and nausea, pharyngitis, and infection, respectively; $P<0.05$ placebo versus buspirone BID or TID). Headache, nausea, and somnolence (incidence of 8% for each) were the most common adverse events for placebo-treated patients.

There were no significant differences between the buspirone BID and TID treatment groups in vital signs, physical exams, clinical laboratory measures, or ECG results.

TABLE 2. Number of patients (%) experiencing adverse events†

Adverse event	Buspirone BID (n=144)	Buspirone TID (n=145)	Placebo (n=74)
Dizziness	85 (59)	78 (54)	3 (4)*
Headache	70 (49)	66 (46)	21 (28)*
Nausea	33 (23)	35 (24)	7 (9)*
Somnolence	17 (12)	13 (9)	6 (8)
Pharyngitis	14 (10)	16 (11)	0 (0)*
Rhinitis	14 (10)	8 (6)	2 (3)
Infection	14 (10)	18 (12)	0 (0)*
Insomnia	13 (9)	11 (8)	5 (7)
Dyspepsia	11 (8)	17 (12)	2 (3)
Nervousness	10 (7)	5 (3)	2 (3)
Diarrhea	7 (5)	15 (10)	5 (7)
Palpitations	7 (5)	1 (1)**	1 (1)
Vomiting	7 (5)	4 (3)	1 (1)
Asthenia	4 (3)	9 (6)	4 (5)

P<0.05 compared to BID or TID.*

***P*<0.05 compared to BID.*

†*Adverse events with a total occurrence rate of 5% or more in either treatment group are shown.*

DISCUSSION

As this meta-analysis is based on a database of nearly 300 patients, it is possible to confidently assess the safety and tolerability of BID compared to TID dosing with buspirone. Buspirone 15 mg BID was well tolerated, with a safety profile virtually indistinguishable from that of buspirone 10 mg TID. No clinically significant differences in the incidence of adverse events were observed between the two dosage regimens.

This report confirms that the most common adverse events associated with buspirone are dizziness, headache, and nausea. The incidence of these adverse events in this report is higher than that observed in previous studies (12%, 6%, and 8% for dizziness, headache, and nausea, respectively [Physicians Desk Reference, 1997]). This difference is potentially due to the higher dose of buspirone employed in the BID/TID studies (30 mg per day), as compared to the doses used in previous studies (10 to 30 mg per day); in a separate study of patients receiving doses of 30 to 45 mg/day, the incidence of adverse events was similar to the results in this report [Sramek et al., 1996]. Adverse events experienced by patients were typically mild and generally did not lead to discontinuation.

Higher compliance with BID than with TID dosing has been reported previously for anti-hypertensive agents [Eisen et al., 1990; Boissel et al., 1986]. BID dosing schedules were also associated with better compliance than more frequent schedules for anti-seizure medication [Zaccara and Galli, 1979; Terrence and Alberts, 1978] and asthma therapy [Mann et al., 1992]. Thus, a BID dosing schedule of buspirone may enhance compliance in patients with persistent anxiety. A previous double-blind study [Sramek et al., 1997] found no differences in efficacy between buspirone 15 mg BID and 10 mg TID, which is consistent with reports from the clinical setting [Sussman, 1994]. These results suggest that buspirone administered on a BID schedule is a safe, well-tolerated, and effective treatment for persistent anxiety.

In conclusion, buspirone 15 mg BID was found to be safe and well tolerated in patients with persistent anxiety. No clinically significant differences in safety between buspirone 15 mg BID and 10 mg TID were observed. Thus, a BID schedule of buspirone may enhance convenience and potentially improve patient compliance in persistent anxiety without compromis-

ing the excellent safety/tolerability profile of the medication.

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