Treatment of Anxiety with Buspirone

By Norman Sussman, MD

Since their introduction in the early 1960s the benzodiazepines have largely fulfilled initial expectations that they would represent a major advance over the barbiturates and carbamate derivatives, the contemporary drugs of choice in the treatment of anxiety. Specific advantages of the benzodiazepines include the reduced risk of tolerance (and consequent dose escalation), low potential for abuse and addiction, mild withdrawal syndrome, and the absence of lethal respiratory depression when taken alone in overdose.

Despite this favorable safety profile, a number of treatment-limiting properties are associated with the benzodiazepines. These include sedation, impairment in functions requiring psychomotor competence, cognitive disturbances, and additive effects when used with alcohol. In addition, there is a degree of abuse and addiction potential as well as a clinically significant withdrawal syndrome, especially following abrupt cessation of treatment.

Buspirone (BuSpar), a new anxiolytic that is chemically and pharmacologically unrelated to the benzodiazepines, has recently been marketed in the United States. This new drug has been established in clinical trials as being comparable to the benzodiazepines in overall anxiolytic efficacy, but having the following atypical characteristics:
- It does not potentiate the effects of alcohol;
- It has no apparent abuse liability;
- It produces no withdrawal syndrome;
- It has no anticonvulsant or muscle relaxant activity.

Given the novel profile of buspirone it is understandable that a common perception of the compound is that it appears too good to be true. This skepticism is reinforced by the recent withdrawal of two new antidepressants—nomifensine (Merital) and bupropion (Wellbutrin)—soon after FDA approval. Each of these drugs was purported to be safer than existing compounds. Nevertheless, each was quickly withdrawn because of serious side effects. In addition, most anxiolytic-sedative drugs have historically been proven over time to have more problems associated with their use than could be appreciated before widespread clinical use. No doubt, only extensive experience will establish the real worth and safety of buspirone. For the moment, however, the new drug is highly promising in many respects. Having reviewed the literature and having worked with buspirone during its clinical trials, I would like to discuss some issues that are of immediate clinical relevance as psychiatrists begin to prescribe buspirone.

**DOSE,** and **BASIC KINETIC CONSIDERATIONS**

Buspirone is available in 5 mg and 10 mg tablets with a recommended initial dosing schedule of one tablet three times a day. The maximum recommended daily dose is 60 mg a day.

Clinical trials have established that the mean therapeutic dose of buspirone is approximately 20 mg per day.\(^1\)

The need for divided doses is inferred from the comparatively short half-life of the drug (the mean half-life values in studies of healthy volunteers were 2 ± 1 to 11 ± 3 hours).\(^2\) It is conceivable that buspirone will ultimately be demonstrated to be effective when given twice or even once a day, because receptor effects of any drug can extend beyond the time when significant drug levels are present in the plasma. It will be interesting to see if efficacy can be maintained with once-daily treatment.

Buspirone is completely and rapidly absorbed, reaching peak plasma levels 60 to 90 minutes after ingestion.\(^2\) Food does not interfere with absorption. Indeed, postprandial administration of buspirone results in a decreased degree of first pass metabolism, increasing the amount of unmetabolized and pharmacologically active drug.\(^2\)

There are no active metabolites of buspirone that contribute significantly to observed pharmacological effects. Both hepatic and renal disease decrease buspirone clearance.\(^2\)

**OVERRIDE**

Doses as high as 375 mg per day have been given to healthy male volunteers. As the maximum dose level was approached, the most commonly observed symptoms were:
- Nausea;
- Vomiting;
Dizziness;
Drowsiness;
Miosis;
Gastric distress. No deaths have been reported either with deliberate or accidental overdose. Toxicology studies in animals suggest that the LD₅₀ dosages of benzodiazepines are between 100 and 550 times the recommended daily dose. No special antidote is known to buspirone and the value of dialysis in treating overdose has not been determined. Treatment of overdose should involve immediate gastric lavage and general symptomatic and supportive measures.

CLINICALLY SIGNIFICANT DRUG INTERACTION

There are no significant drug interactions between buspirone and cimetidine, flurazepam, triazolam, amitriptyline, and diazepam. There is no demonstrated interaction between buspirone and alcohol. The only pharmacokinetic interaction observed with buspirone involves haloperidol. Concurrent administration of buspirone produces an increase in haloperidol serum levels (W.M. Hermann, M.D., unpublished data, 1986). One study suggested that concomitant use of trazodone and buspirone may cause increases of hepatic transaminases in some patients. An attempt to replicate this finding, however, proved negative.

EFFECTS ON THE DOPAMINE SYSTEM

Psychiatrists, more than other medical specialists, may have questions about the clinical implications of buspirone’s effects on the dopaminergic system. Buspirone does bind to central dopamine receptors, causing concern about acute effects, such as parkinsonism or akathisia, and chronic effects, such as tardive dyskinesia. Several observations in animal studies argue against the likelihood of buspirone-induced extrapyramidal effects. These include:

- The specificity of buspirone for presynaptic rather than postsynaptic dopamine receptors;
- Failure to produce catalepsy in animals (and reversal neuroleptic-induced catalepsy); failure of chronic administration to produce dopamine receptor supersensitivity (and reversal of neuroleptic-induced supersensitivity).

In clinical trials involving over 3,000 patients, as well as post-marketing experience in West Germany, no extrapyramidal symptoms have been reported. Parkinsonian patients receiving the therapeutic dose of buspirone for 10 weeks exhibited no deterioration of their symptoms.

TIME COURSE OF IMPROVEMENT

A major consideration in patient compliance with buspirone is the gradual onset of efficacy over a period of several days to weeks. As with antidepressants, patients taking buspirone are unlikely to notice significant improvement in symptoms before 7 days. Maximum therapeutic effects are generally experienced after 3 to 4 weeks of treatment. The observed “lag period” in onset of clinical efficacy argues against the utility of buspirone on a prn basis. However, this question has not been investigated in clinical trials. This gradual time course of improvement is consistent with the concept of adaptive changes in the configuration, number, or sensitivity of receptors in the central nervous system. Buspirone’s mechanism of action has not been elucidated.

PATIENT SELECTION

Not all anxious patients are suitable candidates for buspirone therapy. Those who should be considered for buspirone include:

- Anxious patients with long-standing symptoms (as compared to those with acute, situational anxiety);
- Patients who need to be alert at all times;
- Anxious patients who have a history of alcoholism or other chemical dependence.

It is not known whether or not buspirone is effective in the treatment of panic attacks or panic disorder. The greatest known effectiveness is among patients with generalized or anticipatory anxiety.

One study of long-term benzodiazepine-dependent patients, using 20 mg or more of diazepam or its equivalent, found a striking “lack of preference” for buspirone and an insensitivity to its anxiolytic effect. The investigators speculate that prior exposure to benzodiazepines may result in a “substantially diminished sensitivity to subsequent buspirone anxiolysis.” Patients who are currently receiving benzodiazepines are considered marginal candidates for buspirone therapy.

LACK OF SEDATION OR INTERACTION WITH CNS DEPRESSANTS

Buspirone is purported to be the first anti-anxiety agent without CNS depressant activity. Both animal studies and experience during clinical trials bear out this claim. The incidence of drowsiness reported in controlled studies involving nearly 2,000 patients was no greater than placebo. No enhancement effect between alcohol and buspirone has been discerned.

LACK OF FUNCTIONAL IMPAIRMENT

Benzodiazepines impair psychomotor functions such as balance, reaction time, and eye-to-hand coor-
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loss upon abrupt discontinuation of therapy, a finding that is characteristic of drugs that produce dependence. Subsequent experiences in several human studies, with patients being treated for periods ranging from 4 weeks to 6 months, have reported no withdrawal syndrome in buspirone patients, even with abrupt discontinuation. An obvious implication of this finding is to minimize the likelihood of mistaking rebound anxiety or withdrawal symptoms for a return of the original anxiety symptoms. This would reduce the risk of unnecessary long-term treatment. In contrast, an unknown number of patients probably continue to take benzodiazepines because of the mistaken belief that withdrawal symptoms represent the underlying disorder.

SIDE EFFECT PROFILE

Only six side effects occur with a statistically significant incidence greater than placebo:
- Dizziness (12%);
- Nausea (8%);
- Headache (6%);
- Nervousness (5%);
- Lightheadedness (3%);
- Excitation (2%).

These adverse reactions are generally mild. For example, during clinical trials fewer than 2% of buspirone treated patients considered treatment-emergent headaches to be severe, and fewer than 1% considered lightheadedness or nervousness to be severe. The mechanisms of these side-effects are not known. Most side effects attenuate or disappear with ongoing treatment. Thus, buspirone adverse reactions are unlikely to pose a safety risk or interfere with patient compliance. During clinical trials, approximately 10% of subjects discontinued treatment due to side effects, a small percentage considering the apprehensive nature of anxiety disorder patients.

SWITCHING FROM BENZODIAZEPINES TO BUSPIRONE

Buspirone has not been found to have significant activity at the benzodiazepine receptor. Consequently,
buspironone does not reduce the intensity of the benzodiazepine withdrawal syndrome. Buspironone does not block withdrawal symptoms when chronic alcohol use is discontinued.

**CONCURRENT USE WITH BENZODIAZEPINE**

It is probable that buspironone will be used concurrently with benzodiazepines in several circumstances. These include treatment resistant cases, instances where severe insomnia merits use of a benzodiazepine hypnotic and during a switching period, where rather than withdrawing the benzodiazepine, treatment with buspironone is initiated first.

Such combination therapy has not been evaluated during clinical trials for efficacy. However, a drug interaction study involving co-administration of diazepam and buspironone for 22 days found no statiscally significant changes in diazepam concentrations, but a 20% elevation in the major diazepam metabolite — desmethyldiazepam. Each subject experienced some mild adverse reaction, the symptoms generally being qualitatively similar to the side-effect profile of buspironone. These symptoms included headache, nausea, and dizziness, in two cases muscle twitches occurred. These reactions were mild and for most subjects subsided within a few days.

**USE IN THE ELDERLY**

Elderly patients in clinical trials were not found to be uniquely sensitive to buspironone in pharmacodynamic terms. Nor were pharmacokinetic parameters found to be different. There was no unusual side-effect rate. It is not recommended therefore that dosage be reduced because of age or that there be any change in dose range.

The overall efficacy-safety profile of buspironone suggests that it may be a particularly useful alternative to the benzodiazepines in the elderly. Buspironone does not reduce the ability to process information and appears to lack the memory-impairing effects that characterize the benzodiazepines as a class. Patients can also expect to remain more alert than on benzodiazepines and not experience additive sedative effects with other drugs. Buspironone should also prove of value in patients with sleep apnea and other pulmonary disorders.

**CONCLUSION**

Buspironone appears to satisfy criteria for an ideal anxiolytic agent: it reduces the symptoms of anxiety without impairment of patient functioning, risk of abuse, or withdrawal symptoms. Although the extent of benzodiazepine misuse and toxicity is vastly overstated in much of the literature, their potential for abuse, their association with traffic accidents, and their adverse effects on cognition and respiration — particularly in the elderly — make the “anxiolytic” effects of buspironone highly welcome.

It is unlikely that buspironone will make benzodiazepines obsolete in the immediate or distant future. The proven value of benzodiazepines as hypnotics, as muscle relaxants, and as sedatives will assure their continued use. Until it is established that buspironone has anti-panic activity, the two benzodiazepines alprazolam (Xanax®) and clonazepam (Klonopin®) will represent the alternate drugs of choice to the antidepressant agents which are the treatment of choice for panic disorder.

Physicians are well aware that the promises of safety offered by new drugs often turn out to be false. Confirmation of initial expectations is only possible in the light of extensive post-marketing experience. Among the questions psychiatrists are most likely to have are:

- Does buspironone have abuse potential when combined with other psychoactive substances?
- Will the complex neurochemical spectrum of activity of buspironone — mainly involving serotonin and dopamine — result in any interactions with neuroleptic or antidepressants?
- Will buspironone be shown to be of benefit in other disorders, such as depression, narcolepsy, and attention deficit disorder?

An additional question regarding the necessity of anxiolytic drug therapy at all will probably continue regardless of buspironone’s degree of success. Many psychiatrists still argue that use of anxiolytic drugs compromises normal adaptive responses, interfering with the development of coping skills.

Those who have worked with buspironone during clinical trials feel that the drug is effective and safe, but that it will not necessarily be preferred by many patients over the benzodiazepines. As noted above, extensive and prolonged benzodiazepine use may preclude compliance when attempts are made to switch to buspironone.

**REFERENCES**

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