Buspirone — frontrunner of a new genre of anxiolytics

J. L. STRAUGHAN, E. A. CONRADIE

Summary

Buspirone (Buspar; Bristol) marks a departure from established concepts of anxiolysis. Differing substantially both in its mode of action and in the clinical expression of its action from agents such as barbiturates and benzodiazepines, it would seem to operate chiefly via the 5-HT₁A subtype of serotonin receptor. Such receptor selectivity is likely to be responsible for the novel action of this anxiolytic in that sedation and psychomotor and cognitive dysfunction are minimal, and because dependence is unlikely. The slower onset of full therapeutic benefit further delineates the differences between buspirone and other anxiolytics. However, it is apparent that the benzodiazepines will not readily be displaced from all of their varied applications by buspirone. This review examines buspirone and provides some guidelines for its use.

That buspirone (Buspar; Bristol) represents a new and different psychopharmacological agent is suggested by the statement made in the 7th edition of Goodman and Gilman's The Pharmacological Basis of Therapeutics: 'An entirely new class of drugs with potential utility in the treatment of anxiety, are the azaspirodecanediones, currently represented by buspirone.' Benzodiazepines have held pride of place in the pharmacological management of anxiety disorders for well over 2 decades and have been one of the most remarkable success stories in the history of the pharmaceutical industry. Nevertheless, while benzodiazepines have shown quite singular lack of organ toxicity, the realisation has dawned that a not insignificant number of people receiving these agents in everyday doses demonstrate impaired psychomotor and cognitive performance; furthermore, some become unduly dependent upon regular ingestion of a benzodiazepine and experience disturbing effects in reaction to attempts to withdraw the medication.

The advent of the azaspirodecanedione buspirone is one outcome of the search by the pharmaceutical industry for an agent that departs from the benzodiazepine paradigm. Just how far this agent reflects success in the endeavour is the subject matter of this review.

Buspirone — different from benzodiazepines?
The reply to this query must be an unequivocal: "Yes, very much so." In fact, the only pharmacological property which buspirone shares with benzodiazepines is its anti-anxiety effect and even this is found to be different — both in its clinical expression and in the mechanism whereby it is brought about. The slower onset of full therapeutic benefit further delineates the differences between buspirone and other anxiolytics. However, it is apparent that the benzodiazepines will not readily be displaced from all of their varied applications by buspirone. This review examines buspirone and provides some guidelines for its use.

Table I compares the chief clinical activities of benzodiazepines and buspirone. Benzodiazepines, although less inclined to cause sedation when used in low dosage than are barbiturates or the closely similar carbamates (e.g. meprobamate), do produce sedation. The sedative effects for any particular benzodiazepine are dose-dependent, and constitute one action on a continuum from anti-anxiety effect through sedation to sleep-inducing effect and on to anaesthesia and coma. Buspirone, on the other hand, throughout its recommended dosage range and beyond, remains essentially a non-sedative anxiolytic agent. Benzodiazepines are known to substitute well for alcohol, barbiturates and some other central nervous system (CNS) depressants when these agents produce withdrawal problems. It is also widely recognised that benzodiazepines potentiate the CNS-depressant effects of other CNS-active agents such as alcohol and barbiturates. For buspirone the studies to date show that it has little tendency to interact in this manner, indeed there is some evidence to suggest that alcohol-induced functional impairment may be somewhat reversed by buspirone.

Further differences between buspirone and benzodiazepines, including those relating to impairment of psychomotor and cognitive performance and the development of dependence and withdrawal syndromes are listed in Table II.

Thus, for buspirone it can be stated that it represents an anti-anxiety agent with little or no sedative-hypnotic, muscle-relaxant, anticonvulsant, CNS-depressant-potentiating or withdrawal-problem-provoking propensity. It is this relative limitation of its efficacy to anti-anxiety action that invites the designation 'anxioselective'.

TABLE I. COMPARISON OF THE CLINICAL ACTIVITIES OF BENZODIAZEPINES AND BUSPIRONE

<table>
<thead>
<tr>
<th>Clinical use</th>
<th>Benzodiazepines</th>
<th>Buspirone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytic</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sedative</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hypnotic</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Amnesic (anterograde)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

TABLE II. FURTHER CLINICAL DIFFERENCES BETWEEN BENZODIAZEPINES AND BUSPIRONE

<table>
<thead>
<tr>
<th>Clinical repercussions</th>
<th>Benzodiazepines</th>
<th>Buspirone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment of psychomotor performance</td>
<td>Occurs</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Impairment of cognitive function</td>
<td>Occurs</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Dependence development</td>
<td>Occurs</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Withdrawal syndrome</td>
<td>Occurs</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Appetite increase (food)</td>
<td>Occurs</td>
<td>?</td>
</tr>
</tbody>
</table>

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The therapeutic consequences of the particular mode of action of buspirone deserve careful consideration and include the following:

1. A few days of regular treatment (5-7 days) with buspirone are required before minimal anti-anxiety efficacy is achieved. Patients should, of course, be advised of this to obviate preconceived expectations.

2. Buspirone is as effective as benzodiazepines in the management of anxiety but achieves this effect without notable sedation or interference with psychomotor or cognitive function.

3. Alertness and ability to concentrate are maintained, or even enhanced, as anxiety abates.

4. Enhancement of the CNS effects of CNS depressants is not likely — however, care should be taken in all such situations and patients advised accordingly.

5. Buspirone is unlikely to be of benefit if prescribed in a ‘take one tablet when necessary for anxiety’ situation — at least it is unlikely to be much more effective than placebo under such circumstances.

6. Irritability and aggression are reliably diminished.

7. Development of tolerance to the anti-anxiety efficacy has not been a feature of buspirone; neither have dependence nor withdrawal problems been evident in studies to date.

8. Inertia, ataxia and confusional states have not been associated with buspirone.

9. No euphoric effects are likely to be experienced with buspirone.

10. The elderly seem to tolerate buspirone as well as do younger people. Paradoxical excitation, irritability, hostility, etc., have not been reported with buspirone.

11. According to the data available, overdosage with buspirone has not been associated with life-threatening repercussions.

12. Buspirone is not of value in weaning patients from benzodiazepines and such a course of action is not recommended.

What about the onset of anxiolytic activity?

The onset of action of benzodiazepines follows rapidly after it is taken. (Whether the onset of anti-anxiety effect is prompt because of the prompt onset of sedation is an aspect of benzodiazepine therapy that may well be better defined.) With buspirone, the full expression of its anti-anxiety efficacy may take several days to develop. This gradual onset may perhaps be likened to the similarly delayed onset of full antidepressant efficacy with the tricyclic antidepressants.

How might buspirone work?

Before attempting to reply to this query it is pertinent to remind ourselves that most drugs have been pressed into clinical service quite empirically. This was certainly true for benzodiazepines that have molecular mechanisms of action which are still being elucidated.

At present it is not possible to provide a complete picture of the basic mechanisms of action of buspirone. However, some concepts can be provided, which will be elaborated upon as more data accumulate.

Buspirone would seem to provide its anxiolytic effects by interacting with a matrix of midbrain neuronal pathways. Agonist activity at a particular subtype of serotonin receptor, designated 5-HT\(_{1A}\), in the CNS is, it seems, responsible for the anti-anxiety efficacy; this downgrades postsynaptic activity in these pathways. Antagonist activity at certain presynaptic dopaminergic (D\(_2\)) receptors has been shown to enhance neuronal activity downstream of these particular dopamine receptors and may be responsible in part for the clinical expression of buspirone activity.

Experimental data suggest that buspirone may be antagonistic to \(\gamma\)-aminobutyric acid (GABA) activity. A facilitatory influence on noradrenergic structures in the locus coeruleus is likely to be responsible for the non-sedative, alerting activity of buspirone and probably also for the ‘nervousness’ described as a side-effect in some studies.

Early experience with analogues of buspirone, such as gepirone and ipsapirone, which are also agonists and which demonstrate even higher affinity and selectivity for the midbrain 5-HT\(_{1A}\) receptors, helps to substantiate the important role of this mechanism as the neural basis for the anxiolytic efficacy of buspirone.

Benzodiazepines’ influence is exerted via enhancement of GABA, the latter known to be the most prevalent depressant neurotransmitter in the CNS. The GABA-receptor complex operates via chloride channels, dampening post-synaptic neurotransmission in a multiplicity of neurosystems in the CNS, so producing the spectrum of clinically discernible influences already described above. The ‘umbrella’ activity of benzodiazepines via GABA thus contrasts markedly with the selectivity of the buspirone-type agent. Diagrammatic representation of this situation is presented in Fig. 1.

Buspirone pharmacokinetics

While absorption from the gut is complete, extensive first-pass elimination reduces the systemic bio-availability of the drug. The concurrent intake of food enhances the amount of unchanged buspirone that reaches the systemic circulation. Although buspirone is highly bound to plasma proteins, other highly protein-bound drugs such as warfarin, propranolol and phenytoin are not displaced. However, digoxin may be displaced (see ‘interactions’ below). Hepatic metabolism accounts for much of the elimination of buspirone. In the process a pharmacologically active metabolite, which also has selectivity for the 5-HT\(_{1A}\) receptor, is formed. (This metabolite may thus be partially responsible for the psychotherapeutic benefits of buspirone.)

The range of the means of the elimination half-life (T\(_{1/2}\)) of buspirone itself is 2-11 hours after a single oral dose of 10-40 mg. Single-dose studies indicate that 29-63% of the dose is excreted, chiefly in the form of a variety of biotransformation products. Some 18 - 38% is excreted, chiefly as metabolites, in the faeces. In studies of the elderly, no age-related problems were evident and pharmacokinetic handling remained essentially unchanged.

For whom should buspirone be of value?

At present, buspirone should be considered for use in people with the more chronic and free-floating anxiety disorders (in whom the avoidance of long-term benzodiazepines may well be advantageous). Therapy should not be continued indefinitely; patients should be evaluated regularly for possible
discontinuation of buspirone. In view of the relatively slow onset of full anti-anxiety efficacy alluded to above, buspirone would not be beneficial for relief of acute or short-lived situational anxiety states.

Are there people who should avoid buspirone?

The drug should be used only with due caution in patients with epilepsy, and should be avoided in patients with severe renal impairment (if the glomerular filtration rate is < 20 ml/min) and severe hepatic decompensation. At present, the drug is contraindicated during pregnancy and breastfeeding. Buspirone should not be considered for managing benzodiazepine withdrawal.

What problems may occur with buspirone?

Nausea, diarrhoea, dizziness, light-headedness, headache and feelings of restlessness and nervousness have been described, as have drowsiness and fatigue. Transient hyperprolactinaemia may occur; however, this is unlikely with the currently recommended dosage (package insert). It is contended that, if buspirone therapy is initiated with small doses given with food, and if these doses are not prematurely increased, the incidence of side-effects is likely to be minimal. No problems in human breast-fed infants have been documented; however, rat studies indicate that buspirone does gain access to breast milk. While adequate human studies are not available regarding safety in pregnancy, animal studies do not suggest any likelihood of fetal damage.

Which drugs may interact adversely with buspirone?

The interactions of buspirone when administered concurrently with other medicines seem few. The possibility that buspirone may potentiate the effects of CNS depressants should, however, be borne in mind.

It has been suggested that buspirone may displace digoxin from its serum-binding sites, thus monitoring of digoxin levels is advocated when these agents are administered concurrently. There is evidence that buspirone interferes with the hepatic elimination of nordiazepam — this benzodiazepine derives from a variety of active and inactive precursors such as diazepam, medazepam, ketazolam, prazepam, clorazepate, chlordiazepoxide (all of which are available in the RSA). In any event, combining buspirone with benzodiazepine is not recommended.

Buspirone used concomitantly with mono-amine oxidase inhibitors has been associated with significant elevations in blood pressure — these agents should not be combined (package insert).

Recommended doses

While dosages for people under 18 years of age have not been established adequately, the usual doses recommended in adults are of the order of 15—30 mg/d given in divided doses preferably with meals and at present a maximum of 60 mg/d is advised. It seems wise to initiate buspirone treatment with doses of the order of 5 mg 3 times daily with meals, and to increase the dose gradually after several days only if deemed necessary.

Overdose

Studies in healthy volunteers using doses of 375 mg/d produced no serious adverse effects, indicating a remarkably high level of safety. Symptoms observed were dizziness, nausea, vomiting and miosis. Death by deliberate or accidental overdose has not been reported. There is no specific antidote to buspirone. The stomach should be emptied at the earliest opportunity and further management is symptomatic and supportive. Haemodialysis does not improve the rate of clearance of buspirone.

Conclusions

The benzodiazepines have been in clinical use for some 25 years and their potential for development is still considerable; nevertheless, their clinical application may well be refined and redefined. It is apparent that from the plethora of presently available benzodiazepines, new types with more selective therapeutic profiles will emerge. While the use of the presently available variety of benzodiazepines in the management of the more chronic forms of anxiety may well diminish, these agents retain a very useful spectrum of indications from which they may not easily be displaced.

The advent of buspirone — a unique psychotropic agent, represents a welcome development in psychopharmacological practice. Buspirone exhibits a selective anxiolytic efficacy not previously encountered in pharmacotherapeutics. The anti-anxiety efficacy is equivalent to that of the benzodiazepines, yet is achieved without the notable emergence of other effects such as sedation, dependence or withdrawal problems.

Psychopharmacological development has been in the doldrums for several years, but it may be that psychopharmacology is at present set to take some quantum leaps away from established therapeutic paradigms. The introduction of novel agents offering greater selectivity of action will, it is to be hoped, benefit patients in terms of safety and efficacy. Furthermore, they may push the pace for the better elucidation and delineation of psychiatric disturbances.

REFERENCES

A microbiological study of acute maxillary sinusitis in Bloemfontein

J. SNYMAN, A. J. CLAASSEN, P. L. BOTHA

Summary

Microbiological analyses and antibiotic sensitivity tests were done on 26 patients with acute maxillary sinusitis during the first 9 months of 1986. Positive cultures were obtained in 23 of the patients, with anaerobes cultured in 13 (50%). Haemophilus influenzae was cultured in all non-producers of β-lactamase. Therapy with erythromycin and chloromycetin appeared to be equally effective in aerobic cases and metronidazole was effective in all anaerobic cases.

A number of reports on the microbiological aspects of acute maxillary sinusitis have been published. We undertook this study to establish the bacteriology of acute maxillary sinusitis in Bloemfontein. Two facets were of special interest: (i) the role of anaerobic organisms in acute maxillary sinusitis; and (ii) the prevalence of β-lactamase-producing organisms in the pathogenesis of sinusitis.

Patients and methods

All patients referred to Pelonomi and National Hospitals with acute maxillary sinusitis during the period January - September 1986 were included in this study. Of the 26 patients who received sinus washouts (36 maxillary sinuses) because of radiological evidence of opacity or fluid levels, 2 had a hemipansinusitis on the left side while 1 had involvement of the left ethmoidal sinuses.

More than 1 organism

TABLE I. CULTURE RESULTS

<table>
<thead>
<tr>
<th>Aerobic organisms</th>
<th>Anaerobic organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive culture</td>
<td>18</td>
</tr>
<tr>
<td>More than 1 organism</td>
<td>7</td>
</tr>
<tr>
<td>With anaerobic organisms</td>
<td>8</td>
</tr>
<tr>
<td>Without aerobic organisms</td>
<td>—</td>
</tr>
<tr>
<td>No. of organisms cultured</td>
<td>27</td>
</tr>
</tbody>
</table>

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