Pharmacodynamic effects of buspirone and clobazam

C. ALFORD, J. Z. BHATTI, S. CURRAN, G. MCKAY & I. HINDMARCH

Human Psychopharmacology Research Unit, Robens Institute of Health and Safety, University of Surrey, Guildford GU2 5XH

- 1 The pharmacodynamic effects of buspirone and clobazam were compared in two volunteer studies. Acute doses of buspirone 5 mg, 10 mg and clobazam 10 mg were contrasted with placebo and a verum (lorazepam 1 mg), in a repeated measures design with 10 subjects assessed on a battery of psychometric tests at 1.5, 3.5, and 5.5 h post dose. For the combined results clobazam and the lower dose of buspirone (5 mg) were significantly contrasted with lorazepam on measures of subjective sedation, memory and choice reaction time (CRT). The higher dose of buspirone was not statistically different from lorazepam for all measures except memory; whilst contrasting significantly with placebo and clobazam on movement and total reaction time components respectively. Though failing to achieve significance, a similar trend was seen for critical flicker fusion (CFF) with buspirone 10 mg and lorazepam producing the lowest scores indicative of increased sedation.
- 2 Repeated doses of buspirone 5 mg twice daily, clobazam 10 mg twice daily, or placebo twice daily for 8 consecutive days were compared on the same battery of psychometric tests in a repeated measures design. Nine subjects were assessed on days 1, 3, and 8 of the study. Overall, memory performance significantly decreased with buspirone 5 mg in contrast to both clobazam and placebo whilst the opposite trend was seen with CFF. Clobazam significantly improved TRT in contrast to both placebo and buspirone.
- 3 These results indicate improved reaction time and memory performance with repeated dosing of clobazam in contrast to buspirone. Impairment following acute administration of buspirone appears limited to the higher (10 mg) dose.

Keywords buspirone clobazam psychotropic effects volunteers

Introduction

A number of psychoactive agents are currently available for the treatment of anxiety. As a class the benzodiazepines have been most frequently used (Rickels, 1978), although some are associated with sedative side effects including impairment of psychomotor and cognitive function (Hindmarch, 1980, 1988; Vogel, 1979; Wittenborn, 1979). Consequently, therapeutic efficacy needs to be balanced against unwanted behavioural effects. Buspirone, a nonbenzodiazepine anxiolytic, has been shown to have few sedative side effects and not to impair psychomotor performance (Goa & Ward, 1986).

Psychometric evaluation with both single and repeated doses of buspirone has indicated minimal impairment with doses of 20 mg or less. Results were similar to placebo with 20 mg buspirone given for up to 4 days (Seidel *et al.*, 1985) and superior to diazepam or lorazepam on a variety of tests assessing psychomotor skills including car driving, as well as cognitive function, including memory (Bond & Lader, 1981; Bond *et al.*,

1983; Lucki *et al.*, 1987; Moskowitz & Smiley, 1982; Seppala *et al.*, 1982; Smiley & Moskowitz, 1986).

Clobazam, a 1,5-benzodiazepine, is structurally different from the 1,4-benzodiazepines and also lacks many of the characteristic sedative and amnesic side effects. Psychomotor and cognitive performance measures, including memory, have remained unimpaired with acute doses of clobazam up to and including 30 mg (Hindmarch, 1979, 1982a, 1985; Wittenborn *et al.*, 1979). Clobazam could not be distinguished from placebo in a repeated dose study comparing clobazam 10 mg three times daily on measures of driving performance, whilst lorazepam was significantly worse (Gudgeon & Hindmarch, 1980).

Favourable withdrawal profiles have been observed for both buspirone and clobazam in contrast to clorazepate, diazepam or lorazepam (Figueiredo *et al.*, 1980; Goa & Ward, 1986; Gringras & Beaumont, 1985; Tyrer *et al.*, 1985).

The following experiments were designed to compare

Correspondence: Dr C. Alford, Human Psychopharmacology Research Unit, Robens Institute of Health and Safety, University of Surrey, Guildford GU2 5XH

the pharmacodynamic effects of clobazam and buspirone following both acute and repeated dose regimens of the drugs.

Methods

Subjects

Female volunteers were used in both investigations: 10 women aged between 20–45 years (mean 36.6) for the acute and nine women of the same age range (mean 35.1) for the repeated dose study. These subject numbers have been found adequate for discriminating active treatments in contrast to placebo or a verum in repeated measures designs, with subjects acting as their own controls, and with the tests used here (Hindmarch, 1986).

All volunteers were in good health and with no history of cardiovascular, gastric, renal or hepatic disorders. Concurrent medication, excluding the contraceptive pill, pregnancy or history of psychiatric illness precluded participation.

Subjects provided written informed consent and the study protocol was approved by the Human Psychopharmacology Research Unit Ethics Committee at the University of Leeds. The study was carried out in accordance with the Declaration of Helsinki (Tokyo Amendment).

Experimental design

Both studies used randomised block factorial designs with fully repeated measures, they were double-blind investigations with each subject receiving all treatments and acting as her own control. Subjects were randomly assigned to their treatments in accordance with a code based on latin squares (Kirk, 1968).

For the acute investigation all subjects received buspirone 5 mg, buspirone 10 mg, clobazam 10 mg, lorazepam 1 mg or placebo. The lorazepam treatment was included as a verum (positive control) to verify the sensitivity of the test battery used to evaluate the sedative/amnestic effects of the psychoactive drugs. In the repeated dose study buspirone 5 mg twice daily, clobazam 10 mg twice daily and placebo twice daily were compared on a test battery similar to that used in the acute dose study.

Treatments were presented in identical capsules. On test days no caffeine or alcoholic beverages were allowed; food intake was standardised; and subjects were transported to and from the study centre.

All subjects were trained to criterion performance on all tests prior to the study starting, to limit the effects of learning.

For the acute study, all treatments were administered in the morning (09.45 h) with assessments at 1.5, 3.5, and 5.5 h post-dose.

In the repeated dose study each treatment lasted for 8 days with the first treatment dose administered in the morning, (09.45 h) and the second 3.5 h later. A baseline assessment on the performance tasks was taken prior to drug administration on day 1; the tests were administered again 1 h after the first dose (approximately 10.45 h) and 1.5 h after the second drug dose (14.45 h). This was

repeated on days 3 and 8 but the baseline values from these days were not used in the statistical analysis.

Assessments

The test battery comprised both subjective and objective assessments including psychomotor, amnestic and information processing ability, which have been previously shown to be valid and reliable measures of the effects of psychoactive drugs (Alford & Hindmarch, 1991; Hindmarch, 1975, 1980, 1986).

Line analogue ratings scales (LARS) Subjective rating of 'sedation' were obtained from a set of 100 mm line analogue rating scales (Hindmarch & Gudgeon, 1980) to assess drug response. The mid point of the scale (50 mm) represents their usual value (e.g. pre-treatment), an increase in score representing an increase in sedation. The mean score of ratings of 'tiredness', 'drowsiness', and 'alertness' (included among several distractor scales) was taken as the measure of perceived sedation.

Critical flicker fusion (CFF) This test was used as a measure of overall CNS activity and specifically the ability to distinguish sensory data (Hindmarch, 1982b; Hindmarch & Parrott, 1978). Subjects were required to discriminate flicker in a set of four light emitting diodes held in foveal fixation at 1 m. Flicker fusion threshold was determined for three ascending (flicker/fusion) and three descending (fusion/flicker) scales using the psychophysical method of limits (Woodworth & Schlosberg, 1958) on the Leeds Psychomotor Tester. An increase in CFF threshold represents an improved response whilst a lower threshold indicates reduced performance.

Choice reaction time (CRT) In this test of psychomotor performance subjects were required to extinguish one of 6 red lights illuminated at random by touching the appropriate response button (Hindmarch, 1975; Hindmarch & Parrott, 1978). The mean of 20 stimulus presentations, recorded on the Leeds Psychomotor Tester, was used to determine recognition (RRT) and motor (MRT) components of total reaction time (TRT). Increased reaction time scores correspond with slower responses indicative of increased sedation.

Sternberg memory scanning task (SMT) Scanning and retrieval from short term memory was assessed using the reaction time method in memory search (Sternberg, 1969, 1975). Subjects were required to judge, by giving a yes/no response, whether a test digit was contained in memorised sequences of 1, 2, or 3 digits. The mean response time was determined over 20 trials, presented using a microcomputer. Improved performance is associated with shorter response latencies; increases with slower performance in keeping with the CRT measure.

Side effect check list (SECL) An 18 item check list was completed by subjects at each assessment period to record the frequency and severity of subject side effects to treatments.

Results

Statistical tests

Analysis of variance procedures (ANOVA) were used to assess overall significance ($P < 0.05$) between subjects and treatments, and test times within treatments. Where overall significance was obtained with ANOVA, differences between treatments for combined and separate test times were evaluated using two-tailed 95% confidence intervals (Bulpitt, 1987; Gardner & Altman, 1986; Kirk, 1968). The differences between day 1 treatment baselines were not significant, being used to generate baseline difference scores for the repeated dose performance data.

Mean values and their associated confidence intervals are presented in Tables 1 and 2.

Table 2 Combined scores for 8 days repeated dosing with buspirone 5 mg twice daily, clobazam 10 mg twice daily and placebo twice daily on subjective sedation (LARS), critical flicker fusion (CFF), recognition (RRT), motor (MRT) and total (TRT) reaction time, and memory (SMT). Placebo and drug/placebo differences: Means (95% Confidence intervals)

	Placebo	Clobazam 10 mg	Buspirone 5 mg
LARS	54.5 (1.5)	0.2 (1.5)	-1.7 (1.5)
CFF	28.5 (0.34)	0.07 (0.34)†	0.76 (0.34)*
RRT	367 (13)	-3 (13)	8 (13)
MRT	182 (14)	-18 (14)	7 (14)
TRT	543 (10)	-21 (10)*	0 (10)‡
Memory	425 (19)	-20 (20)†	44 (20)*

$P < 0.05$: * vs placebo twice daily

† vs buspirone 5 mg twice daily

‡ vs clobazam 10 mg twice daily.

Table 1 The effects of acute doses of buspirone 5 mg, 10 mg, clobazam 10 mg, lorazepam 1 mg and placebo on subjective sedation (LARS), critical flicker fusion (CFF), recognition (RRT), motor (MRT) and total (TRT) reaction time, and memory (SMT). Placebo and drug/placebo differences: Means (95% confidence intervals)

Time (h)	Placebo	Clobazam 10 mg	Buspirone 5 mg	Buspirone 10 mg	Lorazepam 1 mg
LARS					
1.5	55.5 (4.6)	-1.9 (4.6)	-5.0 (4.6)†	-0.3 (4.6)	5.9 (4.6)
3.5	53.2 (4.6)	1.4 (4.6)	1.7 (4.6)	3.2 (4.6)	8.0 (4.6)
5.5	56.1 (4.9)	-1.5 (4.9)	-4.6 (4.9)	-1.7 (4.6)	1.2 (4.6)
1.5-5.5	54.9 (2.7)	-0.6 (2.7)†	-2.6 (2.7)†	0.5 (2.7)	5.0 (2.7)
CFF					
1.5	27.2 (0.54)	-0.6 (0.54)	-0.7 (0.54)	-0.9 (0.54)	-0.7 (0.54)
3.5	26.3 (0.54)	0.5 (0.54)	-0.1 (0.54)	-0.1 (0.54)	-0.2 (0.54)
5.5	25.7 (0.57)	0.2 (0.54)	0.0 (0.54)	0.0 (0.54)	-0.2 (0.54)
1.5-5.5	26.4 (0.32)	0.0 (0.31)	-0.32 (0.31)	-0.39 (0.31)	-0.40 (0.31)
RRT					
1.5	383 (26)	-26 (26)†‡	-20 (26)	27 (26)	32 (26)
3.5	372 (23)	-4 (23)†	-1 (23)†	15 (23)	54 (23)*
5.5	397 (25)	-24 (23)	-7 (23)	-21 (23)	1 (25)
1.5-5.5	384 (14)	-17 (14)†	-8 (14)†	6 (14)	29 (14)*
MRT					
1.5	230 (19)	32 (19)	16 (19)‡	56 (19)*	51 (19)*
3.5	251 (17)	2 (17)†	14 (17)	30 (17)	39 (17)*
5.5	253 (18)	6 (17)	10 (17)	5 (17)	9 (17)
1.5-5.5	246 (10)	12 (10)	13 (10)	29 (10)*	32 (10)*
TRT					
1.5	614 (35)	5 (35)†‡	-5 (35)†‡	82 (35)*	82 (35)*
3.5	623 (31)	-1 (31)†	13 (31)†	46 (31)	93 (31)*
5.5	650 (33)	-18 (31)	3 (31)	-16 (31)	10 (31)
1.5-5.5	629 (19)	-5 (19)†‡	5 (19)†	35 (19)	61 (19)*
Memory					
1.5	489 (30)	-12 (32)†	-13 (30)†	12 (30)†	73 (30)*
3.5	494 (30)	9 (36)	-12 (30)†	3 (30)	61 (31)*
5.5	473 (33)	-4 (30)	-3 (30)	10 (30)	48 (30)
1.5-5.5	486 (18)	-6 (18)†	-10 (17)†	8 (17)†	60 (17)*

$P < 0.05$: * vs placebo

† vs lorazepam 1 mg

‡ vs buspirone 10 mg

LARS

A significant difference between drug treatments was found in the acute study ($F = 4.18$, $P < 0.005$). For the combined times both clobazam and buspirone (5 mg) were significantly contrasted with the verum lorazepam whilst significant placebo contrasts were not obtained. Assessment of individual test times revealed a significant contrast between buspirone (5 mg) and lorazepam at 1.5 h post dose.

Similarly, significant placebo contrasts were not obtained following repeated dosing, the overall ANOVA being non significant for treatment effects. These results are presented as difference scores in Figure 1 and indicate the tendency for the lower dose of buspirone to reduce subjective sedation with initial dosing.

CFF

With acute dosing ANOVA revealed a strong time effect ($F = 14.31$, $P < 0.0001$) reflecting a general decrease in CFF threshold across time, whilst a significant treatment effect was not obtained. The overall trends indicated similar levels of increased sedation following either buspirone (10 mg) or lorazepam (Table 1). A significant treatment effect ($F = 7.10$, $P < 0.001$) reflected the relative improvement of buspirone (5 mg) in contrast to either placebo or clobazam for the combined times assessment with repeated dosing, although analysis of separate test times again failed to distinguish any treatment (Figure 2).

CRT

In the acute study the significance between treatments was ($F = 5.55$, $P < 0.0005$) for RRT; ($F = 7.65$, $P < 0.0001$) for TRT; and ($F = 4.81$, $P < 0.005$) for MRT. For the combined time analysis placebo, clobazam and buspirone (5 mg) were significantly contrasted with the sedative lorazepam for both RRT and TRT. Clobazam was significantly improved with respect to buspirone (10 mg) for TRT; whilst placebo was significantly con-

Figure 1 Line analogue rating scales (LARS) for subjective sedation. ---, buspirone 5 mg, twice daily; —, clobazam 10 mg, twice daily; ·····, placebo, twice daily. bar, 95% confidence intervals. $P < 0.05$: *, vs placebo twice daily; B, vs buspirone 5 mg twice daily; C, = vs clobazam 10 mg twice daily. () $P < 0.05$ for combined results.

Figure 2 Critical flicker fusion (CFF) changes from baseline. ---, buspirone 5 mg, twice daily; —, clobazam 10 mg, twice daily; ·····, placebo, twice daily. bar, 95% confidence intervals. $P < 0.05$: *, vs placebo twice daily; B, vs buspirone 5 mg twice daily; C, = vs clobazam 10 mg twice daily. () $P < 0.05$ for combined results.

trasted with both lorazepam and the higher buspirone dose for MRT. Separate time analyses revealed significant contrasts at both 1.5 and 3.5 h post dose. Lorazepam and buspirone (10 mg) impaired performance at 1.5 h in contrast to clobazam with RRT; clobazam and buspirone (5 mg) for TRT; placebo and buspirone (5 mg) contrasting with the higher dose alone, for MRT. At 3.5 h placebo, buspirone (5 mg) and clobazam contrasted with the verum lorazepam for both RRT and TRT; placebo and clobazam contrasting with lorazepam for MRT. These results emphasise consistent sedative effects following acute doses of both lorazepam and the higher buspirone dose on measures of reaction time.

Significant ANOVA treatment effects were limited to TRT for the repeated dose study ($F = 7.10$, $P < 0.005$), with clobazam significantly improving reaction time in contrast to both placebo and buspirone (5 mg) for the combined time analysis. TRT was similarly improved following the second dose assessment for the days combined, and day 8 with the separate day and time analysis indicating a sustained improvement (Figure 3).

Figure 3 Total reaction time (TRT) changes from baseline. ---, buspirone 5 mg, twice daily; —, clobazam 10 mg, twice daily; ·····, placebo, twice daily. bar, 95% confidence intervals. $P < 0.05$: *, vs placebo twice daily; B, vs buspirone 5 mg twice daily; C, = vs clobazam 10 mg twice daily. () $P < 0.05$ for combined results.

Figure 4 Memory (SMT) changes from baseline. ---, buspirone 5 mg, twice daily; —, clobazam 10 mg, twice daily; ·····, placebo, twice daily. bar, 95% confidence intervals. $P < 0.05$: *, vs placebo twice daily; B, vs buspirone 5 mg twice daily; C, = vs clobazam 10 mg twice daily. () $P < 0.05$ for combined results.

SMT

A significant treatment effect was seen in the acute study ($F = 8.94$, $P < 0.0001$), all treatments contrasting significantly with lorazepam which impaired memory reaction time response for set sizes 1, 2 and 3 (overall memory) at 1.5 h; placebo and the lower buspirone (5 mg) dose again contrasting with lorazepam at 3.5 h.

A significant treatment effect was also seen with repeated dosing ($F = 7.65$, $P < 0.001$), combined time analysis significantly contrasting both placebo and clobazam with the increased reaction times for buspirone. Separate analysis for days contrasted clobazam with buspirone on day 1; whilst the results for test times across days indicated a similar contrast at both the first and second psychometric assessments. These results are plotted in Figure 4 indicating a consistent impairment with repeated dosing of buspirone.

SECL

Neither clobazam nor buspirone were distinguishable from placebo in either the acute or repeated studies. The rate of reporting was low throughout both experiments as would be expected in healthy non-anxious subjects.

Discussion

The results for the acute study demonstrate the validity of the design and sensitivity of the psychometric to the sedative and amnesic effects of the verum (lorazepam 1 mg). Significant contrasts between the verum and other treatments were obtained for all measures where an overall significant ANOVA treatment effect was observed. Whilst CFF failed to distinguish significantly the verum, trends were consistent with other measures indicating sedative trends for both the higher (10 mg) buspirone dose and the verum.

Both buspirone 5 mg and clobazam 10 mg failed to produce a significant contrast, either in direct comparison or with placebo, when compared at the first assessment

for both the acute and repeated studies, demonstrating the compatibility of the results obtained.

Increases in subjective sedation were seen following the verum in the acute study, significantly contrasting with both buspirone (5 mg) and clobazam for the combined results across the 3 post drug assessment periods, and being close to significance for placebo. The treatment means indicate reduced levels of subjective sedation in comparisons with placebo for the lower buspirone (5 mg) dose; increases being seen for the higher (10 mg) dose and lorazepam (Table 1). The reduction in perceived sedation was greatest for buspirone (5 mg) achieving significance at the 1.5 h assessment. Overall ANOVA failed to distinguish treatments in the repeated dose study, comparing the lower buspirone (5 mg twice daily) dose in comparison with clobazam (10 mg twice daily) and placebo.

Reduced subjective sedation following initial dosing with the lower buspirone dose is evident from both the acute and repeated investigations, returning to placebo values with repeated administration. Results for clobazam were similar to placebo following initial dosing in both the acute and repeated dose studies, although a non-significant trend towards increased sedation was seen to augment following the second dose with repeated administration (Figure 1).

Results for CFF in the acute investigation failed to achieve statistical significance although the lowest levels, indicative of increased sedation, were seen for both lorazepam and the higher buspirone dose in keeping with the other measures. Whilst the direction of change for lorazepam is also in keeping with previous research (Hindmarch, 1980), and approached significance in this study, the highly significant time effect may have masked more significant treatment findings.

With repeated dosing buspirone resulted in higher CFF scores (days 3 and 8) in contrast to both placebo and clobazam for analysis of the combined time points, although failing to achieve significance for individual days or time points. Results for clobazam could not be distinguished from placebo.

Choice reaction time revealed significant acute sedative effects for the higher buspirone (10 mg) dose in contrast to both placebo for the motoric component, and clobazam for total reaction time; combined means for clobazam being less than placebo for both recognition and total reaction time (Table 1). Analysis of separate post dose assessments again significantly contrasted clobazam with buspirone (10 mg) and lorazepam for RRT and TRT. The sustained improvement in reaction time performance with clobazam was evident in the repeated dose study, being significant for the second assessment periods (5 h) across days combined and the second individual assessment on day 8 (Figure 3); providing an overall significant contrast between both placebo and buspirone.

The dose dependent impairment of reaction time seen by contrasting the lower (5 mg) and higher (10 mg) doses of buspirone was of particular interest in the acute investigation. The lower dose resulted in significantly lower motor and total reaction times at 1.5 h post dose. This dose sensitivity may be shared with other psychoactive compounds where varying effects on separate neurotransmitter systems are seen with different doses.

The Sternberg based memory task most markedly differentiated the sedative effects of lorazepam on amnesic function in contrast to other treatments including the higher buspirone dose in the acute study. Whilst placebo contrasts were not obtained with either buspirone or clobazam in the acute investigation, analysis of the combined results from the repeated dose study indicated a significant impairment with buspirone in contrast to both placebo and clobazam.

Improvement in memory function following clobazam administration was emphasised by significant contrasts between clobazam and buspirone for the combined assessments on day 1 and for the 2 assessment times across combined days. The sustained relative impairment with repeated doses of buspirone may be seen in Figure 4. However, this relative impairment of buspirone (5 mg) was not seen in the acute study. The significant impairment resulted from combined analysis of test times in the repeated study, rather than individual assessments alone; reflecting significant impairment as a result of repeated dosing.

A possible 'alerting' effect was seen with the lower buspirone dose of 5 mg with measures of subjective sedation and CFF. However, both clobazam and buspirone (5 mg) were significantly contrasted with lorazepam on subjective sedation in the acute study whilst the repeated study (which did not include the verum) failed to produce a significant ANOVA treatment effect. Though CFF responses were less marked than predicted from previous research, results indicated a lack of impairment with clobazam in contrast to placebo, and a significant improvement with repeated administration of buspirone for days and test times combined. However, this was not a strong effect, failing to achieve significance for either combined assessments across separate days or for the different assessment times with days combined. Confidence interval analysis for combined assessments is more sensitive to treatment effects than separate assessments where the number of samples is reduced.

More marked were the dose related impairments of buspirone on components of choice reaction time, both in contrast to placebo and clobazam following acute administration; the higher 10 mg dose significantly contrasting with the less sedative 5 mg dose at 1.5 h post administration. This relative lack of impairment for the lower dose was also seen with memory performance, although all treatments were significantly contrasted with the marked impairment produced by lorazepam at 1.5 h.

Repeated dosing emphasised the difference between clobazam and buspirone on measures of memory and reaction time. A significant improvement was seen with clobazam on total reaction time in contrast to both placebo and buspirone; whilst a significant impairment of memory performance was seen with buspirone in contrast to both placebo and clobazam. These relative impairments are of interest as therapeutic efficacy of bus-

pirone is only achieved after repeated dosing.

These present results are in clear contrast to previous work with buspirone. The review by Goa & Ward (1986) suggested minimal impairment of psychomotor skills and cognitive function with buspirone at doses of 20 mg or less. A recent report by Bourin *et al.* (1989) found an acute 10 mg dose of buspirone to significantly improve reaction time in contrast to bromazepam 3 mg; but also found memory impairment with both buspirone and clobazam 10 mg at 2 h post dose with a 30 s free recall task. However, over a 2 min recall their results matched the order seen here in that the least decrement was seen for clobazam in contrast to buspirone. These findings of reduced mnestic function contrast with the absence of memory impairment reported by Lucki *et al.* (1987) for buspirone.

On the other hand the results obtained here for clobazam support previous research, including a lack of memory impairment with either acute or repeated dosing in the range of 10–30 mg (Hindmarch, 1982a, 1985). As the verum reliably produced significant 'sedative' effects for all but CFF scores, where a sedative trend was seen, the general reliability of the results may be accepted. The relative impairment of reaction time seen with buspirone in contrast to clobazam in both the acute and repeated dose studies provides further support. The measures selected for these investigations are known to be highly sensitive to psychoactive drug effects in contrast to some other tests available (Alford & Hindmarch 1991; Hindmarch, 1980, 1986). Differences in test sensitivity might contribute to the discrepancy between these findings and some previous research. However, disruptive effects of buspirone 5 and 10 mg on aspects of psychomotor function and cognitive ability have been demonstrated in a placebo and verum controlled study using an established test battery. Although subjects are measurably impaired they are not subjectively aware of any feelings of sedation. The findings reported here are derived from a group of healthy volunteers and clearly need replicating in a more characteristic patient group. These results do, however, indicate the need for caution in regarding subjective reports alone as indicative of the side effect profiles for psychoactive drugs.

In conclusion, neither clobazam 10 mg nor buspirone 5 mg were seen to result in sedative effects following acute administration; whilst impairment of reaction time performance was seen following the higher buspirone dose of 10 mg. With repeated administration a trend toward increased CFF performance was seen following buspirone 5 mg. This contrasted with the relative impairment of both reaction time and memory performance of buspirone in comparison with clobazam.

The sustained impairment of reaction time and memory following repeated administration of buspirone, in contrast to the nonsedative 1,5-benzodiazepine clobazam, has implications for the administration of these anxiolytics to ambulant outpatients.

References

- Alford, C. A. & Hindmarch, I. (1991). The residual effects of benzodiazepine hypnotics on cognitive function, psychomotor ability and car driving performance. In *Second International Symposium on Medicinal Drugs and Driving Performance, Maastricht, Holland, 1987*, ed. O'Hanlon, J. (in press).
- Bond, A. J. & Lader, M. H. (1981). Comparative effects of diazepam and buspirone on subjective feelings, psychological tests and the EEG. *Int. Pharmacopsych.*, **16**, 212–220.
- Bond, A., Lader, M. H. & Shrotriya, R. (1983). Comparative effects of a repeated dose regime of diazepam and buspirone on subjective ratings, psychological tests and the EEG. *Eur. J. clin. Pharmac.*, **24**, 463–467.
- Bourin, M., Auget, J. L., Colombel, M. C. & Larousse, C. (1989). Effects of single oral doses of bromazepam, buspirone and clobazam on performance tasks and memory. *Pharmacopsychiat.*, **22**, 141–145.
- Bulpitt, C. J. (1987). Confidence intervals. *Lancet*, **i**, 494–497.
- De Figueiredo, R., Franchini, A., Martinho, A. & Hindmarch, I. (1981). Differences in the effect of two benzodiazepines in the treatment of anxious outpatients. *Int. Pharmacopsych.*, **16**, 57–65.
- Gardner, M. J. & Altman, D. G. (1986). Confidence intervals rather than P values: estimation rather than hypothesis testing. *Br. med. J.*, **292**, 746–750.
- Goa, K. L. & Ward, A. (1986). Buspirone: A preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. *Drugs*, **32**, 114–129.
- Gringras, M. & Beaumont, G. (1985). The effectiveness of repeated nocturnal doses of clobazam and dipotassium clorazepate on clinical measures of anxiety, patient ratings of mood and sleep and objective assessments of CNS activity. In *Clobazam: Human Psychopharmacology and Clinical Applications*, eds Hindmarch, I., Stonier, P. D. & Trimble, M. R., Royal Society of Medicine International Symposium Series 74, pp 73–79. Oxford: Oxford University Press.
- Gudgeon, A. C. & Hindmarch, I. (1980). The effects of 1,4 and 1,5-benzodiazepines on aspects of car driving behaviour: A preliminary investigation. *IRCS med. Sci.*, **8**, 709–710.
- Hindmarch, I. (1975). A 1,4-Benzodiazepine, temazepam (K 3917), its effect on some psychological parameters of sleep and behaviour. *Arzneimittel-Forschung (Drug Research)*, **25**, 1836–1839.
- Hindmarch, I. (1979). Some aspects of the effects of clobazam on human psychomotor performance. *Br. J. clin. Pharmac.*, **7**, Suppl. 1, 77S–82S.
- Hindmarch, I. (1980). Psychomotor function and psychoactive drugs. *Br. J. clin. Pharmac.*, **10**, 189–209.
- Hindmarch, I. (1982a). Clobazam and memory. *Neurologia et Psychiatria*, **4**, 10–14.
- Hindmarch, I. (1982b). Critical flicker fusion frequency (CFFF): The effects of psychotropic compounds. *Pharmacopsychiatria*, **15**, Suppl. 1, 44–48.
- Hindmarch, I. (1985). The psychopharmacology of clobazam. In *Clobazam: Human Psychopharmacology and Clinical Applications*, eds Hindmarch, I., Stonier, P. D. & Trimble, M. R., Royal Society of Medicine International Symposium Series 74, pp 3–10. Oxford: Oxford University Press.
- Hindmarch, I. (1986). The effects of psychoactive drugs on car handling and related psychomotor ability: A review. In *Drugs and Driving*, eds O'Hanlon, J. F. & de Gier, J. J., pp 71–79. London: Taylor and Francis.
- Hindmarch, I. (1988). Information processing, psychological performance and anxiolytic drugs. *Postgrad. med. J.*, **64**, Suppl. 2, 10–15.
- Hindmarch, I. & Gudgeon, A. C. (1980). The effects of clobazam and lorazepam on aspects of psychomotor performance and car handling ability. *Br. J. clin. Pharmac.*, **10**, 145–150.
- Hindmarch, I. & Parrott, A. C. (1978). The effect of a subchronic administration of three dose levels of a 1,5-benzodiazepine derivative, clobazam on subjective assessments of sleep and aspects of psychomotor performance the morning following night time medication. *Arzneimittel-Forschung (Drug Research)*, **28**, Suppl. 2, 2169–2172.
- Kirk, R. E. (1968). *Experimental Design: Procedures for the Behavioural Sciences*. Belmont, California: Brooks/Cole.
- Lucki, I., Rickels, K., Giesecke, M. A. & Geller, A. (1987). Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br. J. clin. Pharmac.*, **23**, 207–211.
- Moskowitz, H. & Smiley, A. (1982). Effects of clinically administered buspirone and diazepam on driving related skills performance. *J. clin. Psych.*, **43**, 45–55.
- Rickels, K. (1978). Use of antianxiety agents in anxious outpatients. *Psychopharmac.*, **58**, 1–17.
- Seidel, W. F., Cohen, S. A., Bliwise, N. G. & Dement, W. C. (1985). Buspirone: An anxiolytic without sedative effect. *Psychopharmac.*, **87**, 371–373.
- Seppala, T., Aranko, K., Mattila, M. J. & Shrotriya, R. C. (1982). Effects of alcohol on buspirone and lorazepam actions. *Clin. Pharmac. Ther.*, **32**, 201–207.
- Smiley, A. & Moskowitz, H. (1986). Effects of long-term administration of buspirone and diazepam on driver steering control. *Am. J. Med.*, **80**, 22–29.
- Sternberg, S. (1969). Memory scanning: Mental processes revealed by reaction time experiments. *Am. Scientist*, **57**, 421–457.
- Sternberg, S. (1975). Memory scanning: New findings and current controversies. *Quart. J. exp. Psych.*, **27**, 1–32.
- Tyrer, P., Murphy, S. & Owen, R. T. (1985). The risk of pharmacological dependence with buspirone. *Br. J. clin. Pract.*, **39**, 91–93.
- Vogel, J. R. (1979). Objective measurement of human performance changes produced by antianxiety drugs. In *Anxiolytics*, eds Fielding, S. & Lal, H. New York: Futura Press.
- Wittenborn, J. R. (1979). Effects of benzodiazepines on psychomotor performance. *Br. J. clin. Pharmac.*, **7**, 61S–67S.
- Wittenborn, J. R., Flaherty, C. F., McGough, W. E. & Nash, R. J. (1979). Psychomotor changes during initial day of benzodiazepine medication. *Br. J. clin. Pharmac.*, **7**, 69S–76S.
- Woodworth, R. S. & Scholsberg, H. (1958). *Experimental Psychology*. London: Methuen.

(Received 4 January 1989,
accepted 11 January 1991)