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Abstract

Buspirone is a serotonin 5-HT_{1A} receptor agonist licensed for the treatment of anxiety. Other anxiolytic drugs such as benzodiazepines show significant sedative and other unwanted effects on cognition. Studies to date have yet to investigate cognitive effects of buspirone using well-validated computerized tests.

The aim of this study was to assess acute subjective and cognitive effects of buspirone in healthy volunteers.

Sixty healthy male volunteers received 20 mg buspirone, 30 mg buspirone, or placebo *per os* in a double-blind parallel groups design (N=20 per group). Subjective ratings (visual analogue scales) were completed at baseline, and at 1.5 and 3.5 hours post-capsule. Cognitive assessment was undertaken between 1.5 and 3.5 hours post-capsule, including tests of memory, executive planning, impulse control, decision making and cognitive flexibility.

The 30 mg buspirone group showed significantly higher subjective ratings of contentedness 3.5 hours after capsule relative to placebo. Treatment and placebo groups did not differ significantly on cognitive measures.

In contrast to benzodiazepines, the anxiolytic buspirone appears to lack detectable deleterious effects on cognition when administered acutely at clinically meaningful doses. Future research directions are discussed in relation to acute and chronic studies in neuropsychiatric populations.

Keywords

5-HT, serotonin, anxiety, depression, buspirone, cognition, attention

Introduction

Serotonin (5-HT) is thought to regulate learning, memory and decision making via neuromodulatory actions upon cortico-

subcortical circuitry (Deakin *et al.*, 2004a, 2004b; Robbins, 2005). Abnormalities in 5-HT neurotransmitter systems are implicated in the manifestation of psychiatric illnesses associated with cognitive abnormalities including depression, obsessive compulsive disorder

(OCD) and schizophrenia (Rauch and Jenike, 1993; Charney, 1998; Roth and Hanizavareh, 2004; Chamberlain *et al.*, 2005, 2006a). Traditionally, 5-HT is thought to play a role in impulse control (Soubrié, 1986; Evenden, 1999). Of the various subtypes of 5-HT receptor that may play a role in cognition, the 5-HT_{1A} receptor represents a likely candidate, given its preponderance in hippocampus and cingulate cortex – regions implicated in control of cognition and mnemonic functions (Azmitia *et al.*, 1996; Pache *et al.*, 2003; Roth and Hanizavareh, 2004). Substantial pre-clinical evidence supports modulatory effects of 5-HT_{1A} drugs on cognitive functions (Roth and Hanizavareh, 2004).

Buspirone is a 5-HT_{1A} receptor agonist licensed for human use, with demonstrable efficacy in the treatment of anxiety and depression (Goldberg and Finnerty, 1979; Goldberg, 1984). Unlike other anxiolytics such as benzodiazepines, buspirone appears to lack significant addictive potential or withdrawal syndromes (Goldberg and Finnerty, 1979; Goldberg, 1984; Troisi *et al.*, 1993). In animals, buspirone has been reported to impair aspects of cognition, such as response accuracy on short-term memory tasks (Pache *et al.*, 2003). Human behavioural studies using tests of cognition, including fronto-executive functions, have generally reported no significant effects of acute buspirone (Bond *et al.*, 1983; Schaffler and Klausnitzer, 1989; Barbee *et al.*, 1991; Hart *et al.*, 1991; Unrug-Neervoort *et al.*, 1992; Unrug *et al.*, 1997a; Unrug *et al.*, 1997b). However, many of the extant studies have suffered certain limitations including restricted range of tests, relatively small doses (in comparison to established clinical dosing range for anxiety), and small sample sizes. Nonetheless, in a study combining cognitive assessment with positron emission tomography (PET) and buspirone administration in healthy male volunteers, deleterious effects were reported for verbal memory. Regional cerebral blood flow (rCBF) was quantified during auditory verbal memory tests in which volunteers undertook free recall of sub-span and supra-span word lists in the scanner (Grasby *et al.*, 1992a; Grasby *et al.*, 1992b). In comparison to the placebo condition, buspirone impaired performance on supra-span memory trials, and augmented left dorsolateral prefrontal cortex rCBF during the memory task.

In sum, there has been relatively little systematic analysis of the effects of buspirone on cognitive functions to date, although a number of studies have reported relatively little effect at doses <10 mg. The present study utilised a computerised test battery tapping a number of distinct cognitive domains, including cognitive flexibility, working memory, response inhibition, executive planning and decision making (Chamberlain and Sahakian 2005). Volunteers received 20 mg or 30 mg buspirone acutely, in a double-blind between-subjects placebo-controlled design. It was anticipated that this would help to clarify whether buspirone exerts significant cognitive impairing effects at doses employed for the treatment of general anxiety disorder.

Methods

Subjects

Sixty healthy male volunteers (mean age \pm SD = 23.7 \pm 5.9, range 18–39 years) were recruited using advertisements in the local community. Volunteers provided written informed consent prior to taking part, and were screened for significant history of psychiatric or medical illnesses and recreational drug dependency. Participants were asked to abstain from alcohol and caffeine on the day of testing. The study was approved by Local Research Ethics Committee (Cambridge, reference 01/135), and the Medicines and Healthcare Products Regulatory Agency (London).

Design

Volunteers received 20 mg buspirone, 30 mg buspirone, or placebo *per os* in a double-blind parallel groups design (N=20 per group). Doses were selected to be in the standard treatment range for anxiety disorders (British National Formulary). In line with the established pharmacokinetic profile of buspirone (Goldberg, 1984), neuropsychological assessment was undertaken from 1.5 to 3.5 hours after capsule administration. In the interim, volunteers spent time relaxing in a quiet waiting room.

Subjective measures

Subjective effects were recorded using self-complete Visual Analogue Scales at baseline, and at 1.5 and 3.5 hours after capsule administration. Volunteers marked a cross on each of 16 dimensions for alert–drowsy, calm–excited, strong–feeble, muzzy–clear headed, well-coordinated–clumsy, lethargic–energetic, contented–discontented, troubled–tranquil, mentally slow–quick witted, tense–relaxed, attentive–dreamy, incompetent–proficient, happy–sad, antagonistic–amicable, interested–bored and withdrawn–gregarious. Factors of ‘alertness’, ‘contentedness’, and ‘calmness’ were calculated on the basis of prior factor analysis (Bond and Lader, 1974).

Neuropsychological assessment

Neuropsychological assessment comprised a comprehensive set of well-validated tests from CANTAB (www.camcog.com) and established neuropsychological diagnostics (Lezak *et al.*, 2004). Assessment was conducted in a quiet testing room using a touch-sensitive computer. The battery comprised the following tests (the reader is referred to cited publications for full task descriptions): Auditory Verbal Learning (Lezak *et al.*, 2004), CANTAB Pattern Recognition Memory (Chamberlain *et al.*, 2005), CANTAB Spatial Working Memory (up to twelve search locations) (Chamberlain *et al.*, 2005), CANTAB Paired Associates Learning (Blackwell *et al.*, 2004), Tower of London (up to six move difficulty levels) (Owen *et al.*, 1995), Stop-signal (Aron *et al.*, 2003), Information Sampling (Clark *et al.*, 2006), Cambridge Gamble (Clark *et al.*, 2003) and the three-dimensional intra-dimensional/extra-dimensional set-shift test (3D IDED) (Rogers *et al.*, 1999).

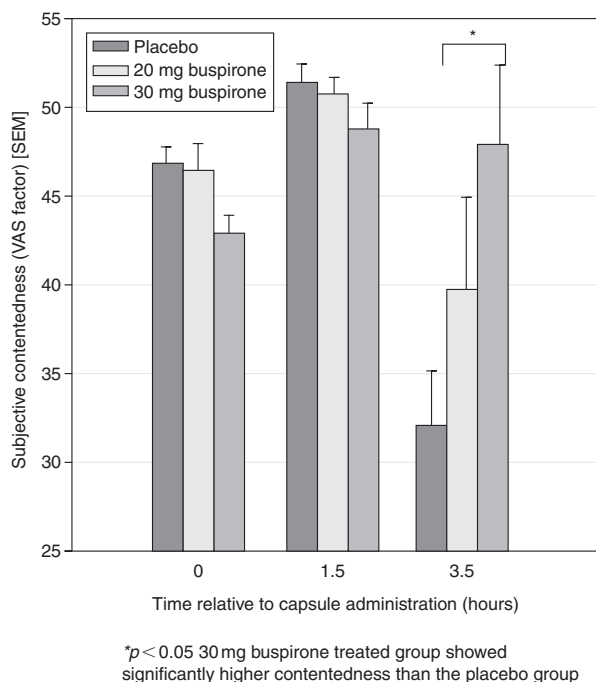


Figure 1 Effects of buspirone on subjective levels of contentedness over the course of the study

Statistical analysis

Data were analysed using one-way or repeated measures analysis of variance (ANOVA), with follow-up Least Significance Difference (LSD) tests as appropriate (Cardinal and Aitken, 2006). Where data did not fulfil normality assumptions, they were subjected to standard transforms or non-parametric tests as indicated.

Results

Groups were well-matched for age and verbal IQ (National Adult Reading Test, NART, Nelson, 1982) (both $p > 0.30$). Mean age and verbal IQ (\pm SD) for the placebo, buspirone 20mg, and buspirone 30mg groups respectively were 23.5 (\pm 6.2), 22.7 (\pm 4.8), 25.0 (\pm 6.7) years; 115.1 (\pm 5.3), 114.1 (\pm 6.1), 115.5 (\pm 6.0) IQ. Buspirone was generally very well tolerated with no reports of adverse events such as nausea or dizziness.

Subjective measures

Factors of alertness, contentedness and calmness were entered into separate repeat-measures ANOVAs. There were no significant group by time interactions or overall group differences for alertness or calmness. However, for contentedness, there was a significant group by time interaction ($p = 0.007$). Follow-up one-way ANOVAs at each time point revealed no significant overall difference between groups on contentedness at baseline and +1.5 hours. As shown in

Fig. 1, there was a significant difference at +3.5 hours ($p = 0.042$) due to the 30mg buspirone group experiencing significantly more contentedness than the placebo group ($p = 0.012$).

Neuropsychological assessment

Data from neuropsychological assessment are presented in Table 1. Groups did not differ significantly overall on any of the neuropsychological test measures (all $p > 0.10$).

Discussion

To the authors' knowledge, this is the first study to assess the acute effects of buspirone using tests designed to tap a comprehensive range of cognitive domains. Prior studies have frequently employed smaller sample sizes and lower doses of buspirone. Sixty healthy male participants received 20 or 30 mg buspirone, or placebo, in a between-subjects double-blind design ($N = 20$ per group). In terms of subjective effects of drug, there was evidence for dose-dependent effects of buspirone on subjective ratings of contentedness. From Fig. 1, it can be seen that contentedness increased for all study groups between the time of capsule administration ($t = 0$ h) and the time at which volunteers finished relaxing in the waiting room prior to cognitive assessment ($t = +1.5$ h). At the end of cognitive assessment, however, there was evidence for reduced contentedness in the placebo group ($t = +3.5$ h). The higher dose buspirone group showed significantly higher contentedness than the placebo group after cognitive assessment. Thus, lengthy cognitive assessment reduced contentedness under placebo and this was blocked by buspirone, arguably consistent with the drug's anxiolytic properties. There were no detectable effects of drug on factors of alertness or calmness. While buspirone was reported to cause subjective drowsiness (suggestive of reduced alertness) in one prior study (Bond *et al.*, 1983), multiple other studies found no significant effects on subjective ratings of arousal/alertness (Grasby *et al.*, 1992a, 1992b; Unrug *et al.*, 1997a; Unrug *et al.*, 1997b). These discrepancies may be due to differing methodologies and methods of assessment between studies. In terms of cognitive performance, there was no evidence of overall differences between the study groups on any measures. These data suggest that, in contrast to other anxiety relieving drugs such as benzodiazepines (Deakin *et al.*, 2004a), buspirone may lack significant deleterious cognitive effects when given acutely at clinically meaningful doses.

Buspirone has been shown to modulate cognitive task performance and neural activity in some healthy volunteer studies (Grasby *et al.*, 1992a; Grasby *et al.*, 1992b). However, despite some evidence that buspirone can modulate aspects of cognition in experimental animals (Pache *et al.*, 2003), prior behavioural studies using buspirone in humans have mostly been negative (Bond *et al.*, 1983; Schaffler and Klausnitzer 1989; Barbee *et al.*, 1991; Hart *et al.*, 1991; Unrug-Neervoort *et al.*, 1992; Unrug *et al.*, 1997a; Unrug *et al.*, 1997b). Consistent with these prior data, the present study confirmed a relative paucity of significant cognitive effects in humans across a range of cognitive domains – including

Table 1 Neuropsychological task performance

Domain	Task, variable	Placebo (N=20)		Buspirone 20 mg (N=20)		Buspirone 30 mg (N=20)		F (df 2,57)	p
		Mean	SD	Mean	SD	Mean	SD		
Memory	AVLT								
	percent correct (1st to 4th recall)	80.21	11.78	81.04	8.28	80.73	10.18	0.034	0.966
	percent correct (interference)	80.83	17.54	81.67	14.96	82.08	13.86	0.034	0.967
	percent correct (delayed)	77.50	18.56	77.50	18.16	75.83	18.52	0.055	0.947
	PRM								
	percent recognition (immediate)	96.25	7.87	95.83	8.33	96.25	7.87	0.018	0.982
	percent recognition (delayed)	93.33	10.68	94.17	9.01	92.92	13.04	0.066	0.936
	SWM								
	between-search errors	18.15	19.00	22.35	21.03	23.60	20.05	0.406	0.668
	within-search errors	1.05	1.93	0.85	1.50	2.40	3.66	2.200	0.120
	double-search errors	0.70	1.42	0.55	1.00	1.45	2.76	1.311	0.277
strategy score	30.95	6.30	31.05	6.42	30.50	6.32	0.043	0.958	
PAL									
total errors	14.45	7.6741	14.20	8.8353	15.30	11.707	0.073	0.930	
trials to criterion, 8 shapes	3.10	0.9119	3.15	1.3089	3.55	1.6051	0.713	0.495	
Executive planning	Tower of London								
	mean moves, easy	1.05	0.08	1.07	0.13	1.08	0.15	0.218	0.805
	mean moves, hard	1.30	0.21	1.47	0.42	1.38	0.36	1.183	0.314
Impulse control	Stop-signal								
	stop signal reaction time (msec)	233.31	53.02	237.47	58.72	252.17	82.58	0.447	0.642
	median 'go' response time (msec)	384.10	44.45	418.26	88.34	446.55	169.79	1.509	0.230
	Information Gathering Task								
boxes opened, fixed reward	14.49	6.52	12.20	3.96	12.41	5.46	1.091	0.343	
boxes opened, decrementing reward	8.74	3.59	8.53	2.20	7.47	3.41	0.945	0.395	
Decision making	Cambridge Gamble Task								
	proportion of rational decisions	0.96	0.08	0.97	0.06	0.93	0.13	0.775	0.465
	mean proportion of points bet	58.40	14.40	59.45	9.93	56.80	11.33	0.246	0.782
mean response time (sec)	1832.01	527.79	2268.85	962.94	2292.19	1139.33	1.610	0.209	
Cognitive flexibility	3D ID/ED								
	pre-ID errors	4.45	2.9643	7.50	8.6054	5.45	5.1245	1.33	0.273
	ID errors	2.05	1.2763	3.7575	5.9429	1.80	0.6959	1.819	0.171
	ED errors	13.716	10.986	11.683	13.245	10.966	11.182	1.641	0.203

AVLT = Auditory Verbal Learning Test; PRM = Pattern Recognition Memory; SWM = Spatial Working Memory; PAL = Paired Associate Learning; 3D ID/ED = 3-dimensional Intra-dimensional Extra-dimensional set shift

memory, executive planning, impulse control, decision making and cognitive flexibility. A range of cognitive tasks was employed, which have previously been shown to be sensitive to pharmacological manipulations.

Potential limitations of this study include the use of relatively high IQ volunteers (which could theoretically contribute to ceiling effects on neuropsychological tasks), and the sample size. However, prior studies have identified cognitive effects of psychiatric medications (including 5-HT drugs, and drugs with sedative effects such as diazepam) using near-identical methodologies, sample sizes and volunteers of comparable IQ for example (Turner *et al.*, 2003; Deakin *et al.*, 2004a, 2004b; Chamberlain *et al.*, 2006b). Nor were the majority of non-significant results consistent with a lack of

power to reveal a systematic effect of the drug, as the means for the two drug groups fell either side of the placebo mean.

Abnormalities in 5-HT neurotransmitter systems have been variably implicated in the manifestation of neuropsychiatric illnesses including anxiety disorders, mood disorders and schizophrenia (Rauch and Jenike 1993; Charney, 1998; Roth and Hanizavareh, 2004; Chamberlain *et al.*, 2005, 2006). It is important to bear in mind that cognitive effects of drugs may differ in people with pre-existing abnormalities in 5-HT systems. It has been suggested that 5-HT_{1A} drugs may be of utility as cognitive enhancers in the treatment of neuropsychiatric illnesses (Roth and Hanizavareh, 2004). Another member of the 5-HT_{1A} agonist class of medications, tandospirone, has been found to improve cognitive

flexibility and verbal memory after chronic treatment as an add-on intervention in people with schizophrenia (Sumiyoshi *et al.*, 2001). Therefore, future studies should investigate cognitive effects of acute and chronic bupirone treatment in people with neuropsychiatric illnesses. Furthermore, 5-HT_{1A} receptors represent just one of many 5-HT receptor subtypes, and the possible involvement of other subtypes in human cognition should also be investigated as safe drugs become available for human use.

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