Lack of deleterious effects of buspirone on cognition in healthy male volunteers

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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 20mg buspirone, 30mg 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 30mg 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, 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 <10mg. 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 20mg or 30mg 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 +/− SD = 23.7 +/− 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 20mg buspirone, 30mg 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 IDE) (Rogers et al., 1999).
Buspirone on cognition

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 (+/− SD) for the placebo, buspirone 20mg, and buspirone 30mg groups respectively were 23.5 (+/− 6.2), 22.7 (+/− 4.8), 25.0 (+/− 6.7) years; 115.1 (+/− 5.3), 114.1 (+/− 6.1), 115.5 (+/− 6.0) IQ. Buspirone was generally very well tolerated with no reports of adverse events such as nausea or dizziness.

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.

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 30mg 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 (\(t=0h\)) and the time at which volunteers finished relaxing in the waiting room prior to cognitive assessment (\(t=+1.5h\)). At the end of cognitive assessment, however, there was evidence for reduced contentedness in the placebo group (\(t=+3.5h\)). 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

![Figure 1: Effects of buspirone on subjective levels of contentedness over the course of the study](image-url)

\(\text{p}<0.05\) 30mg buspirone treated group showed significantly higher contentedness than the placebo group.
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-HT1A drugs may be of utility as cognitive enhancers in the treatment of neuropsychiatric illnesses (Roth and Hanizavareh, 2004). Another member of the 5-HT1A agonist class of medications, tandospirone, has been found to improve cognitive

### Table 1  Neuropsychological task performance

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

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
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 buspirone 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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