Psychopharm

Journal of Psychopharmacology
19(3) (2005) 259–265

ISSN 0269-8811
SAGE Publications Ltd, London, Thousand Oaks, CA and New Delhi
10.1177/0269881105051529

Selective effects of clonidine and temazepam on attention and memory

Brian Tiplady *Department of Anaesthesia, Intensive Care, and Pain Medicine, University of Edinburgh, Edinburgh, UK.*

Ellen Bowness *Department of Neuroscience, University of Edinburgh, Edinburgh, UK.*

Laura Stien *Department of Neuroscience, University of Edinburgh, Edinburgh, UK.*

Gordon Drummond *Department of Anaesthesia, Intensive Care, and Pain Medicine, University of Edinburgh, Edinburgh, UK.*

Abstract

The present study compared the effects of clonidine and temazepam on performance on a range of tasks aiming to assess the role of central noradrenergic mechanisms in cognitive function. Fifteen healthy volunteers (seven male, eight female), aged 18–25 years, took part in a five-period crossover study in which they received placebo, temazepam (15 and 30 mg) and clonidine (150 and 300 μg) by mouth in counterbalanced order in sessions at least 4 days apart. A test battery was administered before treatment and at 45, 90 and 135 min after the dose. Performance on most tests was significantly impaired in a dose-related fashion, and subjective sedation was recorded for both drugs. The greatest impairments with clonidine were on attention in the presence of distractors. Clonidine did not affect the formation of new long-term memories, in contrast to temazepam, but did impair measures of working memory. Subjective effects, especially feelings of drunkenness and abnormality, were particularly marked with clonidine. These results support the suggestion that central noradrenergic function may be involved in preventing distraction, but do not confirm other reports suggesting that some aspects of performance are improved with clonidine.

Keywords

α_2-adrenoceptors, attention, clonidine, cognitive function, learning and memory, noradrenaline, temazepam

Introduction

Noradrenergic systems in the brain appear to be involved in the control of attention and working memory. In non-human primates, depletion of noradrenaline in the prefrontal cortex impairs spatial working memory. Noradrenaline may have an important role in ignoring irrelevant, distracting information (for a review, see Arnsten *et al*., 1996).

Frith *et al*. (1985) studied clonidine, a centrally acting α_2-adrenergic agonist, in humans. They used tests of memory and psychomotor performance, and showed very marked sedation, but the only effect on performance was an impairment to paired associate learning. Clark and co-workers studied the effects of clonidine, methylphenidate (a catecholamine releaser) and droperidol (a dopamine receptor blocker) on attention (Clark *et al*., 1986, 1987). Both clonidine and droperidol impaired speed and accuracy of performance in tests of focussed and divided attention, whereas methylphenidate increased the error rate. In a covert orientation paradigm, droperidol and clonidine both produced apparent reductions in the cost of invalid cueing (the increase in reaction time when a directional cue does not correspond to the direction of the following stimulus), although the response times were substantially increased in all conditions. More recently, Smith and Nutt (1996) showed that clonidine increased the incidence of attention lapses or 'blocks' (Bills, 1931), and that this effect was reversed by idazoxan, an α_2-adrenoceptor antagonist.

These studies have used only drugs specifically affecting catecholaminergic systems. To establish the pharmacological specificity of these effects, comparisons with drugs acting on other systems are required (Tiplady, 1995). Frith *et al*. (1989) compared the effects of clonidine and scopolamine, a muscarinic antagonist, on a skill learning task. Both drugs impaired performance, but scopolamine showed a much greater effect on the permanent acquisition of the skill, suggesting a specific cholinergic effect on this type of learning.

Corresponding author: Dr Brian Tiplady, Department of Anaesthesia, Intensive Care and Pain Medicine, Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SA, UK.
Email: brian@penscreen.com

Coull *et al*. (1995a,b) compared clonidine with diazepam on tests of attention, memory and planning. They used two doses of clonidine, in view of suggestions that the higher dose of clonidine (2.5 µg/kg i.v.) might act differentially on post-synaptic receptors (enhancing adrenergic function) whereas the lower dose (1.5 µg/kg i.v.) might act presynaptically (reducing noradrenergic tone, the generally accepted view of clonidine action; Aghajanian, 1982; Charney *et al*., 1983). Rapid visual information processing was impaired with all treatments. However, paired associate learning performance improved with the higher dose of clonidine and with the lower dose of diazepam. There was also a suggestion of an improvement in spatial working memory at the higher dose of clonidine, and of increased impulsivity with clonidine on the planning paradigm. A subsequent study by Coull *et al*. (1995c) suggested that clonidine acted to broaden the focus of attention. However, the interpretation of these studies is not straightforward. The studies did not include a practice session because the authors wished to investigate the effects of familiarity to the tasks. This led to complex interactions, which do not form a particularly coherent pattern, and it is difficult to avoid the conclusion that there were simply too many variables in a modestly sized study.

Jäkälä *et al*. (1999a,b,c) took a rather different approach, and compared clonidine (oral doses up to 5 µg/kg) to guanfacine, an α_2-agonist selective for the α_2 A subtype found predominantly in the prefrontal cortex. Guanfacine improved performance on tasks that assess planning and working memory, whereas clonidine increased the number of errors in the working memory task, and also slowed performance on choice reaction time. However, both drugs improved performance on paired associate learning. The authors suggested that the improvements in performance result from actions in the prefrontal cortex, whereas impairments are due to actions in the thalamus, associated with sedation. The same group have also reported that clonidine can improve some aspects of performance in patients with Parkinson's disease and Alzheimer's disease.

The suggestion that clonidine may improve functions such as working memory appears surprising in view of the sedative effects of the drug. Many sedative drugs lead to a global pattern of impairment to performance, including very marked effects on various aspects of memory function. Although it is clear that the memory impairment is not simply a by-product of sedation (Veselis *et al*., 2001; Mintzer and Griffiths, 2003), in most cases, different degrees of impairments have been seen rather than improvements of particular functions, and this was the pattern observed in the earlier work with noradrenergic agents (Clark *et al*., 1989; Frith *et al*., 1989). The present study aimed to investigate this further, using a comparison with a drug known to impair memory as well as other aspects of performance. Obtaining reliable and reproducible dissociations between drugs acting on different receptor systems is an important step towards elucidating the role of these systems in behaviour.

Benzodiazepines have been shown to impair both working memory and the formation of new long-term memories, as well as slowing reaction times and impairing attention (Mintzer and Griffiths, 2003; Tiplady *et al*., 2003a). We selected temazepam, as a suitable comparator because its fairly short half-live makes it convenient to use in volunteer studies. We compared two doses of clonidine with two doses of temazepam. Doses were chosen in a range that did not cause excessive sedation or, in the case of clonidine, cardiovascular problems, but that were sufficient to produce reliable effects on performance (Begg *et al*., 2001; Tiplady *et al*., 2003b).

Previous work has used a variety of tests that have not always been used in comparative studies with other classes of drug. Therefore, we studied clonidine and temazepam using a test battery designed to assess a broad range of cognitive and psychomotor functions, including psychomotor speed and accuracy, attention, working memory and the formation of new memories. This battery has been shown previously to be able to distinguish between the performance effects of temazepam and ethanol (Tiplady *et al*., 2003a).

Methods

Design

We used a five-period crossover design comparing the effects of single oral doses of temazepam (15 mg), temazepam (30 mg), clonidine (150 µg), clonidine (300 µg) and placebo in human volunteers.

Subjects

Fifteen volunteers (seven male, eight female), aged 18–25 years (mean 21 years) and weighing 51–127 kg (mean 69 kg), took part. All were healthy as assessed at initial screening, were light to moderate social drinkers, had negative pregnancy tests if female, and were not taking any medication that might have interfered with central nervous system function or drug absorption or elimination. Volunteers provided their written consent to take part in the study, which was approved by the ethics committee of the Lothian Health Board.

Assessments

Spiral maze This paper and pencil maze consisted of a white path bounded by a black spiral, with circular obstacles. The pencil was placed at the centre of the spiral and a line drawn following the spiral as rapidly as possible while avoiding the black sides and the obstacles. Time taken was recorded with a stopwatch, and the error scored obtained by adding one point for each time the line touched the sides of the track or an obstacle, and two points for a penetration (Gibson, 1978).

Rectangular maze (Cameron et al., 2001) A light path appeared on the pen computer screen against a dark background, and the pen was placed on the starting position. When a bell sounded, the volunteer traced the path to the finishing position as quickly as possible while trying stay within the track. Time taken and number of errors (times when the pen left the track) were recorded.

Digit-symbol substitution (Wechsler, 1958; Cameron et al., 2001) In this pencil-and-paper task, a key was provided which matched nine symbols to the digits 1–9. Below this, there was a series of random digits with a box beneath each digit in which the subject wrote the corresponding symbol. The task was to complete as many symbols as possible in 90 s.

Handwriting Volunteers wrote four specified words along a dotted line on the screen of a handheld computer. One word was written at a time, and then the screen was cleared and the next word written. The length and height of each word was recorded by the computer (Tiplady *et al*., 2003a).

Arrow Flanker task A row of five symbols appeared on the screen. The central symbol was an arrow, pointing either right or left, and the task was to tap the button corresponding to the direction of the central arrow as quickly as possible. The other symbols could be either congruent (i.e. arrows pointing in the same direction as the central arrow); non-congruent (i.e, arrows pointing in the opposite direction to the central arrow); neutral (i.e. squares); or nogo (i.e. crosses), which indicated that the volunteer should make no response to the trial. Reaction times to correct responses and the numbers of errors were recorded.

Number pairs A row of five digits appeared on the computer screen, and the task was to tap the 'Yes' button if the second and fourth digits were the same, or a 'No' button otherwise. On some trials, one or more of the non-target digits matched a target, while in others they were different. The reaction times for correct responses and the number of errors was recorded. This task and the preceding task are based on the flanker paradigm described by Eriksen and Eriksen (1974).

Visual search task (Tseng et al., 1998) In each trial, a 6 × 6 array of letter shapes was presented on the computer screen. Each array contained one L-shape, with the rest being Ts. Letter shapes were in any orientation. The task was to detect and tap on the 'L' as quickly as possible. Twenty trials were presented, and the mean correct response time and the total number of correct responses were recorded.

Memory scanning A set of five digits appeared on the computer screen, which the volunteer memorized. Following this, a series of digits appeared one at a time, and the volunteer tapped a 'Yes' button if the digit was in the memorized set, or a 'No' otherwise. Response times for correct responses and numbers of errors were recorded (Sternberg, 1975).

Logical working memory (Kyllonen, 1993) A set of three rules appeared on after the other on the computer screen, each being shown for 3 s, for example, 'The dog comes before the pig'; 'The chair does not come after the table'; 'The furniture comes after the animals'. A set of eight response choices then appears, from which the volunteer taps on the correct one, in this case 'Dog–Pig–Chair–Table'. Twenty-four problems were given, and the total number of correct responses recorded

Selective reminding task (Buschke and Fulde, 1974) The experimenter read a list of 15 words to the volunteer, who then recalled as many words as possible in any order. The experimenter then read out those words not recalled on the first occasion, and the volunteer again attempted to recall the entire list. This procedure was repeated six times. Measures of recall from short- and long-term memory, as well as forgetting from long-term memory, were obtained.

Visual Analogue Scales (VAS) Each scale consisted of a 10-cm line displayed on the computer screen, the ends of which were marked with antonyms (e.g. 'Alert–Drowsy'). Subjects made a mark on the line to indicate how they felt at that moment. The 16 scales described by Bond and Lader (1974) were used, together with 'Sober–Drunk' and 'Normal–Abnormal'.

Equipment Computer-based tests were carried out using an Apple MessagePad MP2000 (Apple Computer Inc, Cupertino, CA, USA), which is a handheld computer with a pen interface.

Procedures

Each volunteer first took part in a familiarization session in which equipment was demonstrated and test procedures practised. The tests were carried out twice, except for selective reminding which was administered once. Volunteers then took part in five treatment sessions, at approximately the same time of day, with an interval of at least 4 days between sessions. Volunteers were instructed not to eat for 4 h before the start of the session, and to drink a maximum of one cup of tea or coffee at breakfast time on the test day (to be the same on each occasion). No further caffeine-containing drinks were permitted on test days until the end of the session. They were instructed to abstain from alcohol from 24 h before the start of the session until 24 h after the end, and not to use tobacco from 2 h before the start until the end of the session.

All test measures except selective reminding were carried out at the start of the session. Volunteers then received the treatment by mouth as matching lactose-filled capsules. The order of treatment administration was randomized using Williams squares (Williams, 1949). The test battery was administered starting at 30, 75 and 120 min post-treatment (mid-points 45, 90 and 135 min, respectively). Selective reminding was carried out only once, at the 90-min time-point, to avoid possible interference between different word lists. The order of test administration was randomized between subjects: for a given volunteer, the order was the same for all test days. At 170 min, volunteers completed the rectangular maze and subjective ratings, and were then evaluated for fitness to return home by taxi.

Statistical analysis

For each test measure except selective reminding, the mean of the three post-dose values was calculated. The mean values were then analysed using analysis of covariance with the baseline (pre-treatment) score as covariate. For selective reminding, the 90-min scores were analysed with analysis of variance. Proc GLM

in SAS was used for these analyses (SAS Inc., Cary, NC, USA), which also provided pairwise comparisons between individual treatments.

For visual analogue scales, the scores for the individual scales were first combined into two factors, Functional Integrity and Mood, as described previously (Cameron *et al*., 2001). Means of the post-dose values of the factor scores as well as the individual scores for the Sober–Drunk, Alert–Drowsy and Normal–Abnormal scales were analysed as described above.

For comparison of effect sizes between the larger doses of the

Table 1 Data from performance tests and visual analogue scales with clonidine and temazepam

Test/measure	Placebo	Temazepam (15 mg)	Temazepam (30 mg)	Clonidine (150 µg)	Clonidine (300 µg)	SE[a]	Treatment, effect, *P*
Spiral maze							
Time taken (s)	22.9	25.1**	28.1***	24.7*	25.1**††	0.80	0.0000
Error score	16.7	14.4	21.7*	19.1†	20.8	2.29	0.0118
Rectangular maze							
Time taken (s)	16.7	19.9**	23.1***	19.1*	21.6***	1.14	0.0000
Errors (*n*)	5.23	5.67	8.03**	6.97	7.67*	0.93	0.0146
Digit-symbol							
Number in 90 s	74.9	69.8*	62.1***	70.6*	66.4***††	2.01	0.0000
Errors (*n*)	0.08	0.02	0.09	0.03	0.02	0.064	0.623
Handwriting							
Word length (pixels)	785	775	778	746	722*††	28.8	0.112
Word height (pixels)	366	369	372	360	351	16.1	0.699
Arrows							
Overall RT (s)	0.664	0.688	0.782***	0.741**†	0.846***††	0.024	0.0000
Overall NE	0.201	0.374	0.686*	0.418	0.655	0.239	0.211
Congruent RT (s)	0.632	0.666	0.751***	0.717***†	0.801***††	0.023	0.0000
Congruent NE	0.053	0.014	0.129	0.032	0.127	0.050	0.0539
Neutral RT (s)	0.653	0.671	0.757***	0.703	0.795***	0.027	0.0000
Neutral NE	0.003	0.087	0.081	0.052	0.211**	0.068	0.0424
Incongruent RT (s)	0.707	0.728	0.826***	0.782**†	0.869***	0.024	0.0000
Incongruent NE	0.108	0.266	0.458*	0.300	0.235	0.152	0.224
Nogo responses (*n*)	0.92	1.20	1.49**	0.96	1.18	0.185	0.0252
Number pairs							
Response time (s)	0.77	0.81	0.99***	0.89*	1.02***	0.045	0.0000
Errors (*n*)	3.94	4.91	6.66**	5.08	6.35*	0.963	0.0406
Visual search							
Response time (s)	2.19	2.20	3.33**	2.50	3.27**	0.373	0.0026
Errors (*n*)	0.062	0.069	0.252*	0.040	–0.000††	0.0916	0.0636
Memory scanning							
Response time (s)	0.77	0.85	1.15***	0.91*	1.12***	0.059	0.0000
Errors (*n*)	12.7	16.1	38.6***	15.4	27.8*	6.12	0.0003
Logical memory							
Number correct	20.28	18.62	15.91***	18.52	15.49***	1.09	0.0001
Selective reminding (%)							
Short-term recall	18.3	28.5	23.6	26.0	26.4	5.74	0.4651
Long-term recall	74.4	70.8	54.0***	76.1	69.0††	4.42	0.0001
Long-term forgetting	4.05	4.02	5.43	5.51	4.78	1.38	0.7099
Visual Analogue Scales							
Sober–Drunk	10.8	13.6	20.1*	22.3*	28.3***	4.39	0.0014
Alert–Drowsy	26.4	31.6	57.0***	48.4***†	60.5***	5.11	0.0000
Normal–Abnormal	16.7	20.7	27.6**	26.0*	37.7***††	3.73	0.0000
Functional integrity	27.8	32.9	52.3***	44.8***†	51.8***	3.54	0.0000
Mood	22.5	23.1	27.3**	25.9*	28.3***	1.42	0.0002

Values are means of the three post-treatment assessments, except for selective reminding, where the mean of the single 90-min time-point is shown. For selective reminding, values are percentages of the maximumpossible score in each case. *P*-values are derived from the analysis of covariance, with baseline (pre-dose) score taken as the covariate, except for selective reminding, where analysis of variance was used. [a]SE indicates the standard error of the estimated differences between treatments. There were no significant differences in baseline scores between treatment conditions. RT, Response time, NE, number of errors. **P* < 0,05; ***P* < 0.01; ****P* < 0.001 compared to placebo. †*P* < 0.05 compared to 15 mg temazepam. ††*P* < 0.05 compared to 30 mg temazepam. Comparisons † and †† were made only between lower doses and higher doses, respectively.

two drugs, the maximum change in the direction of impairment over each test period was taken, and the corresponding placebo value subtracted to give an effect score. The ratios of the effects for clonidine to temazepam were then plotted. These comparisons were only made for measures that showed an significant overall treatment effect.

Results

We found significant impairments after both drugs (Table 1). All tests that included measurement of reaction time or speed of performance showed a significant slowing with the larger dose of both drugs. With the smaller doses, both drugs slowed the two maze tasks and digit-symbol; and clonidine also slowed arrow flankers and number pairs. Error or accuracy scores showed impairment with the larger doses of both drugs for the rectangular maze, number pairs, memory scanning and logical memory; and with the high dose of temazepam for the spiral maze, arrow flanker (both number incorrect and false alarms) and visual search. The pattern of changes for the arrow flanker task was similar for all three types of distractor trials (congruent, neutral and incongruent). Selective reminding was affected only by the larger dose of temazepam, with significant impairment of long-term recall. The length of handwritten words was significantly reduced by the higher dose of clonidine. No measure changed significantly after the smaller drug dose if there was not also a significant effect at the larger dose. No test measure showed significant improvement with clonidine. The visual analogue scales showed the effects of both doses of clonidine and the larger dose of temazepam. Sedation, negative mood and abnormality were reported with both doses of clonidine and with the larger dose of temazepam. The smaller dose of temazepam did not significantly affect subjective reports.

The time course of drug action is shown in Fig. 1, using response time data from number pairs, which is representative of the results obtained. Peak effects were seen at 45 min for temazepam and at 90 min for clonidine, although the difference between the values at these two times was not large.

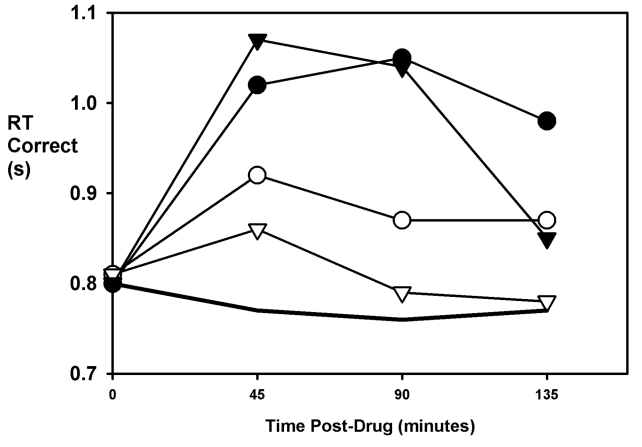

Figure 1 Time course of effects of treatment on response time in the number pairs task. Circles, clonidine; triangles, temazepam; open symbols, smaller dose; closed symbols, larger dose; solid line, placebo

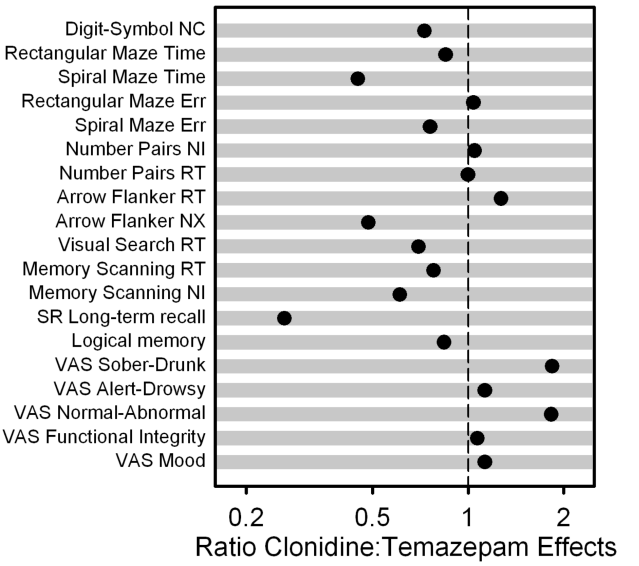

Figure 2 Comparison of the maximum effects (difference from placebo) of the larger doses of clonidine and temazepam (clonidine effect/temazepam effect plotted on a logarithmic scale) A value of 1 indicates identical effects of the two drugs (dashed line). A value to the right indicates that the clonidine effect was larger than that of temazepam, and a value to the left indicates that temazepam was larger than clonidine. NC, number correct; Time, time to complete task; Err, error score; NI, number of incorrect responses; RT, mean reaction time for correct responses; NX, number of false alarms (responses on nogo trials); SR, selective reminding; VAS, visual analogue scales

The effect sizes for the larger doses of the two drugs are compared in Fig. 2, including all measures showing a significant overall treatment effect. The response time for the arrow flanker task showed the greatest effect for clonidine relative to temazepam, whereas the measure of long-term memory from selective reminding showed the smallest relative effect. The subjective effects of clonidine were relatively more marked than those of temazepam. This was particularly true for the ratings of drunk and abnormal feelings.

Discussion

The changes to performance with clonidine shown in this study were exclusively impairments. The three measures with minimal improvements, the error scores from visual search and digit-symbol substitution and short-term recall from selective reminding, were not statistically significant. As expected, temazepam also showed a consistent pattern of impairment to performance.

The pattern of effects of the two drugs was not identical. Clonidine showed a relatively greater effect than temazepam on

reaction time in the arrow flanker test. This supports the suggestion that noradrenaline is involved in focussing attention in the presence of distractors. If the overall effect of clonidine is to decrease noradrenergic function, then distractibility should be increased, thus impairing performance on the flanker task. This is in line with: (i) the impairment of paired associate learning when old associations had to be replaced by new ones (Frith *et al*., 1985); (ii) the suggestion that noradrenaline facilitates disengagement of attention in covert orientation (Clark *et al*., 1989); and (iii) primate studies indicating that enhanced noradrenergic function reduces distractibility (Arnsten and Contant, 1992). The arrow flanker test not only has distractor stimuli, but also the occurrence of the nogo stimuli makes it particularly hard to ignore these non-target distractors.

Clonidine did not affect the formation of new long-term memory in the selective reminding task, in agreement with the results of Frith *et al*. (1985) demonstrating that word list learning is unaffected by clonidine. This lack of effect contrasts with temazepam, which showed a 38% reduction in words correctly recalled in the high dose condition. Ethanol also has a pronounced effect on this aspect of memory, and similar impairments were previously observed after ethanol and temazepam (Tiplady *et al*., 2003a). Because clonidine is at least as sedative as temazepam in the present study, this supports previous work indicating that the effects of benzodiazepines on memory are independent of their sedative effects.

Clonidine did affect other aspects of memory, impairing performance on the memory scanning and logical memory tasks. Both these tasks involve working memory (i.e. the capacity to simultaneously store and process information) (Baddeley, 1996), and are affected to a similar degree by both clonidine and temazepam.

No aspect of memory function was improved by clonidine in the present study. This is in contrast to some, but not all, previous studies in humans (Coull *et al*., 1995a,b; Jäkälä, 1999b). Coull *et al*. (1995a) have suggested that, at higher doses, post-synaptic actions may become prominent, thus increasing noradrenergic tone and leading to performance improvements. The doses used here overlap the high end of the range used by Coull and colleagues. The study by Smith and Nutt (1996) on attention lapses also used a dose comparable to the that of Coull's group, and found only impairment. Taken together, these results support the suggestion that, at doses that can be given to human volunteers, there is an overall reduction in noradrenergic activity. Franowicz and Arnsten (1999) make a similar suggestion about dose relations in the context of comparing animal and human work.

The relationship between speed and accuracy is of interest in view of the finding of a dissociation between temazepam and ethanol, with the latter having much more marked effects on errors, whereas temazepam showed a greater impairment with respect to speed. Our results do not show any clear pattern in this respect, with the effects of the two drugs on speed and error scores being generally similar.

Measurement of handwriting showed a decrease in the length of written words with clonidine. This is an interesting contrast to the previous results obtained with ethanol and nitrous oxide, which showed an increase in word size (Legge *et al*., 1964; Tiplady *et al*., 2003a). As previously shown (Tiplady *et al*., 2003a), temazepam had no apparent effect on word size.

The subjective effects of clonidine were generally more marked than those of temazepam (Fig. 2). This supports earlier studies where the sedation caused by clonidine was particularly marked relative to its effects on objective performance (Ashton and Rawlins, 1978; Frith *et al*., 1985). Clonidine appears to make volunteers 'feel drunk' to a relatively greater extent than temazepam. This is in contrast to the pattern of objective impairment, which does not resemble ethanol.

There was no suggestion in these results of any dissociation of effects by dose. In all cases where a significant drug effect was observed at the larger dose, the value of the measure at the smaller dose was intermediate between the placebo and larger dose values, which is consistent with a monotonic dose–response relationship.

In conclusion, clonidine shows a consistent impairment of performance in human volunteers, with the pattern differing from temazepam in that there are more marked effects on attention and no effect on the formation of new long-term memory.

References

Aghajanian G K (1982) Central noradrenergic neurons: a locus for the functional interplay between alpha-2 adrenoceptors and opiate receptors. J Clin Psychiatry *43*: 20–24

Arnsten A F, Contant T A (1992) Alpha-2 adrenergic agonists decrease distractibility in aged monkeys performing the delayed response task. Psychopharmacology *108*: 159–169

Arnsten A F, Steere J C, Hunt R D (1996) The contribution of alpha 2-noradrenergic mechanisms of prefrontal cortical cognitive function. Potential significance for attention- deficit hyperactivity disorder. Arch Gen Psychiatry *53*: 448–455

Ashton H, Rawlins M D (1978) Central nervous system depressant actions of clonidine and UK-14, 304: partial dissociation of EEG and behavioural effects. Br J Clin Pharmacol *5*: 135–140

Baddeley A (1996) The fractionation of working memory. Proc Natl Acad Sci USA *93*: 13468–13472

Begg A, Drummond G, Tiplady B (2001) Effects of temazepam on memory and psychomotor performance: a dose–response study. Hum Psychopharmacol *16*: 475–480

Bills AG (1931) Blocking – a new principle of mental fatigue. Am J Psychol *43*: 230–245

Bond A, Lader M (1974) The use of analogue scales in rating subjective feelings. Br J Med Psychol *47*: 211–218

Buschke H, Fuld P A (1974) Evaluating storage, retention and retrieval in disordered memory and learning. Neurology *24*: 1019–1025

Cameron E, Sinclair W, Tiplady B (2001) Validity and sensitivity of a pen computer battery of performance tests. J Psychopharmacol *15*: 105–110

Charney D S, Heninger G R, Redmond D E Jr (1983) Yohimbine induced anxiety and increased noradrenergic function in humans: effects of diazepam and clonidine. Life Sci *33*: 19–29

Clark C R, Geffen G M, Geffen L B (1986) Role of monoamines in attention and effort: effects of clonidine and methylphenidate in normal adult humans. Psychopharmacology *90*: 35–39

Clark C R, Geffen G M, Geffen L B (1987) Catecholamines and attention II: Pharmacological studies in normal humans. Neurosci Biobehav Rev *11*: 353–353

Clark C R, Geffen G M, Geffen L B (1989) Catecholamines and the covert orientation of attention in humans, Neuropsychologia *27*: 131–139

Coull J T, Middleton H C, Robbins T W, Sahakian B J (1995a) Clonidine and diazepam have differential effects on tests of attention and learning. Psychopharmacology *120*: 322–332

Coull J T, Middleton H C, Robbins T W, Sahakian B J (1995b) Contrasting effects of clonidine and diazepam on tests of working memory and planning. Psychopharmacology *120*: 311–321

Coull J T, Sahakian B J, Middleton H C, Young A H, Park S B, McShane R H, Cowen P J, Robbins T W (1995c) Differential effects of clonidine, haloperidol, diazepam and tryptophan depletion on focused attention and attentional search. Psychopharmacology (Berl) *121*: 222–230

Eriksen B A, Eriksen C W (1974) Effects of noise letters upon identification of target in a non-search task. Percept Psychophysic *16*: 143–149

Franowicz J S, Arnsten A F (1999) Treatment with the noradrenergic alpha-2 agonist clonidine, but not diazepam, improves spatial working memory in normal young rhesus monkeys. Neuropsychopharmacology *21*: 611–621

Frith C D, Dowdy J, Ferrier I N, Crow T J (1985) Selective impairment of paired associate learning after administration of a centrally acting adrenergic agonist (clonidine). Psychopharmacology *87*: 490–493

Frith C D, McGinty M A, Gergel I, Crow T J (1989) The effects of scopolamine and clonidine upon the performance and learning of a motor skill. Psychopharmacology *98*: 120–125

Gibson H B (1978) Manual to the Gibson Spiral Maze, 2nd edn, Hodder and Stoughton Educational, Sevenoaks

Jäkälä P, Riekkinen M, Sirvio J, Koivisto E, Kejonen K, Vanhanen M, Riekkinen P Jr (1999a) Guanfacine, but not clonidine, improves planning and working memory performance in humans. Neuropsychopharmacology *20*: 460–470

Jäkälä P, Sirvio J, Riekkinen M, Koivisto E, Kejonen K, Vanhanen M, Riekkinen P Jr (1999b) Guanfacine and clonidine, alpha 2-agonists, improve paired associates learning, but not delayed matching to sample, in humans, Neuropsychopharmacology *20*: 119–130

Jäkälä P, Riekkinen M, Sirvio J, Koivisto E, Riekkinen P Jr (1999c) Clonidine, but not guanfacine, impairs choice reaction time performance in young healthy volunteers. Neuropsychopharmacology *21*: 495–502

Kyllonen P C (1993) Aptitude testing inspired by information processing: a test of the four-sources model. J Gen Psychol *120*: 375–405

Legge D, Steinberg H, Summerfield A (1964) Simple measures of handwriting as indices of drug effects. Percept Motor Skills *18*: 549–558

Mintzer M Z, Griffiths R R (2002) Alcohol and triazolam: differential effects on memory, psychomotor performance and subjective ratings of effects. Behav Pharmacol *13*: 653–658

Mintzer M Z, Griffiths R R (2003) Lorazepam and scopolamine: A single-dose comparison of effects on human memory and attentional processes. Exp Clin Psychopharmacol *11*: 56–72

Smith A, Nutt D (1996) Noradrenaline and attention lapses. Nature *380*: 291

Sternberg S (1975) Memory scanning: new findings and current controversies. Quart J Exp Psychol *27*: 1–32

Tiplady, B (1995) The psychopharmacology of attention. In Hindmarch I, Stonier P D (eds), Human Psychopharmacology, vol. 5. Wiley, Chichester, pp. 89–109

Tiplady B, Hiroz J, Holmes L, Drummond G (2003a) Errors in performance testing: a comparison of ethanol and temazepam. J Psychopharmacol *17*: 41–49

Tiplady B, Goodall H, van Rossum B, Drummond G (2003b) Effects of clonidine on psychomotor performance and memory. J Psychopharmacol *17* (Suppl): A73

Tseng H-M, Tiplady B, Macleod H A, Wright P (1998) Computer anxiety: a comparison of pen-based personal digital assistants, conventional computer, and paper assessments of mood and performance. Br J Psychol *89*: 599–610

Veselis R A, Reinsel R A, Feshchenko V A (2001) Drug-induced amnesia is a separate phenomenon from sedation: electrophysiologic evidence. Anesthesiology *95*: 896–907

Wechsler D (1958) The measurement and appraisal of human intelligence, 4th edn. Williams and Wilkins, Baltimore, MD

Williams E J (1949) Experimental designs balanced for the estimation of residual effects of treatments. Austral J Sci Res *2*: 149–168