THE EFFECTS OF NOISE, CLONIDINE, AND IDAZOXAN ON SUBJECTIVE ALERTNESS

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ABSTRACT

Background: The antihypertensive α2-adrenergic receptor agonist, Clonidine, has been shown to impair sustained attention and to slow saccadic eye movements. Noise and the selective antagonist, Idazoxan, reverse clonidine-induced impairment of sustained attention. The present analyses examined the effects of Clonidine on subjective alertness and investigated whether the effects of Clonidine were blocked by Idazoxan and modified by noise. Method: Seventy-six healthy male participants were administered either Clonidine 200μg, Idazoxan 40mg, the combination of Clonidine 200μg plus Idazoxan 40mg, or a placebo in a double-blind, parallel-group design. Half of the participants, balanced across drug treatment groups, were also exposed to 80dB white noise via headphones. At baseline and on three occasions after drug administration, participants rated their alertness. Results: Clonidine significantly decreased alertness, and this effect was reversed by Idazoxan and initially noise. Prolonged exposure to noise did not have an alerting effect in the clonidine condition. Conclusion: Clonidine reduced alertness, and this effect was blocked by Idazoxan and reversed by initial but not pronged exposure to noise.

KEYWORDS: Central Noradrenaline, Noise, Clonidine, Idazoxan, Alertness.

INTRODUCTION

Research on the effects of noise has a long history, and my own research started nearly fifty years ago and has led to over 80 publications on the non-auditory effects of noise on performance and health. One of the explanations of the effects of noise on behaviour has been in terms of arousal. Initially, loud noise increases arousal, which can account for...
some of the improvements found in certain studies.\textsuperscript{[32,74,82,83]} More prolonged exposure leads to over-arousal, which can then be associated with impaired performance and/or a subjective state of increased fatigue. Some of the strongest evidence for the arousal theory of noise comes from studies of the antagonistic effect of noise when a person has a low level of arousal, such as that produced by sleep deprivation.\textsuperscript{[84,85]} Several studies have examined the effects of peripheral catecholamines as indices of arousal. Plasma and urine noradrenaline and adrenaline were increased by noise\textsuperscript{[86]} but were not consistent.\textsuperscript{[87]} However, peripheral measures have many limitations as indices of central noradrenergic function.\textsuperscript{[88]} Smith and Nutt\textsuperscript{[89]} examined the effects of noise following a challenge with the antihypertensive $\alpha_2$-adrenergic receptor agonist clonidine, which produced an effect resembling sleep deprivation. Performance of a sustained attention task was impaired by the Clonidine, and this effect was reversed by noise and blocked by the selective antagonist Idazoxan.

Secondary analyses of other data collected in the original study\textsuperscript{[90]} have examined cardiovascular function and speed of eye movements, both of which might be considered indices of arousal. Clonidine significantly decreased saccade peak velocity compared with placebo. Idazoxan did not show an intrinsic effect on saccades but fully antagonised the effects of Clonidine. Noise had little effect on the speed of eye movements, suggesting that the activation of other neurotransmitter systems may underlie the effects of noise on sustained attention. Blood pressure was relatively stable in the placebo group, increased after Idazoxan and decreased after Clonidine. The effects of the combination of Idazoxan and Clonidine differed for systolic and diastolic blood pressure. Systolic pressure increased, although to a lesser extent than after Idazoxan alone. Diastolic pressure changed little over the first two post-treatment sessions but declined to 95\% of baseline by the third session. At all points, blood pressure was significantly higher in participants who received the combination of Idazoxan and Clonidine than those who received Clonidine alone. There was a trend for a time-by-noise effect for systolic blood pressure, which increased somewhat to 103\% of baseline in the noise condition, but this was only significant in the first post-drug session.

Subjective reports provide another indicator of arousal level. The present study examined the effects of Clonidine and Idazoxan on alertness when the person was in quiet or noise. Based on the results of Smith and Nutt\textsuperscript{[89]}, it was predicted that Clonidine would reduce alertness and that this would be reversed by Idazoxan and initial exposure to noise. It was predicted
that prolonged exposure to noise would not attenuate the reduction in alertness following Clonidine as the noise would no longer be alerting.

**METHODS**

**Participants**
Seventy-six males aged 18-35 years gave written informed consent to participate. All participants were evaluated by checking their medical history, giving them a physical examination and screening haematology and biochemistry tests. Participants who were taking medication, who were drinking more than 21 units of alcohol per week, or who had clinically relevant current or past illnesses, such as hypertension or psychiatric disorders, were excluded. Participants were instructed not to drink alcohol on the night before the test session. The study was approved by the medical ethics committee and conformed to the standards of the Declaration of Helsinki.

**Design**
A randomised, double-blind, between-participants group design was used, in which volunteers were divided into two groups to perform the post-treatment tests, either in quiet conditions or 80dB white noise, administered binaurally via headphones. These two groups were further randomised into four drug treatment groups: placebo, Clonidine 200µg; Idazoxan 40mg or the combination of clonidine 200µg and Idazoxan 40mg, all administered orally. There were thus eight treatment groups with 9-10 participants per group. The drug doses were selected on the basis of behavioural and physiological effects in previous studies. All participants were well practised at a task battery in a separate session prior to testing. On the test days, participants arrived 30 minutes before the tests. The baseline session (conducted in quiet) started at 9.30, and the drugs were administered at 10.30. Post-drug sessions started at 11.00, 13.00 and 15.00. Alertness and other aspects of mood were recorded at the start and end of the test battery, which lasted for approximately one hour. A light lunch was given between the first and second post-drug sessions. All drugs were ingested as two matched opaque capsules.

**Mood rating**
At the start and end of each test battery, the participants rated their mood using visual analogue scales presented on a computer screen.\[91-93\] The ends of each scale had opposite pairs of adjectives (e.g. Drowsy-Alert). The participants moved a cursor across the line, connecting the adjectives until it reflected their current mood. The adjective pairs relating to
alertness were Drowsy-Alert, Weak-Strong, Muzzy-Clear headed, Lethargic-Energetic, Mentally Slow- Quick-witted, Attentive-Dreamy, and Incompetent-Proficient. Scores for each pair could range from 1-50. Pairs were reverse scored if necessary so that high scores reflected greater alertness (maximum score = 350).

**Analysis strategy**

The alertness scores were used as the dependent variables, and separate analyses were conducted for pre- and post-performance ratings. Drug conditions and noise were the between-subject factors. The baseline score was used as a covariate, and the scores from each of the three test sessions were within-subject factors.

**RESULTS**

One participant had incomplete data, and the analyses were based on the data from 75 volunteers.

**Alertness**

The first analysis examined alertness ratings recorded before the start of the performance battery. These results are shown in Table 1. There was a significant effect of the drug (F 3,66 = 3.07 p <0.05). Clonidine led to reduced alertness, an effect that was reduced when Idazoxan was combined with Clonidine. The placebo and Idazoxan conditions were very similar, showing that Idazoxan did not have a stimulant effect. There was a significant interaction between noise conditions and drug conditions. Noise also reduced the effect of Clonidine. In the other drug conditions, noise increased alertness in the placebo condition but led to a slight decrease in alertness in the Idazoxan and Idazoxan + Clonidine conditions.

The post-performance ratings of alertness were lower than the pre-performance ratings. In the analysis of the post-performance ratings of alertness, there was a significant effect of drug conditions (F 3,66 = 2.23 p < 0.05 1-tail) and a non-significant drug x noise interaction. Clonidine again led to reduced alertness (mean = 161.4), which was attenuated in the Idazoxan + Clonidine conditions (mean = 177.1). Idazoxan led to greater alertness than the placebo condition, which may reflect a restoration of function following fatigue.
Table 1: Ratings of alertness before the performance battery (Scores are the adjusted means from the ANCOVA, standard errors in parentheses. Higher scores = greater alertness).

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Idazoxan + Clonidine</th>
<th>Idazoxan</th>
<th>Clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiet</td>
<td>218.4 (18.4)</td>
<td>215.8 (18.6)</td>
<td>233.3 (18.4)</td>
<td>177.9 (18.4)</td>
</tr>
<tr>
<td>Noise</td>
<td>230.0 (17.6)</td>
<td>200.4 (16.7)</td>
<td>211.4 (18.4)</td>
<td>214.1 (18.4)</td>
</tr>
</tbody>
</table>

DISCUSSION

The present results confirm the findings of Smith and Nutt,\textsuperscript{[89]} which showed that Clonidine led to more lapses of attention and that this effect was removed by Idazoxan and by exposure to noise. A major advantage of the present analyses was that they considered the effects of the drugs and noise at two different time points, namely before and after the performance battery. The pre-battery results were the ones which agreed with the results on lapses of attention. At this time, the noise increased alertness, and this effect was very clear in the Clonidine condition, which reduced alertness. In this respect, the results confirm the noise-sleep deprivation literature, which shows that noise can reverse the reduced alertness seen in sleep-deprived individuals.\textsuperscript{[84,85]}

The alerting effect of noise decreases over time, and impairments in performance are often seen following prolonged exposure to noise.\textsuperscript{[82, 83]} This has been interpreted as over-arousal, which manifests itself in terms of fatigue. Given this effect, the prediction was that noise would no longer reverse the effect of Clonidine after prolonged exposure. This result was obtained in the analysis of the post-performance battery alertness ratings. The post-performance alertness ratings showed that the performance of the test battery decreased alertness. Clonidine still reduced alertness at this time, and this effect was attenuated by Idazoxan. Interestingly, Idazoxan alone increased alertness, which suggests that it restores function when it is below the optimal level of alertness but has no stimulant effect when the person has high alertness (e.g., before doing the test battery).

Other results from the study, such as those from the eye movement task\textsuperscript{[90]} showed a different profile of Clonidine and noise effects. This again confirms a common finding in the literature, namely that the effects of noise depend on the task that is being carried out. Another finding is that the type of noise is very important.\textsuperscript{[83]} Indeed, results with rapidly changing noise show different effects to those observed here with continuous white noise.\textsuperscript{[94]} Another limitation of
the present study was that only single doses of the drugs were used, and it is quite likely that a different profile would be observed with larger or smaller doses.

CONCLUSION
In conclusion, previous research has shown that the antihypertensive α2-adrenergic receptor agonist, Clonidine induces a state similar to sleep deprivation and impairs sustained attention and slows saccadic eye movements. Noise and the selective antagonist, Idazoxan, reduced the Clonidine-induced impairment of sustained attention. This effect of noise was not observed in the analyses of saccadic eye movements. The present analyses examined the effects of Clonidine, Idazoxan and noise on subjective alertness before and after a battery of performance tests. In a double-blind, parallel-group design, participants were given either Clonidine 200μg, Idazoxan 40mg, a combination of Clonidine 200μg plus Idazoxan 40mg, or a placebo. Half of the participants were also exposed to 80dB white noise via headphones. At baseline and on three occasions after drug administration, participants rated their alertness before and after a battery of performance tests. Clonidine significantly decreased alertness, and this effect was reversed by Idazoxan and initially by noise. Prolonged exposure to noise did not have an alerting effect in the clonidine condition. Idazoxan increased alertness when it was reduced by the performance of the tasks. Clonidine reduced alertness at both time points, and this effect was blocked by Idazoxan and reversed by initial exposure to noise but not when the noise had been played for approximately one hour.

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REFERENCES


