Computerised psychomotor performance testing: a comparative study of the single dose pharmacodynamics of minaprine and amitriptyline in young and elderly subjects

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The psychomotor and cardiovascular effects of minaprine 100 mg, a novel antidepressant, were compared with amitriptyline 25 mg, as a positive control, and placebo in a single dose randomised double-blind crossover trial using an automated psychomotor test battery (APT), postural sway (PS), blood pressure (BP) and pulse in nine young and nine elderly healthy subjects. Analysis of variance, taking into account baseline values, showed that continuous attention test (CAT), critical flicker fusion threshold (CFFT), decision making test (DMT) and paired word association (PWA) were significantly impaired with amitriptyline compared with minaprine and placebo. Minaprine did not differ from placebo. Amitriptyline significantly lowered supine systolic blood pressure (BP) and all treatments produced significant decreases in heart rate in young and elderly. No age effect on psychomotor performance was seen. Minaprine compared favourably with amitriptyline using the APT with the doses used. The APT is useful in the evaluation of new drugs on psychomotor performance.

Keywords computerised psychomotor performance age antidepressants amitriptyline minaprine

Introduction

Antidepressants have profound effects on sensory, motor, cognitive function and performance, frequently more marked in the elderly [1]. Amitriptyline, in acute single dose with 25 mg [2] and chronic dosing with 25 mg three times daily [3], has been shown to impair critical flicker fusion test (CFFT), decision making test (DMT), choice reaction time, short term memory and data acquisition and verbal recall. Amitriptyline has a half-life ($t_{1/2}$) of 20 h [4] and is frequently used as a positive control in phase 1 studies of novel antidepressants.

Minaprine, 4-methyl-6-phenylpyridazine-3-yl(2-morpholioethyl)amine, is a novel antidepressant, chemically unrelated to other antidepressants. Minaprine enhances serotonergic and dopaminergic neurotransmission but without effects of noradrenergic transmission while it is devoid of anticholinergic effects [5, 6]. Minaprine has a $t_{1/2}$ of 2 h while its major metabolite, the activity of which is still unknown, has a $t_{1/2}$ of 20 h [7]. Minaprine 100 mg twice daily compared with imipramine 50 mg twice daily, in a randomised double-blind trial of 104 patients with DSM-III defined depression, had comparable efficacy, as judged by the

Hamilton Depression Rating Scale, a clinical global impression and the Zung self-rating scale while having fewer adverse effects [8]. This clinical study suggests an active role for the metabolite of minaprine.

Psychomotor testing has been used in the assessment of many antidepressants including tricyclics [1, 2]. Tricyclic antidepressants, including amitriptyline, have been reported to increase the odds ratio of falling to 1.8 [9]. Ray *et al.* [9] concluded that, while cause and effect was not proved, a need for evaluation of newer psychotropics was desirable. Any improvement in adverse effect profile, while providing therapeutic efficacy, would be beneficial. A drug with less psychomotor adverse effects would be advantageous especially in the elderly. There has been no formal assessment of the psychomotor effects of minaprine in healthy subjects.

The comparison of low dose of amitriptyline with a higher dose, in efficacy terms, of minaprine serves to bias the comparison against minaprine. If minaprine were to compare favourably with such a low dose of amitriptyline, this would be strong evidence for a

potential advantage for minaprine. Therefore, the aim of this study was to compare the pharmacodynamic profile of a single dose of amitriptyline 25 mg and minaprine 100 mg with placebo using an automated psychomotor testing (APT) [10], postural sway (PS) and blood pressure (BP) and pulse in healthy young and elderly subjects.

Methods

Nine young (mean age: 25; range: 21–29 years; all male; mean weight: 68 kg) and nine elderly (mean age: 68; range: 60–80 years; three male; mean weight: 78 kg) healthy subjects were recruited. The study was designed to detect an age effect on CFFT of 3 Hz ($\alpha = 0.05$; $\beta = 0.8$) based on previous studies [11, 12]. This sample size would offer greater power to detect a treatment effect of minaprine. Clinical examination, haematological, biochemical and electrocardiographic investigation were undertaken together with urinalysis to exclude significant illness. Regular medication precluded entry. Subjects abstained from caffeine containing products, alcohol and smoking for 24 h prior to study days. Subjects were familiarised with the APT battery and undertook two practice sessions prior to entry to minimise the impact of learning on APT results. Subjects gave written informed consent and the study was approved by the Camberwell Research Ethics Committee. The study design was controlled (positive and placebo), randomised, double-blind with crossover and a minimum 1 week washout was required between each limb of the study. All study days commenced between 08.00–10.00 h in the same study room with similar lighting and distance from the computer. All medication was identical in appearance.

Measurements performed were:

1. Continuous Attention Test (CAT) [13].
2. Critical Flicker Fusion (CFFT) [14].

3. Decision Making Test (DMT) [15].

4. Paired Word Association (PWA) [16].

5. Cognitive Flexibility (CF) [17].

6. Postural Sway (PS) [18] was recorded as degrees of sway from the upright stance in the anterior-posterior plane at baseline, 1, 2, 3, 4, 6, 9 and 24 h.

The APT was recorded at baseline, 2, 4 and 6 h. CFFT was also recorded at 1, 9 and 24 h. Supine, erect and 2 min standing BP and pulse were recorded at baseline, 2, 4 and 6 h. A random zero sphygmomanometer was used for BP recordings.

Statistical analysis

Post treatment changes were determined by calculating the area under the curve (AUC) for each effect vs time curve using the linear trapezoidal rule which was then divided by the time interval (hours) and the baseline score was subtracted to give a mean absolute post treatment score for the total time period. Statistical significance was determined by absolute post treatment change for CAT, DMT, PWA, CF, BP and pulse at 6 h and for CFFT and PS at 9 h and 24 h for each subject using analysis of covariance with baseline as covariate and treatment and age group as factors. Statistical significance was taken at the $P < 0.05$ level.

Results

Psychomotor performance

No age effects were noted for any variable (Table 1). Treatment effects are documented in Table 2. Amitriptyline significantly decreased the CAT score for correctly identified matching pairs by 3.3 compared with minaprine ($P < 0.001$) and by 3.2 compared with placebo ($P < 0.001$) at 6 h. Minaprine did not differ

Table 1 Mean differences (with 95% confidence intervals) after minaprine, amitriptyline and placebo on psychomotor performance between young and elderly subjects

	Minaprine Young–Elderly	Amitriptyline Young–Elderly	Placebo Young–Elderly
CAT (Correct score)	–2.18 (–7.51 to 3.14)	2.06 (–3.26 to 7.38)	–3.47 (–8.79 to 1.85)
CFFT (Hz)	–0.45 (–2.12 to 1.21)	–0.53 (–2.20 to 1.13)	–0.10 (–1.77 to 1.56)
DMT (ms)	–85.25 (–190.7 to 20.2)	–2.94 (–105.4 to 99.5)	–27.9 (–130.4 to 74.6)
PWA (Correct number of pairs)	–3.03 (–8.74 to 2.69)	–3.13 (–8.84 to 2.59)	2.66 (–3.05 to 8.38)
CF (Score out of 16)	–0.96 (–2.43 to 0.51)	0.32 (–1.15 to 1.79)	0.03 (–1.44 to 1.5)
PS (Degree of sway)	–4.07 (–23.2 to 15.1)	8.87 (–10.3 to 28.0)	12.2 (–6.91 to 31.4)

Table 2 Mean difference (with 95% confidence intervals) after minaprine (M), amitriptyline (A) and placebo (P) on psychomotor performance in all subjects

	A–M	P–M	P–A
CAT (Correct score)	–3.3 (–5.03 to –1.57)*	–0.1 (–1.83 to 1.63)	3.2 (1.47 to 4.93)*
CFFT (Hz)	–1.7 (–2.28 to –1.12)*	0.2 (–0.38 to 0.78)	1.9 (1.32 to 2.48)*
DMT (ms)	27.6 (2.31 to 52.9)**	–13.1 (–47.5 to 21.3)	–40.7 (–64.6 to –16.8)**
PWA (Correct number of pairs)	3.06 (1.69 to 4.43)*	0.45 (–0.93 to 1.83)	–2.61 (–4.01 to –1.21)*
CF (Score out of 16)	–0.2 (–0.63 to 0.23)	0.05 (–0.38 to 0.48)	0.25 (–0.18 to 0.68)
PS (Degrees of sway)	5.54 (–3.38 to 14.46)	–1.48 (–10.4 to 7.45)	–7.02 (–15.9 to 1.84)

* = $P < 0.001$; ** = $P < 0.05$.

significantly from placebo. Amitriptyline significantly decreased CFFT by 1.7 Hz compared with minaprine ($P < 0.001$) and by 1.9 Hz compared with placebo ($P < 0.001$) at 9 h. Minaprine did not differ significantly from placebo. By 24 h, the effects of amitriptyline were no longer detectable. Total response time to DMT was significantly increased by amitriptyline by 27.6 ms compared with minaprine ($P < 0.05$). Amitriptyline increased response time by 40.7 ms compared with placebo ($P < 0.05$). Minaprine did not differ significantly from placebo. Amitriptyline significantly impaired PWA score by 3.06 compared with minaprine ($P < 0.001$) and by 2.61 compared with placebo ($P < 0.001$) at 6 h. No significant difference was noted between minaprine and placebo. CF did not distinguish between either drug or placebo and PS did not distinguish statistically between either drug or placebo. Amitriptyline increased PS by 4.07 degrees of sway compared with minaprine and by 12.2 compared with placebo. However, there was no significant differences between the treatment groups.

Cardiovascular response

Amitriptyline significantly lowered supine systolic BP by 3.79 mm Hg compared with minaprine ($P < 0.01$), and by 2.9 mm Hg compared with placebo ($P < 0.01$). There were no other statistically significant differences noted with BP treatment groups. Analysis of the pulse data documented significant differences between young and elderly and between treatment groups at 6 h (results not shown). However, these differences were not felt to be clinically relevant as no subject reported symptoms with changes in either BP or pulse.

No subject reported any adverse effects with either drug in response to a questionnaire which included common anticholinergic symptoms (results not shown) and all subjects completed the study.

Discussion

We have used a computerised program of APT in the assessment of a novel antidepressant, minaprine. We have documented significant differences in CNS performance between single doses of minaprine 100 mg

and amitriptyline 25mg. We have demonstrated that amitriptyline impaired sensorimotor function (indicated by increased PS and delay in DMT), impaired central processing (indicated by reduced CAT score), impaired central integration of sensory input (indicated by CFFT) and impaired memory recall (indicated by PWA) [19]. Minaprine did not produce the changes known and demonstrated here, to be associated with amitriptyline [2, 3]. Minaprine did not differ significantly from placebo. Both minaprine and placebo differed significantly from amitriptyline in CAT, CFFT, DMT and PWA.

In order to identify a difference between the young and elderly in, for example, CFFT of 3 Hz, our study had an 80% power to detect such a difference at the 5% level of significance. The use of a multivariate approach tended to increase power by reducing variance attributable to age independent of other effects. In the absence of an age effect, the data were pooled and analysed by treatment only.

Although this study was designed primarily to investigate psychomotor performance, amitriptyline significantly lowered supine BP compared with minaprine and placebo. Though this was not remarked on by the subjects and was not felt to be clinically relevant, in patients on chronic dosing, hypotension can be a problem [20].

Minaprine, at a dose of 100 mg twice daily, has been proven to be effective in clinical trials of depression [21]. More recent research with minaprine, has suggested a potential additional role in the treatment of Alzheimer's disease and multi-infarct dementia [22].

In summary, significant alterations in psychomotor performance have been consistently detected with older antidepressants including amitriptyline. None of the newer drugs has superior efficacy compared with amitriptyline [23]. However, psychomotor performance testing using the APT can distinguish newer drugs with improved side effect profiles. At the dose studied, minaprine has psychomotor performance advantages over amitriptyline in healthy subjects. Our study demonstrates the usefulness of the APT battery in determining the effects of new compounds on psychomotor performance.

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