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Clinical pharmacology of sibutramine hydrochloride (BTS 54524), a new antidepressant, in healthy volunteers

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The cardiovascular, anticholinergic and central effects of single doses of 30, 45 and 60 mg of sibutramine hydrochloride (BTS 54524), a new potential antidepressant, were compared with amitriptyline (50 mg) and placebo given at weekly intervals in a randomised design to six healthy male volunteers. Sibutramine was associated with increases in both supine heart rate and systolic blood pressure at 1, 2 and 6 h after 60 mg ($P < 0.05$). Amitriptyline caused a significant 50–60% decrease in salivation compared with placebo at 2 and 6 h but there were no changes with sibutramine. No significant changes in pupil size were detected with either drug. Visual analogue rating scales (VARS) revealed significant drowsiness with amitriptyline but neither sedative nor stimulant effects with sibutramine. Impairments of simple auditory and visual reaction times, visual two-choice reaction time, finger tapping and trail making, measured using an automated test battery, occurred with amitriptyline compared with sibutramine. If sibutramine proves to be an effective antidepressant it should be devoid of anticholinergic or central depressant effects. Chronic dosage studies are indicated to evaluate the clinical significance of its cardiovascular effects.

Keywords sibutramine cardiovascular anticholinergic and CNS effects volunteers

Introduction

Preclinical studies have shown that sibutramine hydrochloride (BTS 54524) (*N*-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl-*N*, *N*-dimethylamine hydrochloride monohydrate) has properties suggestive of a potent and rapidly acting potentially stimulant antidepressant drug which is free from anticholinergic and cardiovascular side-effects. It is a monoamine reuptake inhibitor active against noradrenaline and serotonin and to a lesser extent dopamine, and rapidly down-regulates both β-adrenergic receptor binding as well as the noradrenaline-stimulated adenylate cyclase system (Buckett *et al.*, 1987a, b).

The present phase 1 study was a double-blind comparison of the cardiovascular, anticholinergic and central effects of three single doses of sibutramine (30 mg, 45 mg and 60 mg) with those of a standard antidepressant, amitriptyline (50 mg) and placebo.

Methods

Subjects and study design

Six healthy male volunteers, aged 20–26 (mean 22) years weighing 62.5–83.5 (mean 72.0) kg who had given informed written consent, received single doses of 30 mg, 45 mg and 60 mg of sibutramine in ascending order as well as placebo and amitriptyline 50 mg at intervals of 1 week. Amitriptyline and placebo were given in random order on randomised occasions but full randomisation was not possible since this was the first time sibutramine was being given to man at these

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dose levels. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Queen's University of Belfast. Exclusion criteria were as follows: history of cardiovascular, respiratory, hepatic or renal disease; allergy or hypersensitivity to any drug; psychiatric or neurological disease; drug abuse; or drug ingestion 14 days prior to the study. The volunteers were fasted overnight from 22.00 h, permitted only one cup of tea or coffee before the study and drinks containing caffeine were not permitted until after completion of the tests. No alcohol was permitted from 08.30 h on the day before until 08.30 h on the day after each study day. Volunteers were screened for hepatitis B (Australia antigen) and routine haematological and biochemical screening were performed at baseline and 24 h after drug ingestion. After baseline assessments the drugs were taken at 09.00 h and assessments of cardiovascular, anticholinergic and central effects measured over the following 24 h.

Assessment procedures

Supine and standing heart rate (HR) and blood pressure (BP) were recorded by an automated device after 8 min supine rest at baseline and at 1, 2 and 6 h. A 12-lead ECG was carried out at baseline and at 3 h. Salivary secretion was measured over 2 min using a dental roll technique (Turner, 1980) and pupil size using a pupilometer disc supplied by the Boots Company plc. Both measures were carried out at baseline and at 1, 2 and 6 h. Sixteen visual analogue rating scales (VARS) (Norris, 1971) for a variety of moods and subjective feelings were administered at 1, 2, 3, 6 and 24 h. In addition any subjective adverse effects were recorded at these times. Psychomotor effects were measured using an automated psychological assessment system (APAS) for use with an Apple IIe microcomputer devised by Elithorn and Lavander (Elithorn *et al.*, 1982). These assessments included finger tapping, simple auditory and visual reaction times, two visual two-choice reaction time tests, trail making, trigram (recognition of 3 letter words and non-words), Necker cube and the perceptual maze test (Smith *et al.*, 1978). The latter test yields four measures: latency, motor time, total number of correct mazes and processing time. A total of 25 measures are produced by the Elithorn APAS. Each subject had two pre-study practice sessions on the complete test battery, which took 30–40 min to administer. This APAS battery was then carried out between 3.5 and 4.5 h after drug ingestion on each study day.

Statistical analysis

HR, BP and pupil size data were analysed using an analysis of variance of repeated measures and where a significant interaction between treatment and time was detected ($P < 0.10$) an analysis to compare treatments was performed at each time using one way analysis of variance and the Newman Keuls multiple range test (statistical significance: $P < 0.05$) (Armitage, 1971). Salivary flow, VARS and psychomotor data were analysed by the Friedman two-way non-parametric analysis of variance (ANOVA) (statistical significance: $P < 0.05$) followed by the Wilcoxon Signed Rank Test (statistical significance: $P < 0.01$).

Results

Cardiovascular effects

Sibutramine was associated with dose-dependent increases in both supine and standing HR which were statistically significantly different from placebo for supine HR at 6 h after 45 mg, and at 1, 2 and 6 h after 60 mg ($P < 0.05$). Supine systolic BP was significantly elevated by the 60 mg dose at all times and by 30 mg at 2 h, compared with placebo. The effects of amitriptyline were not significantly different from placebo but the effects on supine HR and systolic BP were significantly different from those of sibutramine (60 mg) at all times after baseline.

Anticholinergic effects

Salivary flow was analysed by percentage change because of wide individual variations in baseline values. Highly significant decreases in salivation occurred with amitriptyline compared with placebo at 2 and 6 h ($P < 0.005$, Wilcoxon) but no changes with any of the doses of sibutramine (Figure 1). There were no statistically significant differences in pupil diameter with either amitriptyline or any of the doses of sibutramine compared with placebo.

Central effects

Three of the 16 Norris VARS which measure the main factors identified by Bond & Lader (1974) and shown to be sensitive to drug effects, *viz.* alertness, contentedness and calmness were analysed. Highly significant sedative effects were found with amitriptyline compared with placebo at 2 and 3 h on the alert-drowsy scale ($P < 0.005$). No other significant differences were found nor any subjective stimulant effects detected. The

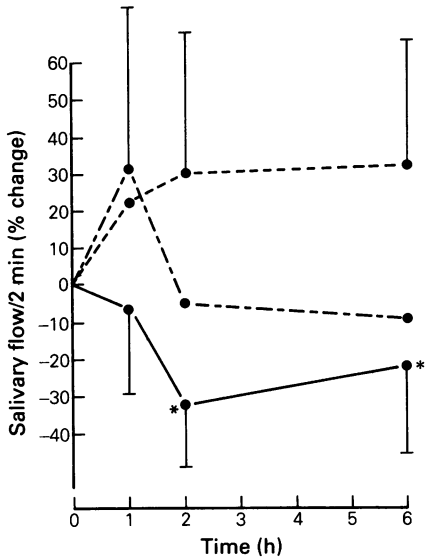

Figure 1 Effects of amitriptyline (50 mg, ——) and sibutramine (60 mg, — · —) on salivary flow compared with placebo (----), expressed as percentage change from baseline (mean ± s.d.). 30 mg and 45 mg doses of sibutramine also did not differ from placebo and have been excluded in the interests of clarity. * $P < 0.005$ from placebo (Wilcoxon).

subjective adverse effects recorded all six volunteers reporting drowsiness (but not dry mouth) with amitriptyline. One volunteer complained of dry mouth with each dose of sibutramine. Drowsiness was reported by one volunteer after 30 mg sibutramine and by another after 45 mg, while one volunteer complained of a 'nervous feeling' after 45 mg sibutramine and another of 'tension' after 60 mg.

In spite of wide inter-individual variations in response in all of the APAS tests, a general trend towards impairment was observed for amitriptyline but for none of the doses of sibutramine. The Friedman ANOVA was statistically significant for 7 of the 25 tests. These were auditory, visual and visual two-choice reaction times on the left-side and finger tapping and three trail-making tests (Table 1). The majority of these were due to significant differences in function with amitriptyline compared with one of the doses of sibutramine. No statistically significant differences were found with the tests with a larger cognitive component (perceptual maze or trigram). With the perceptual maze test there was no consistent change in the number of mazes correctly completed, mean search time was increased, and there was a mean 17.5% fall in processing speed (nodes/second) with amitriptyline compared with placebo.

Discussion

The clinical pharmacological profile of sibutramine was quite different from amitriptyline. Sibutramine was associated with small but statistically significant increases in supine HR and systolic BP, while amitriptyline caused a (non-significant) rise in standing HR in association with falls in both supine and standing systolic and diastolic BP.

Amitriptyline was associated with an expected 30% decrease in salivation compared with a 30% increase with placebo (Longmore *et al.*, 1985; Szabadi & Bradshaw, 1986) but there were no consistent changes with sibutramine. None of the drugs significantly altered pupil size. Amitriptyline has variously been reported to cause mydriasis, miosis and no change in resting pupil size (Szabadi & Bradshaw, 1986) the effect appearing to depend on the interaction of muscarinic, α-adrenoceptor blocking effects and the level of arousal of the subject. The lack of statistical significance of our findings with sibutramine might have been due to the relative insensitivity of our method of measurement.

Neither subjective, sedative or stimulant effects of sibutramine were detected with the VARS for alertness, contentedness or calmness. Amitriptyline on the other hand was invariably associated with drowsiness and with marked and highly significant changes on the VARS alertness scale at 2 and 3 h.

Both subjective and psychomotor effects of single doses of amitriptyline have been reported to persist from 90 to 300 min after dosing (Bye *et al.*, 1978) and the peak plasma concentration occurs at 235 min (Warrington *et al.*, 1984). Our psychomotor tests were performed between 210 and 270 min after dosing. The APAS tests which proved sensitive to acute drug effects were finger tapping, trail making and reaction times on the non-dominant side. Only one of these showed a significant placebo-drug difference (effect of amitriptyline on finger tapping), the remaining differences being between amitriptyline and one of the doses of sibutramine. This was partly because the small number of subjects reduced the statistical power of this preliminary study in which the Wilcoxon Signed Rank Test was not able to evaluate differences in a number of the tests because of tied ranks. However the data suggest that the effects of sibutramine may be in the opposite direction to amitriptyline, i.e. towards improvement in psychomotor performance (Table 1). Stimulant effects on performance, however, are often more difficult to demonstrate than impairments (Loke & Meliska, 1984).

Table 1 Effects of sibutramine and amitriptyline on psychomotor performance (mean ± s.d.)

	Placebo	*Amitriptyline*	*Sibutramine* 30 mg	45 mg	60 mg
Reaction times (ms)					
Auditory (L)	193.20 ± 23.35	210.45 ± 32.22	201.62 ± 22.01	200.4 ± 25.88	181.15 ± 14.64†
Visual (L)	235.88 ± 21.23	389.30 ± 275.14	253.45 ± 50.51†	225.25 ± 18.41†	240.45 ± 33.78
Visual two-choice (L)	334.62 ± 46.99	429.33 ± 143.17	349.53 ± 58.46	337.45 ± 57.41†	328.45 ± 49.23†
Finger tapping (number s^{-1})					
(Alternating L/R)	4.33 ± 0.65	3.95 ± 0.69*	4.53 ± 0.80	4.33 ± 0.74	4.5 ± 0.73†
Trail making (s/digit)					
Digits (1)	1.6 ± 0.38	1.82 ± 0.62	1.97 ± 0.59	1.50 ± 0.28Δ	1.38 ± 0.26Δ
Digits (2)	1.47 ± 0.24	1.97 ± 0.96	1.48 ± 0.16†	1.32 ± 0.23†	1.40 ± 0.20
Alternating digits/letters	1.82 ± 0.23	2.28 ± 0.62	1.88 ± 0.16	1.80 ± 0.36	1.55 ± 0.14†

* different from placebo $P < 0.01$ (Wilcoxon); † different from amitriptyline $P < 0.01$ (Wilcoxon); Δ different from sibutramine 30 mg $P < 0.01$ (Wilcoxon).

The effects of practice were controlled by two pre-study sessions on the APAS which a previous, unpublished study with six volunteers suggested was adequate to reach a plateau of performance in all the tests, except for the perceptual maze. McClelland (1987) has shown that four practice sessions are adequate for most psychomotor function tests. Our inability to use a fully balanced design may, however, have reduced the sensitivity of our APAS tests due to continued learning effects particularly with the perceptual maze test.

In conclusion, single doses of sibutramine had sympathomimetic effects on the cardiovascular system but lacked clinically significant anticholinergic effects and was devoid of sedative effects. However, the cardiovascular effects may limit the doses that can be safely used in clinical trials and further studies are also required to elicit possible psychostimulant properties.

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