Pharmacological studies of fluphenazine and nortriptyline in combination in man

Combinations of fluphenazine and nortriptyline are being assessed in the management of patients with anxiety states complicated by depression according to Drs N. G. Lambert and P. V. Pigott (personal communication). Although fluphenazine in single doses of 1 and 2 mg has been shown to have no significant effect on critical flicker frequency (Turner, 1966; Lind & Turner, 1968), it was considered desirable to study the effects of these combinations on central nervous function in man, after single and multi-dose administration, and to compare them with those of an alternative form of treatment, such as diazepam.

Eight healthy volunteers of either sex aged 18–30 years received no other oral or parenteral medication during the week before entering the study or during the experimental period. Pregnant women were excluded. Subjects were randomly allocated, on the basis of two latin square designs, to the following treatments: (1) fluphenazine 0·5 mg + nortriptyline 10 mg, 1 capsule three times daily for 4 days; (2) fluphenazine 0·5 mg + nortriptyline 20 mg, 1 capsule three times daily for 4 days; (3) diazepam 2 mg, three times daily for 4 days; (4) matching placebo capsules, 1 three times daily for 4 days. All subjects received all treatments with 10 days elapsing between treatments.

Immediately before starting each treatment, 3 h after the first dose and 3 h after the last dose the following tests were made: (i) critical flicker frequency (Turner, 1968); (ii) disc dotting (Hedges, Hills & others, 1971); (iii) serial subtraction (Hedges & others, 1971) and (iv) reaction time, using electronic recording apparatus. Salivary volume was measured by the method of Herxheimer & Haefeli (1966) 3 h after the last dose.

The results were subjected to an analysis of variance, the treatment sum of the squares being proportioned to provide independent tests of (*a*) placebo x active drugs, (*b*) diazepam x both combination treatments (*c*) fluphenazine plus nortriptyline 10 mg x fluphenazine plus nortriptyline 20 mg.

The salivary volume showed a significant difference between treatments ($P < 0{\cdot}05$), and this was due to the difference of both combination forms from placebo ($P < 0{\cdot}01$). Although the mean sputum volumes after each combination were not significantly different, the greater fall in volume when compared with placebo was seen, not unexpectedly, with that combination containing nortriptyline 20 mg. The only other statistically significant treatment differences were at the 5% level between the combination containing nortriptyline 10 mg and that containing nortriptyline 20 mg in disc dotting (day 1) and reaction time (day 5). Neither differed from placebo, however, and it is unlikely that these were important, as there was no significant difference in the changes from initial control values to those after treatment on day 1 or day 5.

It would appear, therefore, that while both treatments containing the anticholinergic compound nortriptyline produced a significant reduction in salivary volume, none of the treatments significantly impaired central nervous function as measured by critical flicker frequency, disc dotting or reaction time, either after single-dose administration or after treatment for 4 days. The critical flicker frequency in particular is a sensitive test of central function, permitting discrimination of many centrally acting drugs in single normal therapeutic doses from placebo preparations (Turner, 1968).

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Promethazine on hand-eye co-ordination and visual function

Although it is widely recognized that compounds with central depressant and sedative effects may seriously impair driving ability and other skills, there is a lack of screening tests that will demonstrate such impairment in small numbers of subjects. Measurement of critical flicker frequency (c.f.f.) may show significant changes in visual discrimination induced by single therapeutic doses of many centrally acting drugs (Turner, 1968).

Molson, Mackey & others (1966) described a test that demonstrated significant impairment of hand-eye co-ordination after promethazine hydrochloride (50 mg) in four subjects. The apparatus then used has been adapted slightly to study the effect of promethazine hydrochloride (25 mg) in this test, and other aspects of visual function have also been examined.

The apparatus consists of a rotating metal drum 16 cm long and 14 cm diameter covered with an insulating material. Punched into this material are 224 holes, each 5 mm in diameter, in the form of an irregular spiral. The drum is turned at a constant speed of 8 rev/min by an electric motor. A metal pointer with a graphite top can be moved across the drum by means of a small steering wheel 16 cm in diameter and a shaft mechanism. When the pointer is accurately controlled along the course of the spiral track, an electrical current is completed each time the pointer strikes a hole in the insulating material. The number of such contacts is recorded electrically by a digital counter.

Retinal sensitivity, colour vision, oculomotor balance, pupil diameter and amplitude of accommodation were measured by conventional methods (Bedwell, 1967; Austen, Gilmartin & Turner, 1971).

Six male students, aged 20–22 years, in good health, with visual acuities of 6/4·5 or better in both eyes, and who were receiving no other medication, were given promethazine, 25 mg, orally or a placebo in random order under double-blind conditions. At least one week elapsed between each treatment. Each subject was fully familiarized with the techniques to minimize learning effects, and abstained from stimulants, alcohol and nicotine during the experiments. Measurements were made before and at 1½ and 3 h after administration of the treatment. The tests were made between 12 noon and 3 p.m.

Promethazine produced a significant reduction in the hand-eye co-ordination test score when compared with placebo, which was most marked at 3 h ($d = 16{\cdot}8$, s.c. $= 4{\cdot}23$, $t = 3{\cdot}906$, $P < 0{\cdot}02$). No significant differences were observed on retinal sensitivity, colour vision, oculomotor balance, pupil diameter and amplitude of accommodation.