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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.

Turner (1968) found that promethazine (25 mg) produced significant reduction in c.f.f. and the present study has also shown that the same dose impairs hand-eye co-ordination. The absence of effects on the peripheral components of visual function that were measured would suggest that these effects of promethazine are predominantly, if not wholly, central. No subjective effects of sedation were reported during the 3 h of the experiment when changes in co-ordination were observed, although sedation about 6 h after taking promethazine was noted by all the subjects. This suggests that the hand-eye co-ordination test described, like c.f.f., is able to demonstrate central effects of drugs at a time, or at a dose, when subjective evidence of sedation is not noted. For this reason, and because of its simplicity and the few subjects required, it may prove a useful test in the screening of new drugs for effects on the central nervous system.

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Brain acetylcholine and monoamines during experimental catatonia

Disorders of the extrapyramidal motor system occur in man after large doses of chlorpromazine and reserpine. When given to animals in correspondingly large doses, these drugs bring about a state of catatonic immobility. Bulbocapnine, a drug classically associated with experimental catatonia (De Jong, 1945) also evokes extrapyramidal signs in man (Henner, 1928). It is known that chlorpromazine and reserpine affect the function of monoamine-containing neurons in the brain. We have, therefore, measured the concentrations of 5-hydroxytryptamine (5-HT), noradrenaline and dopamine in the brains of rats made catatonic with bulbocapnine, and also in rats subjected to sound-induced seizures, a procedure which is followed immediately by a period of catatonia (Stainbrook & De Jong, 1943). There is also some evidence that the catatonic state in animals might be associated with an excess of free acetylcholine in the brain, since intracerebral injection of acetylcholine or cholinesterase-inhibiting drugs produces catatonia (Feldberg & Sherwood, 1954; Wada, 1962; Kassil, Latash & Ruthman, 1963). Furthermore, remission from catatonic stupor has been obtained both in animals (Sherwood, Ridley & McCullock, 1952) and in man (Sherwood, 1952) by the intraventricular administration of cholinesterase. We have examined the effect of drug-induced and post-seizure catatonia on the concentration of "free" and "bound" acetylcholine and also the total concentration of acetylcholine in rat brain. No assertions have been made concerning the identity and significance of the "free" and "bound" fractions of brain acetylcholine, but a number of drugs have been shown to affect them differently