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Hangover effects of hypnotics in man

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Using a battery of psychological tests, Kornetsky, Vates & Kessler (1959) found significant impairment of performance 15 h after a hypnotic dose (200 mg) of chlorpromazine or quinalbarbitone. Similarly Malpas, Rowan, Joyce & Scott (1970) reported behavioural impairment and electroencephalographic changes 12 h or more after nitrazepam or amylobarbitone sodium. Such effects detectible the morning after taking a sleeping tablet, can be termed residual or 'hangover'.

The study to be reported investigated the hangover effects of two commonly prescribed hypnotics: butobarbitone sodium (100 and 200 mg doses) and nitrazepam (5 and 10 mg doses) as compared with placebo. Ten normal subjects each received all five treatments at weekly intervals as part of a balanced design, using double-blind procedures. The drug was taken at 23·00 h and the battery of physiological and psychological tests was carried out between 11·5 and 12·5 h later. The physiological tests included recording the electroencephalograph (E.E.G.) both at rest and during an auditory reaction time task, and palmar sweat gland activity. Psychological tests included tapping rate (a measure of simple motor speed), the digit symbol substitution test (a measure of coding and associative skills) and linear scales on which the subjects rated themselves for such features as quality of sleey the previous night and their feeling of alertness at the time of testing.

In general, on the mornings following drug induced sleep, tapping was slower, auditory reaction time was prolonged and fewer items of the digit symbol substitution test were completed than on placebo occasions. Impairment of performance was marked after the higher doses of each drug and was mainly due to a slowing down process as performance times were increased much more than were errors. Subjectively, quality of sleep was improved after the drugs but alertness at the time of testing was diminished only after the higher doses.

The E.E.G. also showed significant changes: the slow wave-bands were decreased and the fast bands increased. For example, the proportion of fast wave activity (13·5–26·0 Hz) was increased by both drugs and this variable was very sensitive to drug effects.

Thus, definite hangover effects are demonstrable 12 h after hypnotic doses of a barbiturate and a new, widely used, non-barbiturate hypnotic. Although these hypnotics lessen the distress of the insomniac patient, attention is drawn to the psychological impairment and electrophysiological changes which are inevitably left the next morning.

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Tyramine metabolism and migraine: a metabolic defect

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A possible role for tyramine in the pathogenesis of migraine was suggested by the demonstration, in patients who gave a history of dietary precipitation of attacks, that oral tyramine could induce migraine (Hanington, 1967). Analysis of the urinary metabolites following oral tyramine in subjects with dietary migraine demonstrated a significant decrease in the excretion of conjugated tyramine when compared with normal controls (Smith, Kellow, Mullen & Hanington, 1970). Our present work was aimed at elucidating the nature of the conjugate whose excretion was reduced and determining whether this reduction could be demonstrated, not only in patients with dietary migraine, but also in migrainous subjects who did not relate their attacks to diet.

Four controls and nine migrainous subjects were investigated, the migrainous group consisting of five dietary and four non-dietary cases. All subjects ingested a capsule containing isotopically labelled tyramine (10 μCi *p*-hydroxyphenylethylamine-2-^{14}C) at 10.00 h, and urine was collected over the subsequent 12 hours. Over 98% of the recovered activity was excreted in the first 12 h, therefore we confined our investigations to this period.

When chromatograms of whole urine specimens run in butanol–acetic acid–water (60–15–25) were photographed using a spark chamber scanner (Hesselbo, 1968) four distinct spots were found. After acid hydrolysis two of these spots disappeared suggesting that they were conjugates. Known volumes of each urine specimen were chromatographed and the bands given by the conjugate cut out, and their activity calculated using a TriCarb scintillation counter. The activity of one of these spots was reduced in the migrainous group as compared with the controls. By the use of preparatory chromatograms and elution a quantity of this substance was obtained. It was a single chromatographically pure substance which was totally hydrolysed by acid liberating a single compound which co-chromatographed with tyramine in three different solvents. On enzymic hydrolysis, using either limpet arylsulphatase B or mylase (Koch Light), it was again totally hydrolysed liberating tyramine. Authentic tyramine-O-sulphate (Mattock & Jones, 1970) co-chromatographed with our unknown, confirming that it was indeed tyramine-O-sulphate.

Tyramine-O-sulphate would appear to be a quantitatively important urinary metabolite accounting for about 15% of the ingested dose in normal controls. The migrainous group excreted some 10% of the dose which is significantly less than the controls (P=0·02). Even when considered separately, both the dietary and non-dietary group excreted significantly less tyramine-O-sulphate than controls, though the values for the dietary group tended to be lower than those of the non-dietary group.