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EFFECTS OF HYPNOTIC AND SLEEP-INDUCING DRUGS ON OBJECTIVE ASSESSMENTS OF HUMAN PSYCHOMOTOR PERFORMANCE AND SUBJECTIVE APPRAISALS OF SLEEP AND EARLY MORNING BEHAVIOUR

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1 An acute dose comparison against placebo of the effects of nitrazepam 5 mg and temazepam 15 and 30 mg on measures of arousal and performance and on subjective assessment of sleep was carried out in 20 subjects with a history of using night-time medication for insomnia.

2 Amylobarbitone (100 mg) was included as an active control and each drug was given in hard gelatin capsules. Subjects reported improved sleep with nitrazepam 5 mg and temazepam 30 mg, but there was evidence of impaired performance the next day with temazepam 30 mg.

3 The effect of temazepam 20 mg prepared in the Scherer formulation was compared against placebo in a further ten subjects. The subjects reported improved sleep without evidence of impaired performance the next day.

Introduction

BIXLER *et al.* (1972) have maintained that an early morning "hangover" and disruption of behaviour are an inevitable consequence of the nocturnal administration of an effective hypnotic. Hypnotics have been shown to disrupt psychomotor performance after both single and repeated doses, and several benzodiazepines used as hypnotics have been shown to disrupt sleep and early morning behaviour (Bond & Lader, 1972; 1973; Gaillard *et al.*, 1973; Malpas *et al.*, 1974; Hindmarch, 1975).

Disruption of psychomotor integration in the early morning after both single and repeated doses of hypnotics assumes importance in patients having to drive motor vehicles or operate complex machinery. Concern has been expressed by traffic and health authorities (WHO, 1971) regarding the interference with car driving skills produced by psychoactive compounds. Lader (1975) has drawn attention to the effect of the widely prescribed benzodiazepines on psychomotor skills analogous to car driving. Studies of benzodiazepines on real car driving performance (Betts *et al.*, 1972) have shown that some interfere with low speed skills, but results from real car driving studies are somewhat equivocal due to the interaction of experience and learning with the performance measure.

Driving simulators (Fargus & Hindmarch, 1974) and analogues of aspects of car driving such as motion sickness susceptibility (Croucher & Hindmarch, 1973) and psychomotor integration (Linnoila & Mattila, 1973) have indicated that a wide range of benzodiazepines might interefere with such skilled behaviour; and the latter authors suggest that laboratory assessments of psychomotor performance are important analogues of car driving behaviour, as such sensorimotor integration is a necessary component of the skilled behaviours used in driving motor vehicles.

This paper reports studies aimed at the acute and chronic effects of a variety of benzodiazepines and other hypnotics on laboratory assessments of psychomotor performance the morning after overnight medication. As these drugs are to be used as hypnotics in patients, the subjective appraisal of sleep and early morning behaviour is also studied.

Methods

Assessments

The studies reported here all use the following three assessments:

Choice reaction time (CRT) In the choice reaction time apparatus the subject is required to scan an array of small lights which are illuminated on a random basis. As soon as the subject detects the light, he is expected to touch the appropriate response button to extinguish the light. The latency of this response is an assessment of the integrity of the sensorimotor system and an accurate measure of

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psychomotor performance. If the distance the subject has to move his hand to touch the response button is the same for each response light then it is possible to measure both the movement time as separate from the recognition time. The apparatus used is described in full elsewhere (Hindmarch, 1975; Hindmarch *et al.*, 1977) and later versions have been controlled on-line using a Nova 1B computer.

Critical flicker fusion threshold (CFF) The critical flicker fusion threshold is used as an index of the state of CNS arousal or the ability to integrate discrete units of sensory data. For this assessment, subjects are required to detect flicker in a set of four light-emitting diodes in foveal fixation at 1 metre according to the psychophysical method of limits for ascending and descending thresholds (Woodworth & Schlosberg, 1958).

Leeds Sleep Evaluation Questionnaire (SEQ) This set of 10 cm line analogue rating scales has been used extensively to measure the subjective assessments of four aspects of sleep and early morning behaviour — ease of getting to sleep (GTS), quality of induced sleep (QOS), ease of awakening (AFS) and integrity of behaviour following wakefulness (BFW). A detailed description of the scale and its use is to be found elsewhere (Parrott & Hindmarch, 1978).

Subjects

Throughout these studies all subjects were consenting adult volunteers in the age range 22-58 years. All volunteers were in good physical and mental health and signed consent forms claiming they were free from a history of renal, hepatic, cardiac, psychiatric or any other disease requiring prolonged medical attention. Pregnancy (possible or actual) and concurrent treatment by a medical practitioner also precluded participation in any of the experiments. For the duration of the studies all subjects refrained from excessive alcohol and used public transport, but there were no restrictions as to diet or fluid intake in order to represent the situation experienced by patient populations prescribed hypnotic preparations.

Results from acute dose studies

Twenty subjects, with a history of night-time medication for insomnia, took part in a study in which temazepam 15 mg, temazepam 30 mg, amylobarbitone sodium 100 mg, nitrazepam 5 mg or placebo were given as a single nocturnal dose. Each subject acted as his own control and thus received each treatment condition at 4-d intervals to allow for excretion of drugs and metabolites. All treatments were packaged in identical hard gelatin capsules, and the morning following treatment all subjects were assessed on the three assessment measures — CRT, CFF and SEQ. The results are given in Table 1 as mean ± s.d. together with levels of significance from paired *t* tests carried out between placebo and drug conditions.

Ten subjects (mean age 26.2 yr) were given an acute dose of temazepam 20 mg or matching placebo presented as a solution in a soft gelatin Scherer capsule. Each subject acted as his own control and was assessed on the three assessment measures the morning following night-time medication with the drug. The design was a simple crossover between the treatment conditions and the results are given in Table 2 for the change produced by the active drug with respect to placebo values. Levels of significance are indicated from paired *t* tests carried out between the two conditions.

Discussion

The acute dose studies reported here show that the established benzodiazepine hypnotic, nitrazepam, significantly improves the ease of GTS and the QOS

Table 1 Mean values (±s.d.) obtained for each assessment following acute doses of four hypnotics and placebo

			Placebo	*Amylobarbitone sodium 100 mg*	*Nitrazepam 5 mg*	*Temazepam 15 mg*	*Temazepam 30 mg*
SEQ	GTS	cm	5.09(1.64)	5.50(1.34)	6.99*(1.56)	5.56(1.36)	6.63*(1.59)
	QOS	cm	4.62(1.43)	5.38(1.17)	5.58**(1.68)	4.67(0.94)	5.31(1.71)
	AFS	cm	4.98(1.76)	4.48(1.76)	4.37(2.24)	4.01(1.51)	3.89(2.09)
	BFW	cm	5.14(1.04)	4.60(1.09)	3.93**(1.74)	4.69(1.39)	3.41***(1.36)
	CRT	seconds	0.45(0.09)	0.45(0.10)	0.48(0.10)	0.47(0.08)	0.48*(0.10)
	CFF	H2	35.9(3.5)	34.3(3.1)*	35.3(3.0)	35.2(3.1)	35.1*(2.9)

For a two-tailed *t* test between placebo and drug treatments: *$P<0.05$; **$P<0.02$; ***$P<0.05$.

(Table 1). Equally effective is an acute dose of temazepam 30 mg in a hard gelatin capsule. However, both these benzodiazepines achieve their hypnotic/sleep-inducing effect at the expense of a significant impairment of performance the morning following night-time medication, as evidenced in the significant impairment of the perceived integrity of the behaviour following wakefulness. Although nitrazepam does not impair CRT at any level of acceptable significance, it produces the same mean change from placebo value as does the acute dose of temazepam 30 mg. The latter compound significantly impairs the objective measures of early morning psychomotor performance and the integrity of CNS processing (CFF). Although amylobarbitone sodium does not produce significant results for the SEQ ratings, the perceived improvements in GTS and QOS are mirrored in the impairments of AFS and BFW. It seems that temazepam 15 mg is too low a dose to be very effective as an hypnotic, although it seems to behave similarly to amylobarbitone sodium 100 mg. It is interesting to note that temazepam 30 mg produces an impairment of CFF threshold. The lowering of CFF threshold with the barbiturate is to be expected from its action on cortical mechanisms, but temazepam, as a benzodiazepine, is thought to act primarily in mid-brain regions. The lowering of CFF in this instance is due most probably to the 'hangover' perceived in the subjective ratings and to a metabolic 'hangover' of both drug and active metabolites.

In Table 2, where the changes produced by an acute dose of temazepam 20 mg in a Scherer capsule are presented with respect to placebo values, we find that temazepam is an effective sleep inducer and improver of the perceived quality of sleep. This sleep-inducing activity is manifest without any noticeable hangover of effects to the morning of the next day. As it has been shown (Hindmarch, 1975) that an acute dose of temazepam 20 mg in a conventional hard gelatin capsule produces a perceived hangover in disrupting both BFW and AFS measures, this lack of impairment can be attributed to the different presentations of the medication. When presented as a solution in a soft gelatin capsule the maximal effect will be experienced more rapidly and the metabolic processes of elimination begun almost immediately, so making it possible for any residual effects to subside before the morning of the following day.

These acute dose studies do show efficacy of some benzodiazepine derivatives as sleep inducers, but also indicate the importance of the presentation of the medication. Nevertheless, it seems that the effectiveness of a hypnotic is manifest as a disruption of performance the morning following treatment, an important consideration for patients taking the first doses of chronic regimens.

A repeated dose study of temazepam 10, 20 and 30 mg in Scherer capsules (Hindmarch, 1976) has shown a clear dose–response relationship for all subjective measures on the SEQ and for objective assessments of CRT. The most interesting finding from this study was that as the ease of GTS is significantly improved by repeated doses of temazepam 30 mg, so the objective measure of early morning performance (CRT) is significantly impaired. This repeated dose study showed no evidence of a rebound of detrimental effects following cessation of treatment on either of the objective measures (CFF and CRT); but both GTS and BFW assessments were impaired some four nights following cessation of treatment with temazepam 30 mg.

Conclusions

Effectiveness of the sleep induction and improvement of the perceived quality of sleep is often mirrored in the subjective reports of impairment in early morning behaviour and difficulty in awakening from sleep. In some instances the impairment of behaviour produced by hypnotics is also apparent at an objective level as a disruption of complex reaction time and for critical flicker fusion thresholds. Objective measures of psychomotor performance, such as CRT, relate closely to performance in everyday situations where skilled sensorimotor integration is needed — for example, car driving and lathe operating. It is therefore important that the effects of hypnotics on early morning performance be noted and patients warned about the possible interference with their everyday behaviour.

Table 2 Change, with respect to placebo, produced by an acute dose of temazepam 20 mg presented in a Scherer capsule

	CRT (seconds)	*CFF (H2)*	*GTS (cm)*	*QOS (cm)*	*AFS (cm)*	*BFW (cm)*
Temazepam 20 mg Scherer WRT Placebo	+0.04	+0.2	$P<0.01$ +1.74	$P<0.02$ +1.7	+0.32	−0.02

Levels of significance are indicated from paired tests carried out between the two treatment conditions.

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