Clobazam in Combination With Nomifensine (HOE 8476):
Effects on Mood, Sleep, and Psychomotor Performance Relating to Car-Driving Ability

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ABSTRACT

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The effects of three dose regimens of HOE 8476, a combination of nomifensine (25 mg) and clobazam (7.5 mg), placebo, and a combination of amitriptyline (25 mg) and chlordiazepoxide (10 mg) were compared in a five-period double-blind randomised crossover study. Ten healthy volunteer drivers took part in the study, and were tested at weekly intervals preceded by a 48-hr predosing period and followed by a 4-day washout period. The sedative activity of amitriptyline/chlordiazepoxide (AMI/CHLOR) was shown on nearly all the subjective and objective measures of behaviour employed, while, in contrast, there was a relative lack of sedation and performance impairment attributed to HOE 8476, except with complex tasks at the higher dose level. The results of the study confirm previous results in volunteers that HOE 8476 has psychotropic activity which differs from that of a standard antidepressant/benzodiazepine combination in that it is not accompanied by significant sedation or impairment of psychomotor performance.

Key words: HOE 8476, psychomotor, performance, mood, sleep, car driving, nomifensine, clobazam

INTRODUCTION

Nomifensine is an antidepressant with a novel chemical structure and pharmacological profile [Hanks, 1977]. In extensive clinical studies it has been shown to be an effective antidepressant in comparison with placebo and to have equal efficacy to the tricyclic antidepressants while being relatively free from troublesome side effects [Brogden et al., 1979]. In particular, it has minimal

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anticholinergic activity and is free from sedative effects [Hanks, 1977]. Studies with nomifensine on psychomotor performance [Hindmarch and Parrott, 1977] and simulated aspects of car-driving ability [Hindmarch, 1977] have shown the drug to be relatively free from disruptive effects.

Clobazam is a 1,5-benzodiazepine which has been shown to be an effective anxiolytic in comparison with placebo and standard 1,4-benzodiazepines [Brogden et al., 1980]. At the anxiolytic dosage of 20–30 mg per day it has minimal sedative activity and does not impair psychomotor performance [Hindmarch, 1979a; Borland and Nicholson, 1974]. In particular clobazam has been shown not to impair laboratory assessments of skills related to car-driving [Hindmarch, 1979a,b] or actual car-handling ability [Hindmarch et al., 1977].

HOE 8476 is a fixed-ratio combination (10:3) of nomifensine 25 mg and clobazam 7.5 mg. The monosubstances have been shown not to have pharmacokinetic interactions [Rupp et al., 1979]. In a previous volunteer study, HOE 8476 was shown not to impair car-driving ability and to be free from significant effects on psychomotor performance in comparison with amitriptyline 25 mg/ chlordiazepoxide 10 mg (AMI/CHLOR) [Hindmarch et al., 1980]. In this previous study HOE 8476 (25 mg/7.5 mg) was administered for a 48-hr treatment period, one capsule three times daily.

The aim of the present study was to compare the effects of HOE 8476, one capsule three times daily (t.d.s.), two capsules t.d.s., and three capsules at night; with AMI/CHLOR, one capsule t.d.s.; and placebo on measures of mood, sleep, and psychomotor performance, including car-handling ability in a group of volunteer subjects. The AMI/CHLOR acts as a positive control.

METHODS

Ten female volunteers (age range 26 to 38 years; mean age 32 years), who were all experienced drivers, were selected for the study. They were all physically healthy and had no significant past or current medical history. They were not receiving concurrent medication apart from the contraceptive pill. All subjects used public transport for the duration of the study; alcohol was discouraged throughout the study and not permitted during the pretreatment days and on the study days.

Medication was given for 48 hr prior to testing and consisted of the following: HOE 8476 one capsule t.d.s.; two capsules t.d.s.; three capsules at night; AMI/CHLOR one capsule t.d.s.; placebo. Each subject received each treatment in turn. The order of treatment was allocated according to a randomised balanced-block design. Testing took place at weekly intervals preceded by the 48-hr period of drug administration, leaving a 4-day washout period between treatments. A further single dose of medication (or placebo) was administered on the morning of the test day approximately 1 hr prior to testing. Following the morning session subjects were given a light lunch followed by a further dose of medication (or placebo) 1 hr prior to the afternoon test session, during which many of the tests were repeated.

Subjects were familiarised with the assessment procedures and allowed to practise on all measures prior to the start of the study.

Assessments

Middlesex Hospital Questionnaire (MHQ).   [Crown & Crisp, 1970]. All subjects completed the MHQ before entry into the study. All other measures were repeated on each test day.

Leeds Sleep Evaluation Questionnaire (LSEQ).   [Hindmarch, 1975; Hindmarch and Parrott, 1978, 1980] The effects of treatment on subjective sleep factors, namely, getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS), and behaviour following wakening (BFW) were assessed on the LSEQ, which consists of a series of 10-cm visual analogue scales grouped according to the four sleep factors under consideration. The LSEQ was completed on the morning of the test day.

Linear Analogue Rating Scales (LARS).   These consist of a series of 10-cm visual analogue scales relating to mood and subjective feeling states (e.g., alertness, anxiety, tension, depression, etc.), which in normal volunteers are thought to represent responses to general sedative properties of medications.

Critical Flicker Fusion Threshold (CFFT). [Hindmarch, 1975] This was used as an objective index of CNS arousal and measured using the Leeds Psychomotor Tester. The mean threshold was determined from six presentations according to the psychophysical method of limits.

Choice Reaction Time (CRT). [Hindmarch and Parrott, 1978] was used as an index of sensory-motor performance, the mean latency of response for 25 presentations being the assessment measure recorded.

Serial subtraction of numbers (SSN). This was used to assess mental arithmetic ability at three levels of difficulty, namely, the mean time taken to make 20 sequential subtractions of 3s, 7s, or 17s from a five-figure random number.

Car-driving performance. Performance was scored on a ten-point scale by marshals of the Tockwith Driver Training Centre on a set of tests similar to those used in other studies [Betts et al., 1972; Hindmarch, 1976; Hindmarch et al., 1977; Hindmarch and Gudgeon, 1980]. Five aspects of car handling were assessed, namely, reversing, parking, width estimation, brake reaction time, and slalom driving. Each test was repeated twice and the mean score taken as the assessment measure.

Card sorting. was used as a measure of psychomotor performance comprising a conceptual and a motor element; three levels of difficulty were assessed, namely, colours, suits, and numbers. The time taken for sorting was recorded.

Peg board. A standard peg board was used to assess motor coordination, and the times taken for construct and break-up were measured.

Concept Identification Test (COITEST). A COITEST was used to measure the speed of processing cognitive information.

The results were analysed using analysis of variance; factors for drug and period of administration were included. Pairwise comparisons of treatment means were made using the Duncan New Multiple Range Test.

RESULTS

All the subjects fell within the normal range on subscales of the MHQ (Anxiety = 8.2 ± 0.9; Phobia = 5.0 ± 0.8; Obsession = 5.7 ± 0.8; Somatic Symptoms = 2.9 ± 0.6; Depression = 2.8 ± 0.4; Hysteria = 6.8 ± 0.8).

Side effects of treatment recorded throughout the study were: HOE 8476 I t.d.s., 3; HOE 8476 II t.d.s., 5; HOE 8476 III at night, 1; AMI/CHLOR I t.d.s., 17; placebo, 4.

Of the assessment measures used, CRT, Peg Board, COITEST, and the car-driving tests failed to discriminate drug effects. The results are summarised in Table 1.

The results for the LARS and for the CFFT, which represent indices of subjective and objective sedative effects, respectively, are shown in Figure 1. On the LARS no dose of HOE 8476 showed significant differences from placebo, in contrast to AMI/CHLOR, which did ($P <$ ($P < 0.01$). Similar results were obtained with CFFT, an objective index of sedation (Fig. 1). In addition there was a significant deterioration of performance on this test in the afternoon ($P < 0.05$).

The results from the card sorting are shown in Figure 2. While there are no treatment effects for colour sorting, the more complex tasks of sorting suits and numbers show significant treatment effects. AMI/CHLOR significantly impairs performance compared with placebo in card sorting. HOE 8476 I t.d.s. or III at night are not different from placebo, but HOE 8476 II t.d.s. shows significant impairment compared with both placebo and with the other doses of HOE 8476 ($P < 0.05$), thus demonstrating a dose-response relationship on this test measure.

The SSN mental arithmetic task produced inconsistent results, which are shown in Table 2. The simple task, subtraction of 3s, produced no impairment by any of the medications. In the more complex tasks, subtraction of 7s and 17s, HOE 8476 did not produce any impairment of performance while AMI/CHLOR produced impairment of subtraction of 17s in the morning session and of 7s in the afternoon session.
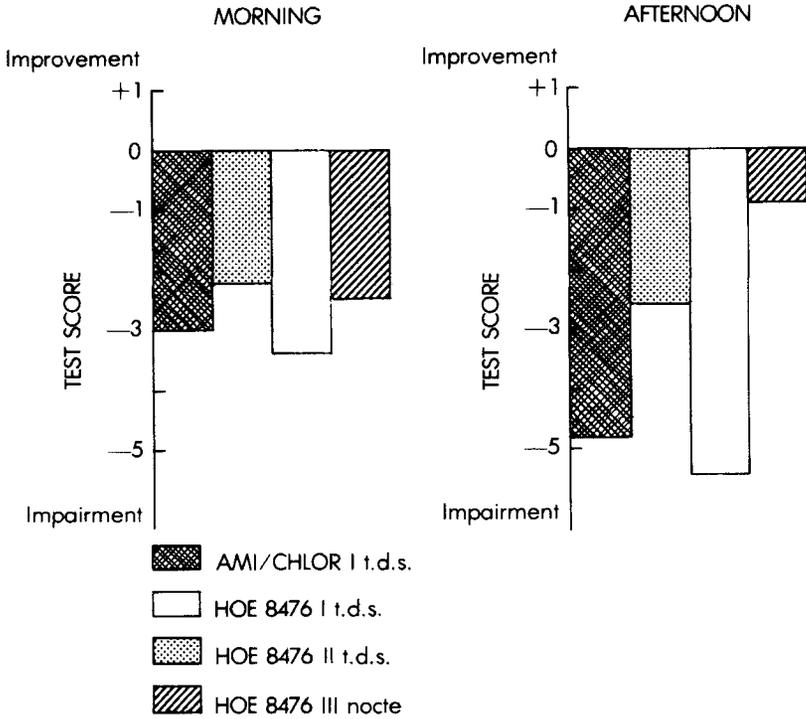
MORNING   AFTERNOON

Fig. 1.   Linear Analogue Rating (LAR) scales and Critical Flicker Fusion Threshold (CFFT) (change in mean total score with respect to placebo).

TABLE 1. Summary of Results on Nondiscriminant Tests (Anovar)

Test	F-ratio	Treatment Mean (± SEM)				
		A	B	C	D	E
CRT (msec)						
Morning	0.61	516.0	515.3	506.0	519.8	514.3
		(12.2)	(11.8)	(9.8)	(10.1)	(12.0)
Afternoon	1.84	507.4	509.0	515.2	526.6	503.7
		(8.8)	(12.8)	(14.0)	(15.5)	(9.4)
Peg board (sec)						
Construct	1.28	109.1	107.0	110.8	114.7	107.1
		(4.3)	(3.5)	(5.3)	(3.6)	(5.7)
Break-up	1.39	65.3	64.4	64.3	66.9	60.8
		(2.6)	(3.3)	(3.3)	(2.3)	(3.8)
COITEST (sec)	1.56	10.7	10.6	8.3	11.7	9.3
		(1.5)	(1.7)	(0.8)	(1.3)	(0.8)
Car-driving (ten-point scale)						
Morning	0.75	7.52	7.40	7.49	7.44	7.74
		(0.18)	(0.21)	(0.15)	(0.17)	(0.17)
Afternoon	1.96	7.76	7.48	7.93	7.54	8.02
		(0.13)	(0.24)	(0.16)	(0.18)	(0.11)

A = HOE 8476 I t.d.s.
B = HOE 8476 II t.d.s.
C = HOE 8476 III at night.
D = AMI/CHLOR I t.d.s.
E = Placebo.

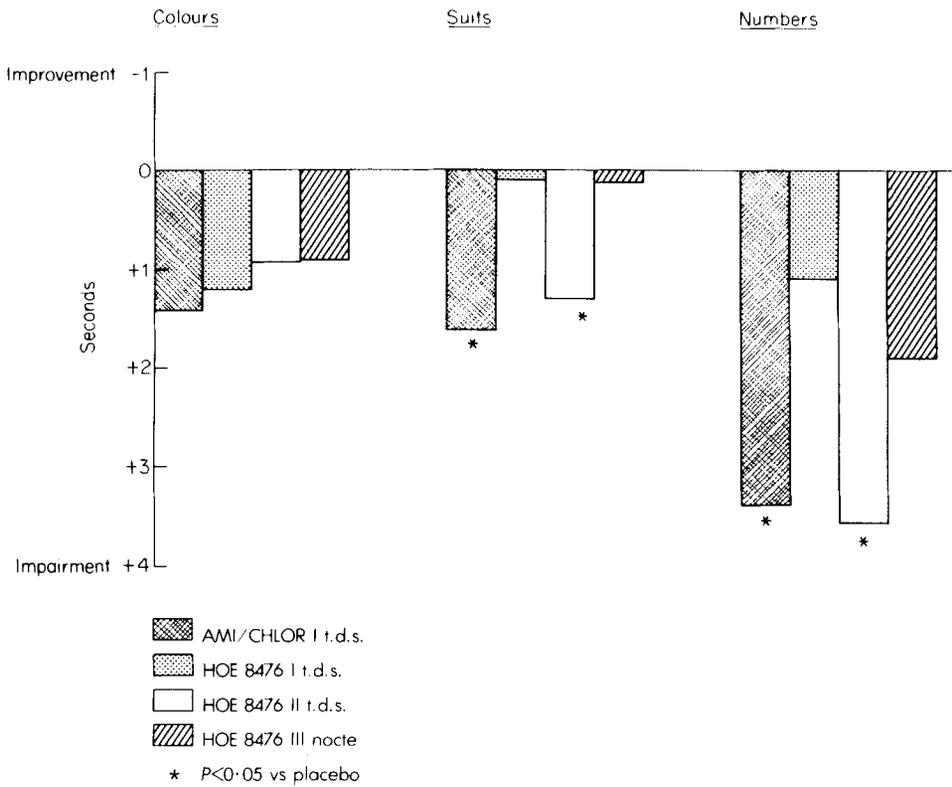Colours   Suits   Numbers

AMI/CHLOR I t.d.s.

HOE 8476 I t.d.s.

HOE 8476 II t.d.s.

HOE 8476 III nocte

★ P<0·05 vs placebo

Fig. 2.   Card sorting (change in mean total score with respect to placebo).

TABLE 2. Serial Subtraction of Numbers (SSN)

	F-ratio	Treatment Mean (sec ± SEM)				
		A	B	C	D	E
Threes						
Morning	0.991	29.8	29.6	30.8	30.9	28.3
		(3.4)	(2.9)	(3.3)	(3.1)	(2.3)
Afternoon	1.699	28.4	26.3	27.1	32.0	28.6
		(2.9)	(2.2)	(2.7)	(4.9)	(3.3)
Sevens						
Morning	1.667	42.3	40.1	44.2	45.0	39.2
		(5.7)	(3.0)	(4.3)	(4.6)	(3.0)
Afternoon	3.509	36.8	37.2	40.0	46.4*	38.7
		(2.5)	(3.1)	(4.1)	(6.0)	(3.3)
Seventeens						
Morning	2.722	60.4	56.0	55.3	67.0*	53.1
		(10.1)	(6.4)	(5.9)	(9.0)	(5.9)
Afternoon	1.124	63.7	54.5	61.2	65.3	52.4
		(16.0)	(6.9)	(7.9)	(10.0)	(4.9)

A = HOE 8476 I t.d.s.
B = HOE 8476 II t.d.s.
C = HOE 8476 III at night.
D = AMI/CHLOR I t.d.s.
E = Placebo.
* = $P < 0.05$ pairwise comparison with Placebo from Duncan New Multiple Range Test.

The car-driving tests failed to show statistically significant drug effects. However, a clear pattern emerges (Fig. 3) with AMI/CHLOR and the high dose of HOE 8476 showing greater performance impairment than the lower dose of HOE 8476. In addition the effect of the nocturnal administration of HOE 8476 appears to be less in the afternoon of the following day compared with the morning.

The effects of the medications on sleep factors measured by the LSEQ are shown in Figure 4. AMI/CHLOR has hypnotic activity and improves the quality of sleep. While in this study it does not significantly impair ease of awakening, it does impair early-morning behaviour. In contrast, no dose of HOE 8476 shows hypnotic activity in terms of getting to sleep; all doses improve the quality of sleep without impairing ease of awakening or early-morning behaviour.

DISCUSSION

As in the previous study [Hindmarch et al., 1980], the inclusion of AMI/CHLOR as a positive control showed that the battery of tests used here included those sensitive to the impairment produced by a sedative drug combination. Some tests failed to discriminate significantly between the treatments; nevertheless, the positive control, AMI/CHLOR, shows a noticeable impairment, compared with placebo, on CRT, peg board, COITEST, and the car-driving tests.

The results of the mental arithmetic tasks (SSN) are inconsistent. The simplest task, subtraction of 3s, failed to demonstrate any drug discriminant trends. With increasing difficulty of the task, subtraction of 7s and 17s, there was a tendency for AMI/CHLOR to show impairment compared with placebo. While there is inconsistency in the data, in that these impairments were, respectively, subtraction of 7s in the afternoon and subtraction of 17s in the morning, none of the treatments with HOE 8476 showed any noticeable or statistically significant change from placebo values.
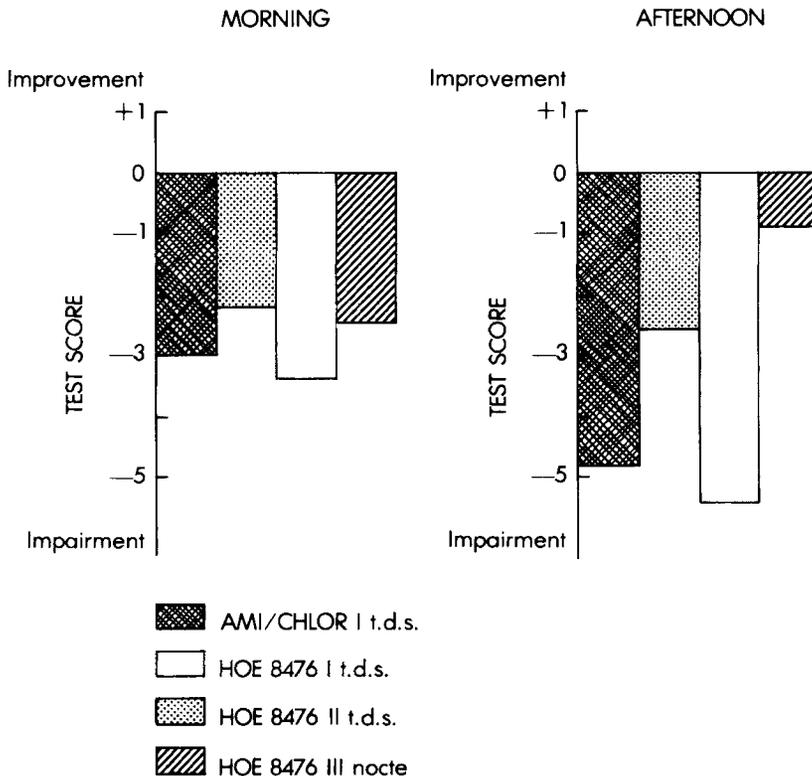

Fig. 3.   Driving tests (change in mean total score with respect to placebo).

In the assessments of sedative properties with objective (CFFT) and subjective (LARS) measures, AMI/CHLOR shows its profound sedative activity with significant impairment, compared with placebo, on the CFFT ($P < 0.01$), which was mirrored by similar impairment on the subjective measure of sedation, the linear analogue scales (LARS). None of the doses of HOE 8476 is significantly different from placebo in its effects on the LARS ($P < 0.01$) and on the CFFT in the morning and afternoon.

In the card sorting tasks, there is no significant difference between any of the active treatments and placebo at the low level of difficulty (sorting into colours). As the level of difficulty is increased (sorting into suits), AMI/CHLOR and the high dose of HOE 8476 are significantly different from placebo ($P < 0.05$) and the two low doses of HOE 8476 are significantly different from AMI/CHLOR ($P < 0.05$). There is a worsening of performance when the level of complexity is increased to sorting into numbers; AMI/CHLOR and the high dose of HOE 8476 both produce a noticeable and significant impairment of performance. While the low doses of HOE 8476 do not significantly
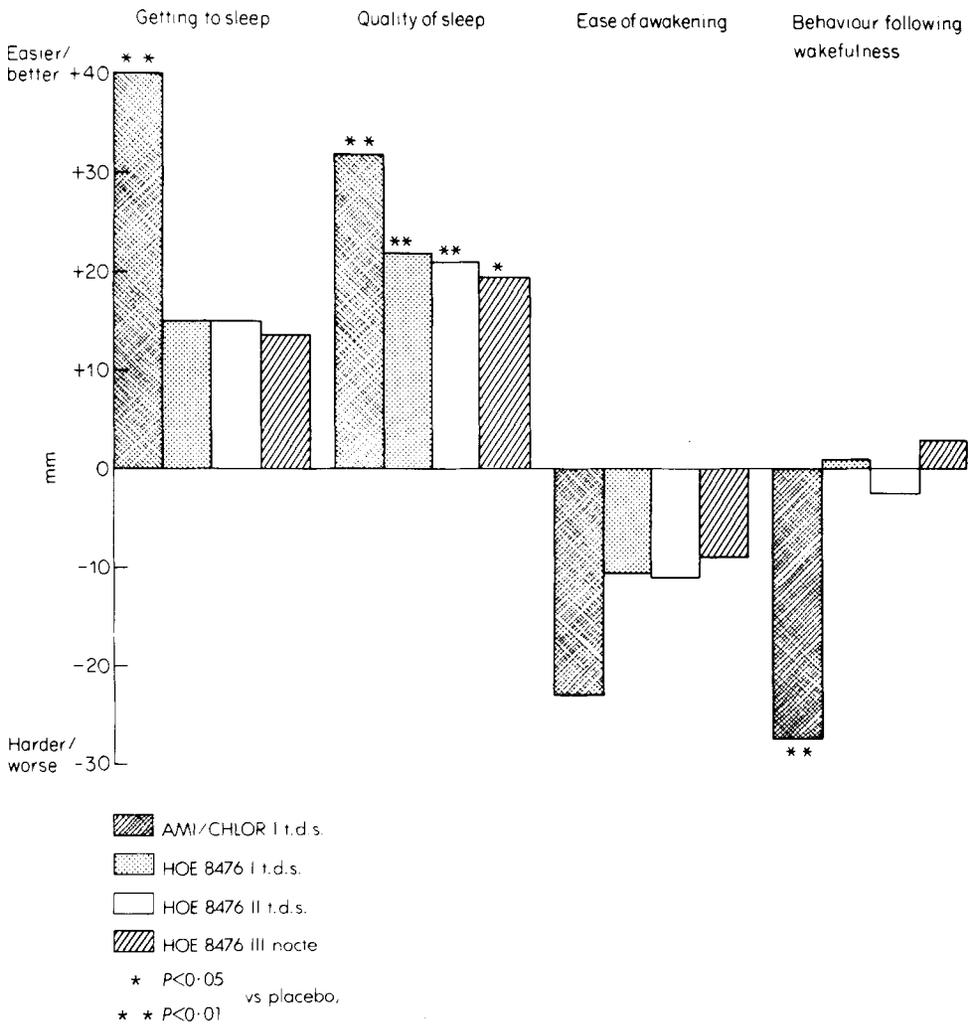

Fig. 4.   Leeds Sleep Evaluation Questionnaire (SEQ) (change in mean total score with respect to placebo).

impair performance, there is evidence that at this high level of performance difficulty, they too disrupt behaviour.

These results, taken together with the results described previously on the measures of sedation, namely CFFT and LARS, suggest that any impairment of performance with HOE 8476 is not due to a sedative effect. It can be postulated that AMI/CHLOR produces impairment of cognitive function by sedation, which has been recorded subjectively and measured in objective tests, whereas with HOE 8476 such impairment that can be demonstrated may be due to a paradoxical psychotropic effect in normal volunteers.

The impairment of car-driving performance seen with both AMI/CHLOR and HOE 8476 in comparison with placebo is not significant, but the trends shown in this assessment of overall performance are very much in keeping with those demonstrated in tests of cognitive and psychomotor function. In both the morning and afternoon sessions, AMI/CHLOR and the high dose of HOE 8476 have a greater tendency to impair performance than low doses of HOE 8476, in comparison with placebo. The effects of the nocturnal dose of HOE 8476 are greater in the morning test session than in the afternoon of the day following dosing, as would be expected. The effects of the divided dosage regimens are seen to be greater in the afternoon following the administration of morning and lunchtime doses.

In the subjectively assessed sleep factors of the LSEQ, AMI/CHLOR shows a profile characteristic of all hypnotics [Bixler et al., 1972] in that getting to sleep is eased and the quality of sleep improved. There is a tendency for AMI/CHLOR to impair the ease of awakening and there is a highly significant impairment of behaviour following wakening. HOE 8476 has a distinctly different profile; while it does not ease getting to sleep to the same significant degree as AMI/CHLOR, it does significantly improve the quality of sleep. This property is not accompanied, however, by a significant hangover the next morning, as is seen with AMI/CHLOR.

As in the previous study [Hindmarch et al., 1980] this study demonstrates important differences between AMI/CHLOR and HOE 8476. The sedative activity of AMI/CHLOR is shown on virtually all these subjective and objective measures of behaviour, while in contrast there is a relative lack of sedation attributed to HOE 8476. Nevertheless, the effects of HOE 8476 on the card sorting task and on the quality of sleep factor of the LSEQ indicate its powerful psychotropic properties, although this psychotropic activity is present in a different form from that characterising AMI/CHLOR, as it is not accompanied by sedation and drowsiness.

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