DIFFERENCES BETWEEN LIGHT AND SOUND SLEEPERS IN THE RESIDUAL EFFECTS OF NITRAZEPAM

A.W. PECK, C.E. BYE & R. CLARIDGE

The Department of Clinical Pharmacology, The Wellcome Research Laboratories, Beckenham, Kent

1 Residual effects of nitrazepam 2.5, 5 and 10 mg, and lactose dummy administered at night (23.00 h) on performance and subjective effects the following day, were measured in two groups, ten sound sleepers and ten light sleepers. Treatments were given orally at weekly intervals in a balanced order with double-blind conditions.

2 Auditory vigilance of sound sleepers was unaffected by treatments. Light sleepers, by contrast, showed significant ($P < 0.05$) improvement after nitrazepam (5 mg) and impairment after 10 mg.

3 Auditory reaction time was prolonged after nitrazepam (10 mg) in light sleepers and also by 5 mg in the sound sleepers. Tapping, short term memory and digit symbol substitution were all impaired by nitrazepam (10 mg) but there was no difference in response of the two groups.

4 Mental sedation was rated higher by light sleepers after lactose than by sound sleepers. After nitrazepam (10 mg) sound sleepers had significantly higher ratings than after lactose, but light sleepers did not. Ratings of mental sedation indicated that after nitrazepam (2.5 mg) light sleepers were more alert than after lactose, and after both 2.5 and 5.0 mg they were more alert than after nitrazepam (10 mg).

5 The implications of the findings that subjects with unsatisfactory sleep patterns may be rendered more alert, and perform certain prolonged monotonous tasks more efficiently, after an optimal dose of hypnotic are discussed.

Introduction

In a recent study Peck, Adams, Bye & Wilkinson (1976) failed to find any impairment of auditory vigilance in a group of healthy volunteers, during the day following administration of butobarbitone or nitrazepam on the previous evening. By contrast digit symbol substitution and tapping rates were impaired following the hypnotics as found previously by Kornetsky, Vates & Kessler (1959) and numerous later workers. Examination of the data suggested that the lack of effect of the hypnotics on vigilance could be explained on the basis of consistent differences in the responses of individual subjects. One group of subjects responded to the active drugs by consistently rating themselves as more drowsy and performing the vigilance task less well than after lactose dummy. A second group, however, were subjectively more alert and more vigilant on the days after active drugs. It was postulated that the improvement seen in this group could have resulted from an improved sleep pattern following the hypnotics, though there was no evidence for this from the data available in the study. Explanation of unusual findings based on

retrospective analysis of data are often unsatisfactory, and it was decided to test the explanation proffered in a second investigation. Two groups of healthy subjects, one composed of sound sleepers and the other of light, restless, or easily disturbed sleepers were recruited on the assumption that hypnotics were unlikely to improve the sleep quality of the first group, while they might be expected to improve the sleep quality of the second. The effects of nitrazepam on the two groups were examined and the results are reported here.

Methods

Recruitment and selection of volunteers

This was done by a notice explaining briefly that the after effects of doses of nitrazepam were to be investigated. Employees of the Wellcome Research Laboratories were sought who felt they fell into either a group of 'good sleepers who never have

Table 1 Details of age for male (M) and female (F) subjects in the two groups of subjects are shown.

<i>Light sleepers</i>				<i>Sound sleepers</i>			
Sex	Age (years)	Sex	Age (years)	Sex	Age (years)	Sex	Age (years)
M	21	F	21	M	23	F	23
M	28	F	22	M	26	F	23
M	39	F	24	M	42	F	24
M	42	F	28	M	49	F	24
		F	29			F	25
		F	53			F	51

had any sleep disturbance, easily getting off to sleep, and have never required hypnotic drugs' or 'a group of poor sleepers who have difficulty falling asleep, are easily disturbed by, for example, noise, and who may on occasions have had to use sleeping tablets or request them'. Interested subjects were then interviewed in groups and the nature of the study explained in detail. Those subjects still interested were then interviewed about past medical history and any with a past serious physical or mental illness excluded. No subject currently using either hypnotics or psychotropic drugs, or who had taken any within a month of interview, was accepted. Subjects using alcohol regularly at night were excluded. Suitable subjects were then interviewed about their sleep type and an assessment made whether they were suitable for inclusion in one of the two groups. Particular attention was given to the following features: rapidity of sleep onset; frequency of awakening; degree of disturbance by noise, strange beds or mental stress; satisfaction with the sleep quality; and whether insomnia had ever been complained of or treated. On the basis of this interview two groups, ten light sleepers and ten sound sleepers, were matched as closely as possible for age and sex. Details are given in Table 1. The two groups were very similar, but unfortunately it was not possible to obtain equal numbers of men and women of each sleep type. Each subject completed the Maudsley Personality Inventory (MPI, Eysenck, 1959).

Drugs and treatments

The following four treatments were taken at weekly intervals by all subjects: nitrazepam 2.5, 5 or 10 mg and lactose dummy, all prepared in gelatin capsules identical in appearance. Treatments were taken at 23.00 h the night before testing, the order of administration of treatments for each subject being based on a balanced design using five, 4-sided latin square arrangements, two light and two sound sleepers constituting each

group of 4. Neither subjects nor the investigator knew the nature of treatments until after completion of the study.

The experimental day

Approximately 30 min after awakening subjects made an assessment of the following subjective feelings using visual analogue scales: rapidity of onset of sleep (rapid-slow), alertness on awakening (alert-drowsy) and sleep quality (good-bad). The number of times of waking during the night was recorded. These will be referred to as the sleep ratings. Subjects also recorded their feelings on these 4 ratings in the mornings after the non-treatment nights of each week. After a light breakfast, without tea, coffee or cigarettes, the subjects were transported to the laboratory. Four subjects (two light and two sound sleepers) were studied on each weekday. On four days two men and two women were studied but on one day the group was all female.

The test schedule

On arrival subjects recorded their subjective feelings using eighteen visual analogue scales described by Lader & Norris (1969). Then followed a test schedule conducted in a sound proof room, air conditioned and held at 70°F with an individual cubicle for each subject. Subjects were allowed to keep their watches. Testing began at 08 h 30 min and comprised:

- (1) Auditory vigilance. The Wilkinson test (Wilkinson, 1968) lasting 60 min was used in which a series of tones 0.5 s long occurring every 2 s set in white noise were presented through headphones. Randomly occurring shorter tones, 0.4 s, were the signals to be reported. Subjects indicated recognition of signals by pressing a button, and both correct detections and false reports were recorded.
- (2) Short term memory. Series of eight digits were presented by loud speaker, and 5 s were allowed for recall and recording of the series. Ninety series were presented in 15 min, and the total number of errors and the number of series containing one or more errors (line errors) were counted.
- (3) Digit symbol substitution was measured over 90 s using the standard test (Wechsler, 1955). The number of substitutions completed and the number of errors were recorded.
- (4) Auditory reaction time was measured over 15 min, the subject pressing a microswitch in response to short tones occurring randomly

Figure 1 Mean number of signals detected for ten subjects for each 15 min of the 1 h vigilance test for (a) sound and (b) light sleepers are shown. The test began at 08 h 30 min, i.e. 9 h 30 min after administration of the four treatments, indicated by $\square$, lactose dummy; $\triangle$, nitrazepam 2.5 mg; $\circ$, nitrazepam 5 mg; $\bullet$, nitrazepam 10 mg. Where significant differences occurred these are shown in Table 3.

with a mean interval of 7 s varying between 5 and 9 s.

- (5) Tapping rate was measured by tapping a microswitch for 60 s.

Analysis of results

Scores for each of the performance tests were pooled for both groups and analysed without transformation by the method of analysis of variance. Main effects of treatments and sleep type

were sought, and also interaction between the two. Values of $P < 0.05$ were taken as significant. Where an interaction between treatment and sleep type was found, the effect of treatments on the two sleep types was examined separately. Where no interaction occurred results for the group as a whole are presented together with the significance of any differences. Values for the two groups are also presented in Table 3, in order to illustrate possible trends not achieving the 5% level of significance. This was felt justified in view of the fact that subjects were placed in defined groups at the beginning of the investigation. For analysis of the sleep ratings, and subjective effects, scores from visual analogue scales were transformed by arc-sine transformation to obtain a theoretically more normal distribution as suggested by Aitken (1969). These together with numbers of times of awakening were analysed by analysis of variance as before, for both treatment and non-treatment nights, and both main effects and interactions sought. The extraversion and neuroticism scores from the MPI were compared by the Student's *t*-test, and Wilcoxon's signed rank test.

Results

Differences between the two groups in their sleep ratings are shown in Table 2. It can be seen that on non-treatment nights sound sleepers rated their sleep quality better than that of light sleepers and woke up fewer times. There was a tendency for sound sleepers to rate onset as more rapid ($2P = 0.08$) but on awakening there was no difference in alert-drowsy ratings between the two groups. Analysis of ratings after lactose on the

Table 2 Evidence for differences between the sound and light sleepers. Mean scores $\pm$ (s.d.) in radians derived for the twenty subjects from the four-visual analogue scales, after arc-sine transformation are shown. On non-treatment nights, the mean value for the whole week (usually 6 days) for each subject, was used. Significance of differences was tested using the *t*-test (2 tail).

<i>Non-treatment nights</i>			
<i>Dimension</i>	<i>Sound sleepers</i>	<i>Light sleepers</i>	<i>Significance</i>
On awakening Alert/drowsy	0.72 $\pm$ 0.16	0.76 $\pm$ 0.08	2P = 0.51
Sleep onset Rapid/slow	0.52 $\pm$ 0.12	0.65 $\pm$ 0.17	2P = 0.08
Sleep quality Good/bad	0.52 $\pm$ 0.13	0.77 $\pm$ 0.12	2P < 0.01
Number of times awakening per night	0.31 $\pm$ 0.42	2.34 $\pm$ 1.93	2P < 0.01
<i>Treatment nights after lactose dummy</i>			
On awakening Alert/drowsy	0.60 $\pm$ 0.26	0.80 $\pm$ 0.20	2P < 0.10
Sleep onset Rapid/slow	0.50 $\pm$ 0.19	0.74 $\pm$ 0.29	2P < 0.05
Sleep quality Good/bad	0.54 $\pm$ 0.20	0.81 $\pm$ 0.26	2P < 0.05
Number of times awakening per night	0.20 $\pm$ 0.42	2.00 $\pm$ 1.15	2P < 0.01

treatment nights gave similar results for sleep quality and awakenings, but the trend towards a more rapid onset in sound sleepers now became significant. There was no differences in the extraversion and neuroticism scores between the groups of light and sound sleepers.

Vigilance performance is illustrated in Figure 1 and the significance of differences given in Table 3. There was no main effect of sleep type on vigilance performance, but significant interaction

between sleep type, treatments and quarter hour periods of the test justified separate analyses of the sleep groups quarter by quarter. This revealed that treatment effects were confined to the light sleepers. Nitrazepam (10 mg) reduced signals detected in this group when compared with lactose in quarter 3 and nitrazepam (5 mg) in quarters 1 and 3. A significant increase in signals detected, however, followed nitrazepam (5 mg) in quarter 4 compared with lactose.

Table 3 Performance tests. Mean values for twenty subjects are shown. Where analysis of variance indicated significant ($P < 0.05$) main effects of treatment or sleep type, or an interaction between the two, this is shown on the left.

Treatment		LAC	N2.5	N5	N10	Significant ($P < 0.05$)
<i>Test</i>						
<i>Auditory vigilance</i>						
Signals detected						Interaction: sleep type x treatment x quarter
Sound sleepers	quarter 1	6.8	6.4	7.4	6.1	—
	2	4.8	4.8	4.3	4.7	—
	3	3.6	4.8	3.7	3.7	—
	4	4.2	4.1	4.0	4.1	—
Light sleepers	quarter 1	6.8	6.9	7.8	6.0	N5 v N10
	2	5.8	6.0	5.5	5.4	—
	3	4.6	4.4	5.4	3.0	N10 v LAC, N5
	4	3.9	4.3	5.9	4.6	N5 v LAC, N2.5
<i>Reaction time (ms)</i>						
						Main effect: treatment; interaction: sleep type x treatment
All subjects		250	251	258	273	N10, N5 v LAC, N2.5
Sound sleepers		248	252	262	267	N10 v LAC, N2.5; N5 v LAC
Light sleepers		252	250	255	273	N10 v LAC, N2.5, N5
<i>Tapping (taps/min)</i>						
						Main effect: treatment
All subjects		349	347	339	330	N10 v LAC, N2.5
Sound sleepers		336	330	326	318	
Light sleepers		362	364	353	343	
<i>Short term memory</i>						
Line errors						Main effect: treatment
All subjects		23.3	23.7	24.4	32.4	N10 v LAC, N2.5, N5
Sound sleepers		17.6	20.3	21.9	29.4	
Light sleepers		29.0	27.0	26.9	35.4	
Total errors						Main effect: treatment
All subjects		49.0	49.2	55.2	74.7	N10 v LAC, N2.5, N5
Sound sleepers		36.3	42.5	48.0	63.9	
Light sleepers		61.6	55.8	62.4	85.4	
<i>Digit symbol substitution</i>						
Number of substitutions						Main effect: treatment
All subjects		69.2	67.6	67.7	64.4	N10 v LAC, N2.5, N5
Sound sleepers		64.5	64.3	64.1	59.9	
Light sleepers		73.8	70.8	71.3	68.8	

LAC lactose dummy; N2.5, N5 and N10, nitrazepam 2.5, 5 and 10 mg respectively.

Figure 2 The mental sedation score in (a) sound and (b) light sleepers. The mental sedation score was derived by averaging the scores from visual analogue lines indicating alert/drowsy, clear-headed/muzzy, attentive/dreamy, and quick-witted/mentally slow, completed at 10 h 15 min. After arc-sine transformation scores were analysed by analysis of variance. The bar indicates ± 1 s.e. mean. LAC, lactose dummy; N2.5, N5 and N10, nitrazepam 2.5, 5 and 10 mg respectively.

The reaction time of sound sleepers was prolonged by nitrazepam 5 and 10 mg compared with values after lactose. In the case of light sleepers, however, prolongation followed only the 10 mg dose.

Impairment of tapping rate, short term memory and digit symbol substitution occurred after nitrazepam (10 mg) compared with lactose, but not after the lower doses of hypnotic. There was no difference between the response of the two groups.

Effects on mental sedation calculated from the four dimensions as suggested by Norris (1971) are illustrated in Figure 2. Analysis of variance performed on these scores revealed a significant main drug effect: the group as a whole was more drowsy after nitrazepam (10 mg) than after lactose. A significant interaction was also found between sleep type and treatment, further evaluation indicating that light sleepers rated themselves at the time of testing as more mentally sedated than sound sleepers following lactose. There was a trend for sound sleepers to rate their degree of drowsiness following hypnotic treatment in a dose related manner increasing with dose of drug. Light sleepers by contrast were more alert after nitraze-

pam (2.5 mg) than after both lactose and nitrazepam (10 mg). The same tendency followed nitrazepam (5 mg) in light sleepers where subjects were significantly more alert than after nitrazepam (10 mg) only. The same trends occurred in ratings of physical sedation but only the main drug effect, impairment following nitrazepam (10 mg) was significant.

Because light sleepers rated themselves as significantly more drowsy than sound sleepers after lactose, and as the two groups were selected on the basis of sleep-type and defined before the investigations began, it was felt that separate analysis of the eighteen dimensions comprising the subjective ratings of the two groups was justifiable. Significant differences in the ratings of subjective effects on visual analogue scales are shown in Table 4. In the case of sound sleepers there was obvious significant impairment on mental and physical state at 08 h 30 min after nitrazepam (10 mg) compared with ratings after lactose dummy. In general the usual dose response relationship was seen. Significant effects on five dimensions persisted to 10 h 15 min. A different pattern was seen for light sleepers and significant effects were fewer, occurring on two dimensions only, alert-drowsy at 08 h 30 min and energetic-lethargic at 10 h 15 min. On both these dimensions, subjects rated themselves significantly less impaired after nitrazepam (5 mg) than after nitrazepam (10 mg). On no occasion did responses after any dose of active drug differ from that after lactose dummy. While significant differences failed to occur on the other dimensions, the general pattern of greatest impairment after nitrazepam (10 mg), and a trend suggesting improvement after nitrazepam (5 mg) compared with lactose, was seen.

Analysis of the sleep ratings: sleep quality, rate of onset, and number of times awakening failed to reveal any significant change ascribable to the different treatments.

Discussion

Investigations into the residual effects of hypnotics the morning after administration have been reported for groups of normal healthy volunteers and also for patients. If one presupposes that the sleep function of all healthy volunteers is optimal for each subject then it would be naive to expect any finding other than impairment in performance tests and increased drowsiness following hypnotics. Evidence that this impairment occurs has been amply documented by Kornetsky *et al.* (1959); Malpas, Rowan, Joyce & Scott (1970) Bond and Lader (1972, 1973, 1975) and Borland & Nicholson (1974).

Table 4 Subjective effects at time of testing. A series of eighteen visual analogue scales (Lader & Norris, 1969) were completed before (08 h 30 min) and after (10 h 15 min) the performance tests. Scores after different treatments were transformed by arc-sin transformation averaged and ranked in ascending order. Treatments underlined by a common bar failed to differ significantly. Where treatments are not underlined by a common bar the difference between scores was significant ($P < 0.05$). Scales not showing significant differences in either group have been omitted. Asterisks indicate scales which have been reversed for clarity of tabulation.

<i>Dimension</i>	<i>Sound sleepers</i>				<i>Light sleepers</i>			
08 h 30 min								
Alert/drowsy	LAC	N5	<u>N2.5</u>	N10	N5	<u>LAC</u>	<u>N2.5</u>	N10
Clearheaded/muzzy*	LAC	<u>N2.5</u>	<u>N5</u>	N10	N5	<u>N2.5</u>	LAC	N10
Well co-ordinated/clumsy	LAC	N5	<u>N2.5</u>	N10	N5	<u>N2.5</u>	LAC	N10
Energetic/lethargic*	LAC	<u>N2.5</u>	<u>N5</u>	N10	N5	LAC	<u>N2.5</u>	N10
Quick-witted/mentally slow*	<u>N2.5</u>	LAC	<u>N5</u>	N10	N5	LAC	<u>N2.5</u>	N10
Attentive/dreamy	<u>N2.5</u>	LAC	<u>N5</u>	N10	N5	LAC	<u>N2.5</u>	N10
Happy/sad	<u>LAC</u>	N5	<u>N10</u>	<u>N2.5</u>	N5	<u>N2.5</u>	LAC	N10
10 h 15 min								
Alert/drowsy	<u>N5</u>	LAC	<u>N2.5</u>	N10	<u>N2.5</u>	N5	LAC	N10
Clearheaded/muzzy*	<u>LAC</u>	N5	<u>N2.5</u>	N10	<u>N2.5</u>	N5	LAC	N10
Energetic/lethargic*	<u>N2.5</u>	LAC	<u>N5</u>	N10	N5	<u>N2.5</u>	LAC	N10
Quick-witted/mentally slow*	LAC	N5	<u>N2.5</u>	N10	<u>N2.5</u>	N5	LAC	N10
Happy/sad	N5	LAC	N10	<u>N2.5</u>	<u>N2.5</u>	LAC	N5	N10

LAC, lactose dummy; N2.5, N5 and N10, nitrazepam 2.5, 5 and 10 mg respectively.

The more complex problem of assessing the effect of hypnotics on the subsequent performance of anxious patients complaining of insomnia has received less attention. Malpas, Legg & Scott (1974) examined the effects of amylobarbitone, nitrazepam and placebo administered at night for a week to anxious women outpatients. No significant subjective 'hangover' effects followed any active hypnotic treatment, and no difference in behavioural tests occurred between drugs and placebo. Significant electroencephalographic changes were seen after hypnotics but were small compared with that seen in the previous study on normal subjects (Malpas *et al.*, 1970), when significant subjective and behavioural changes were also obtained. Tansella, Zimmerman-Tansella & Lader (1974) have also studied the problem and point out that sleep improved after the benzodiazepine examined (N-desmethyldiazepam), so that the patients felt refreshed on awakening. In this study significant ($P < 0.05$) residual effects ascribable to administration of hypnotics occurred rarely, and then only after 7 days treatment. Clinically used doses of the drug were investigated, 10 and 20 mg of the benzodiazepine and amylobarbitone 200 mg, and

fifteen patients received each treatment. The conclusion that any drug induced residual impairment was at least nullified by improvement in sleep pattern certainly appears the most reasonable. Similarly Salkind & Silverstone (1975) studying the effects of flurazepam in anxious patients found residual effects after 30 mg, but not after 15 mg, though the latter does produce an adequate hypnotic effect.

While it can reasonably be assumed that the sleep pattern of patients complaining of insomnia is not optimal for their functional needs, it is not reasonable to assume that sleep of healthy volunteers is always optimal for their needs. In a study designed to examine the residual effects of hypnotics on vigilance performance, a function known to be sensitive to changes in sleep deprivation (Wilkinson, 1968), or extension (Taub, Globus, Phoebus & Drury, 1971), no impairment was found by Peck *et al.* (1976). Examination of vigilance performance of individual subjects suggested that certain subjects were consistently rating themselves more drowsy after hypnotics than after lactose dummy and their vigilance was impaired. By contrast, another group consistently rated themselves more alert after hypnotics and

their vigilance was improved. It was not possible, however, to show that those subjects rendered more alert were those with improvement in sleep quality and vice versa.

The results reported here show that it is possible to select on the basis of interview two polar groups, sound sleepers and light sleepers. The simple hypothesis, that hypnotics would impair tests and ratings in sound sleepers, while light sleepers would be improved, is only partially verified and depends on test or rating chosen, and on the dosage of hypnotic. In the case of vigilance, no significant drug effect was seen in sound sleepers. Light sleepers, by contrast, showed improvement after nitrazepam (5 mg) relative to lactose, at the end of the test. The highest dose, nitrazepam (10 mg), impaired performance in the third quarter hour, compared with lactose, but more impressive was the fact that the main differences in performance occurred between nitrazepam (5 mg) and nitrazepam (10 mg). Thus the lower dose of hypnotic altered the pattern so that improved performance followed. The higher dose, however, resulted in impairment either from altered sleep or residual drug effect.

Subjective ratings of mental sedation reflected the changes in vigilance performance in light sleepers who rated themselves as more alert after nitrazepam (2.5 mg) than after lactose, and the same trend (though not significant) followed nitrazepam (5 mg). Sound sleepers, by contrast, always rated themselves as more drowsy following administration of hypnotic. Presumably consequent upon their more disturbed sleep pattern, light sleepers rated themselves drowsier after lactose than sound sleepers.

It is possible that the light sleepers were more anxious than the sound sleepers, i.e. showing similarities with the patients studied by Tansella *et al.* (1974) and Salkind & Silverstone (1975), where residual drug effects were most probably negated by improved sleep following administration of an effective hypnotic. Any difference in personality type between the two groups was not apparent on the MPI scores, and other measures of anxiety were not made.

While this study demonstrates that a group of light sleepers felt subjectively more alert and showed improved performance on a vigilance test after a hypnotic compared with after lactose, any practical application of this finding for normal subjects is likely to be limited. The objective improvement occurred only in performance of this simple discrimination in a prolonged monotonous test. All other tests were impaired by nitrazepam including the measure of short-term memory known to be sensitive to both barbiturates and benzodiazepine drugs (Hart, Hill, Bye, Wilkinson & Peck, 1975). Adjustment of hypnotic dose to achieve improvement would be critical and difficult for an individual subject. Nitrazepam (10 mg) produced typical residual impairment irrespective of sleep type. Assessment of the optimal dose required to produce an improvement of vigilance by negating the effects of sleep disturbance due to say travel, or air flights involving time zone changes, is unlikely to be possible with any certainty.

The authors are grateful to Dr Louis Arenillas of Roche Products Ltd for the preparation and gift of the nitrazepam.

References

- AITKEN, R.C.B. (1969). A growing edge of measurement of feelings. *Proc. Roy. Soc. Med.*, **62**, 989-993.
- BOND, A.J. & LADER, M.H. (1972). Residual effects of hypnotics. *Psychopharmacologia (Berl.)*, **25**, 117-132.
- BOND, A.J. & LADER, M.H. (1973). Residual effects of flurazepam. *Psychopharmacologia (Berl.)*, **32**, 223-235.
- BOND, A.J. & LADER, M.H. (1975). Residual effects of flunitrazepam. *Br. J. clin. Pharmacol.*, **2**, 143-150.
- BORLAND, R.G. & NICHOLSON, A.N. (1974). Human performance after a barbiturate (heptabarbitalone). *Br. J. clin. Pharmacol.*, **1**, 209-215.
- EYSENCK, H.J. (1959). *Manual of the Maudsley Personality Inventory*. London: University of London Press.
- HART, J., HILL, H.M., BYE, C.E., WILKINSON, R.T. & PECK, A.W. (1976). The effects of low doses of amylobarbitone and diazepam in human performance. *Br. J. clin. Pharmacol.*, **3**, 289-298.
- KORNETSKY, C., VATES, T.S. & KESSLER, E.K. (1959). A comparison of hypnotic and residual psychological effects of single doses of chlorpromazine and secobarbital in man. *J. Pharmac. exp. Ther.*, **127**, 51-54.
- LADER, M.H. & NORRIS, H. (1969). The effects of nitrous oxide on the human auditory evoked response. *Psychopharmacologia (Berl.)*, **16**, 115-127.
- MALPAS, A., LEGG, N.J. & SCOTT, D.F. (1974). Effects of hypnotics in anxious patients. *Br. J. Psychiat.*, **124**, 482-484.
- MALPAS, A., ROWAN, A.J., JOYCE, C.R.B. & SCOTT, D.F. (1970). Persistent behavioural and encephalographic changes after single doses of nitrazepam and amylobarbitone sodium. *Br. med. J.*, **2**, 762-764.
- NORRIS, H. (1971). The actions of sedatives on brain stem oculomotor systems in man. *Neuropharmacology*, **10**, 181-189.
- PECK, A.W., ADAMS, R., BYE, C.E. & WILKINSON, R.T. (1976). Residual effects of hypnotic drugs: evidence for individual differences on vigilance. *Psychopharmacology*, **47**, 213-216.

- SALKIND, M.R. & SILVERSTONE, T. (1975). A clinical and psychometric evaluation of flurazepam. *Br. J. clin. Pharmac.*, 2, 223-226.
- TANSELLA, M., ZIMMERMAN-TANSELLA, C. & LADER, M.H. (1974). The residual effects of N-desmethyldiazepam in patients. *Psychopharmacologia (Berl.)*, 38, 81-90.
- TAUB, J.M., GLOBUS, G.G., PHEOBUS, E. & DRURY, R. (1971). Extended sleep and performance. *Nature, Lond.*, 233, 142-143.
- WECHSLER, D. (1955). *Manual for the Wechsler adult intelligence scale*, p. 44. New York: Psychological Corporation; London: National Foundation for Educational Research.
- WILKINSON, R.T. (1968). Sleep deprivation: performance tests for partial and selective sleep deprivation. *Prog. clin. Psychol.*, 8, 28-43.

(Received May 11, 1976)