Br. J. clin. Pharmac. (1976), 3, 289-298

THE EFFECTS OF LOW DOSES OF AMYLOBARBITONE SODIUM AND DIAZEPAM ON HUMAN PERFORMANCE

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1 The effects of diazepam (2.5 and 5 mg) and amylobarbitone sodium (50 and 100 mg) on performance and subjective effects were assessed in a group of twelve healthy subjects under standardised conditions. Treatments were administered orally at weekly intervals according to a balanced design and under double-blind conditions.

2 The tests of performance most sensitive to drug effects in these healthy subjects were either prolonged and monotonous and gave the subject no feedback on performance, or required short term memory for efficient execution.

3 Auditory vigilance was significantly impaired ($P < 0.05$) between 45 min and 1 h 45 min after all drug treatments except amylobarbitone sodium (100 mg), compared with performance after lactose. At the same time false reports were significantly increased after amylobarbitone sodium (100 mg) compared with all other active drugs but not with lactose. These effects had disappeared 4-5 h post drug.

4 Short term memory was impaired 1 h 45 min after all treatments and impairment was dose related. No significant effects occurred 5 h after treatment.

5 Simple auditory reaction time was prolonged 2 h after the highest doses of amylobarbitone sodium and diazepam, and by amylobarbitone sodium (50 mg) 5 h 15 min after treatment. At this time the effects of diazepam had worn off. Digit symbol substitution was impaired by amylobarbitone sodium (50 and 100 mg), and diazepam (5 mg) after 2 h 45 minutes. No significant changes in visual search or tapping occurred after active drugs compared with lactose.

6 Subjective ratings indicated both mental and motor impairment 2 h 45 min after all active preparations compared with scores after lactose though significant changes followed diazepam (2.5 mg) infrequently.

7 Both correct detections and false reports in auditory vigilance tended to fall over the 6 separate days of testing, indicating an increase in caution. Visual search, short term memory, tapping and digit symbol substitution significantly improved with time, but there was no change in reaction time.

8 From the limited information obtained by sampling blood at 3 and 6 h, no relationship between change in performance and plasma level was found in these subjects.

Introduction

Administration of barbiturate or benzodiazepine drugs to normal volunteers has produced significant impairment in performance only when relatively high doses have been used and even then such effects were sporadic, appearing in some experiments and some tests but not in others. Few significant changes were reported in a group of ten subjects in card sorting and digit symbol substitution by Malpas & Joyce (1969) except after doses of amylobarbitone sodium (200 mg) and nitrazepam (10 mg). In a second study (Malpas, 1972) obtained no significant changes in card dealing, digit symbol substitution or subjective ratings following amylobarbitone sodium (100 mg) administered to ten healthy subjects. Jäättelä, Männistö, Paatero & Tuomisto (1971) using two hundred and seventy medical students, showed impairment in digit symbol substitution and short

term memory following diazepam (10 mg) in men, while in women impairment occurred on the former test only. In the study by Ideström & Schalling (1970) few significant changes occurred in a battery of short tests performed by groups of twenty-two subjects following amylobarbitone sodium (150 mg), but changes were more apparent after 300 mg. Hughes, Forney & Richards (1965) failed to obtain significant impairment in verbal and arithmetic tests after diazepam (6 mg) in a group of eighteen subjects. Haffner, Mørland, Setekleiv, Strømsaether, Danielson, Frivik & Dybing (1973), using a group of eight subjects, examined the effect of diazepam (10 and 20 mg) on a series of short tests. With the exception of changes in critical flicker fusion they found no significant changes ascribable to diazepam (10 mg). Not surprisingly they noted that their subjects were obviously sleepy following diazepam but made no attempt to measure this while admitting that this could be highly relevant to both driving and flying ability.

In all of these studies the tests were of relatively short duration that is usually less than 5 min when an indication of test duration is given.

In the present experiment longer tests were used on the assumption that as with sleep deprivation, so with drugs which lower the level of arousal, the adverse effect on performance may only become apparent with considerable time spent at work as reported by Wilkinson (1965). Also it was felt that the short tests used in many previous studies have little relevance to many tasks performed in everyday life. The present study was designed to investigate the effects of amylobarbitone sodium and diazepam in doses comparable to those frequently used clinically in commencing treatment of mild anxiety states.

Methods

Subjects

Twelve healthy volunteer subjects, seven female and five male aged 21-48 years were examined by medical interview, and their general practitioners contacted to check their past medical history. On days of the study they ate a light breakfast at least 1.5 h before drug administration and were transported both to the laboratory and home after the experiment. No tea, coffee, cigarettes or alcohol were allowed through the day.

Drugs

Each subject received each of the following six preparations in identical soft gelatin capsules: amylobarbitone sodium, 50 and 100 mg; diazepam, 2.5 and 5 mg; and two lactose filled dummy capsules. All were administered at 09.00 h.

Experimental design

Subjects attended the laboratory in groups of four on the same day each week at weekly intervals for 6 weeks. Treatments were administered in a balanced order based on two six sided latin squares. Neither subjects nor experimenters were aware of the nature of the treatments given on any occasion until the end of the study.

Schedule of tests

Before administration of treatments subjects completed a sheet of analogue lines designed to measure subjective effects. The following test schedule lasting 2 h was begun 45 min after treatment and conducted in a soundproof room air-conditioned at 21° C:

(1) the Wilkinson Auditory Vigilance Test (Wilkinson, 1970) lasting 1 h in which subjects listened using headphones to tones 0.5 s in duration occurring every 2 s set in a background of white noise. Signals to be detected were tones of 0.4 s instead of 0.5 s, ten of which occurred randomly every 15 minutes. Subjects registered their detection by pressing a button. Both correct detections and false reports were recorded for each 15 min period of each test hour.

(2) a short term memory test comprising the standard digit recall procedure lasting 15 min and consisting of ninety 8 digit sequences relayed to subjects through loudspeakers from a tape-recording. As each sequence ended, subjects had 5 s to write down the 8 digits from short term memory. Both the total errors and the number of 8 digit lines containing an error were counted for the three 5 min periods of the test.

(3) a reaction time test, similar to that used by Lisper & Kjellberg (1972), lasting 15 min in which subjects pressed a microswitch as quickly as possible on hearing brief tones. The tones were set in white noise administered through headphones from a tape-recording. The tones occurred with a mean interval of 7 s and intervals varied from 5 to 9 s. Mean reaction time was determined for each 5 min of the test and for the full 15 min period. Due to limitations imposed by the automatic clock and teletype recording necessary for studying four subjects simultaneously, reaction times of more than 899 ms could not be recorded.

Occasionally, owing to drowsiness, a subject imperfectly pressed the button which resulted in the machine recording a value of 899. This value was excluded from subsequent calculations.

(4) a visual search test lasting 15 min in which subjects systematically searched pages of random letters for five target letters on each page, and on finding them all proceeded to the next page. The number of pages completed and the number of rechecks required were counted for each 5 min period and for the whole test.

(5) a tapping test lasting 1 min in which subjects tapped a microswitch as rapidly as possible. The total number of taps were recorded.

(6) a digit symbol substitution test lasting 90 s (Weschler, 1955), in which the number of substitutions were counted.

(7) measurement of subjective effects using the analogue line technique of Lader & Norris (1969) in which subjects marked a 100 mm line the ends of which denoted the extremes of various aspects of mental state, e.g. alertness and drowsiness. Scores were transformed by arc-sine transformation to obtain a theoretically more normal distribution and analysed by three way analysis of variance.

At the end of the 2 h schedule a venous blood sample of 20 ml was taken followed by a standardized light lunch during a 1 h rest period. At 13.00 h the whole schedule was repeated.

Before commencement of the formal study all subjects received practice on the tests on 1 day each week for 2 weeks before administration of treatments. After this practice period no information on test performances was given either to individual subjects or the group as a whole until the end of the investigation.

Analysis of results

Each of the performance test scores was analyzed for the whole post-drug testing time by analysis of variance appropriate to a latin square design with repeated measures in the 'subject' factor (Winer, 1962). Main effects of treatments, weeks, sessions, periods and interactions between these factors were computed. Where a significant interaction was found between treatments or weeks and any of the 'time on test' factors (session, period or session x period), the analysis of variance was repeated for separate sessions, periods or sessions and periods as appropriate, to determine the significance of the treatment or week effects at those times.

Following a significant effect indicated by the *F*-ratio, means were compared using Duncan's Multiple Range test, taking the significance level at the 5% level. The means for the two lactose dummy occasions were combined throughout.

Analysis of plasma drug concentrations

Heparinized blood (20 ml) was centrifuged and plasma separated and stored deep-frozen before analysis.

Amylobarbitone sodium was measured by a method modified from those described by Inaba & Kalow (1972) and Drattan, Clare & Williams (1973). Phenobarbitone (5 μg in 0.1 ml) was added to plasma (1 or 2 ml) and 0.3 M KH_2PO_4 buffer pH 5.3 (0.5 or 1 ml) added. Extraction with 2 x 5 ml volumes of an ether (90%) chloroform (10%) mixture for 10 min was carried out on a tilt shaker. The ether-chloroform phase was transferred to a silanized centrifuge tube, reduced to 200 μl using O_2 free N_2 and evacuated over P_2O_5 for 30 min to remove water and avoid problems with 'ghost' peaks in the subsequent analysis. This was performed using a Hewlett Packard, FM 5750 gas chromatograph using 4 mm (i.d.) 122 cm glass columns containing 5% SE 30 on Chromosorb G 80-100 mesh and a flame ionization detector. Injector-port and detector were held at 260° C and the oven at 240° C.

Diazepam was measured using the combined methods of Zingales (1973), and Guelen & Van der Kleyn (1973). Plasma (1 ml) and 1 N HCl (0.25 ml) were extracted with 2 x 5 ml ether and this discarded. Ammonium-carbonate, pH 9.3 (3 ml) was added to the aqueous phase and this was extracted with 7 ml of a mixture of toluene (79%), *n*-heptane (19%) and isoamylalcohol (2%). This was evaporated in a water bath at 60° C under dry, O_2 free, N_2. Excess water was removed *in vacuo* and acetonitrile (40 μl) containing griseofulvin (20 ng) added. Diazepam was analysed using an electron capture detector at 330° C, a 122 cm glass column containing chromosorb W-HP (80-100 mesh) and OV17 liquid phase. Carrier gas was argon (90%) methane (10%) with an oven temperature of 255° C and injector port temperature 290° C.

Results

The main results of all the performance tests are summarized in Table 1. Details of the analysis of variance for correct detections in the auditory vigilance test are given in Table 2. Table 3 shows the significant changes in subjective effects while Table 4 summarizes the changes in performance

Table 1 Effect of treatment on performance tests

Time post-treatment						
				Auditory vigilance		
	Treatment	D2.5	A50	D5	A100	L
45 min – 1 h 45 min	Mean number of correct detections/h	22.8	23.3	24.0	24.8	27.7
	Treatment	A100	D5	A50	L	D2.5
4 h – 5 h	Mean number of correct detections/h	20.8	22.3	22.8	23.7	23.8
	Treatment	A50	D5	D2.5	L	A100
1 h 15 min – 1 h 30 min	Mean number of false reports/15 min	0.5	0.6	0.7	0.8	1.2
				Short term memory		
	Treatment	L	A50	D2.5	A100	D5
1 h 45 min – 2 h	Mean number of line errors/ 15 min	16.1	21.9	22.0	23.9	26.8
5 h – 5 h 15 min	Mean number of line errors/ 15 min	17.0	18.0	20.5	20.9	21.6
1 h 45 min – 2 h) 5 h – 5 h 15 min)	Mean number of total errors/ 15 min	32.3	42.3	42.9	49.8	55.9
				Auditory reaction time		
	Treatment	L	D2.5	A50	D5	A100
2 h – 2 h 15 min	Mean ms	231	235	251	264	273
	Treatment	L	D2.5	D5	A100	A50
5 h 15 min – 5 h 30 min	Mean ms	237	246	246	252	261
				Visual search		
2 h 15 min – 2 h 30 min) 5 h 30 min – 5 h 45 min)	Treatment	A50	D2.5	D5	A100	L
	Mean letters found/15 min	15.8	16.1	16.5	16.9	17.0
				Tapping		
	Treatment	D5	A100	L	D2.5	A50
2 h 45 min	Mean taps/min	344	346	355	357	360
	Treatment	D5	D2.5	A50	A100	L
6 h	Mean taps/min	353	354	356	357	359

Table 1—*cont.*

Digit symbol substitution

	Treatment	A100	D5	A50	D2.5	L
2 h 45 min	Mean number of substitutions	76.0	76.5	78.2	80.3	81.0
	Treatment	A50	A100	D5	D2.5	L
6 h	Mean number of substitutions	78.8	79.3	79.5	80.2	80.5

Mean values for twelve subjects obtained on different performance tests after the different treatments are shown, where abbreviations are:

Amylobarbitone sodium (50 mg and 100 mg), A50 and A100 respectively;
Diazepam (2.5 mg and 5 mg), D2.5 and D5 respectively;
L is mean value after the two lactose dummy treatments.

Values after different treatments have been ranked in ascending order, and where underlined by a common bar are not significantly different ($P > 0.05$). Values not underlined by a common bar are different at $P < 0.05$. Where analysis of variance indicated an interaction between the first and second test sessions and a drug effect, separate results for each session are shown. Where no interaction occurred between drug effect and test session, mean values for the two test sessions are shown (short term memory, total errors and visual search). In the case of auditory vigilance false reports there was an interaction between treatments and quarter hour periods of the test, and the significant drug effects in the third quarter of test 1 are shown. Values for the other quarters where there were no significant effects ascribable to treatments have been omitted.

Table 2 Main analysis of variance for auditory vigilance: correct detections

Source	*Degrees of freedom*	*Sum of squares*	*Mean sum of squares*	F-*Ratio*
Subjects	11	932.52	84.77	–
Treatments (T)	5	69.90	13.98	3.21*
Weeks (W)	5	105.90	21.18	4.87**
T x W x Subjects	50	217.63	4.35	–
Sessions	1	44.44	44.44	4.63
Sessions x Subjects	11	105.56	9.60	–
Quarters (Q)	3	683.74	227.91	42.69**
Q x Subjects	33	176.17	5.53	–
Sessions x Q	3	4.06	1.35	0.64
Sessions x Q x Subjects	33	69.78	2.11	–
T x Session	5	34.51	6.90	2.54*
T x Q	15	51.55	3.44	1.26
T x Session x Q	15	50.90	3.39	1.25
W x Session	5	27.51	5.50	2.02
W x Q	15	79.13	5.28	1.94*
W x Session x Q	15	67.49	4.50	1.66
Residual	350	951.15	2.72	–

Each effect was tested against the corresponding interaction mean squares within subjects. $*P < 0.05$; $**P < 0.01$.

Because of the significance of the treatment x test session interaction, each session was next considered separately to assess treatment effects. Similarly each quarter was considered separately to assess week effects.

Table 3 Differences in subjective scores 2 h 45 min after treatment

Alert — Drowsy	L	D2.5	A100	A50	D5
Clear headed — Muzzy	L	D2.5	A50	A100	D5
Quickwitted — Mentally slow	L	D2.5	A50	A100	D5
Attentive — Dreamy	L	D2.5	A100	A50	D5
Strong — Feeble	L	A100	D2.5	A50	D5
Energetic — Lethargic	L	D2.5	A100	D5	A50
Proficient — Incompetent	L	D2.5	A100	A50	D5
Elated — Depressed	L	A100	A50	D5	D2.5

Mean scores for twelve subjects, after different treatments (amylobarbitone sodium 50 mg and 100 mg, A50 and A100 respectively; diazepam, 2.5 mg and 5 mg, D2.5 and D5 respectively; L is mean value for two lactose dummy treatments), obtained from the analogue lines indicating the dimensions shown were ranked in order. Where treatments are underlined by a common bar scores failed to differ significantly ($P > 0.05$). Conversely where treatments are not underlined by a common bar, scores were significantly different. Ten dimensions failed to show significant changes in scores ascribable to drug treatment.

Table 4 Effect of weeks on performance tests

Test time		*Auditory vigilance*					
Tests 1 and 2	Week number	3	4	6	5	2	1
First 15 min	Mean number of correct detections/h	29.7	30.2	30.5	30.7	32.5	33.5
	Week number	4	3	6	5	2	1
Second 15 min	Mean number of correct detections/h	22.0	22.7	22.8	23.5	23.7	27.3
	Week number	4	6	5	3	2	1
Third 15 min	Mean number of correct detections/h	17.8	18.2	18.5	20.5	21.8	26.0
	Week number	5	3	1	4	6	2
Fourth 15 min	Mean number of correct detections/h	17.8	18.2	19.8	20.2	21.2	26.2
Test 1	Week number	5	4	6	3	1	2
Third 15 min	Mean number of false reports/15 min	0.3	0.6	0.6	0.8	1.1	1.3

Table 4—*cont.*

	Week number	5	6	3	2	4	1
Fourth 15 min	Mean number of false reports/15 min	0.2	0.3	0.3	0.5	0.5	1.4
Test 2	Week number	5	6	3	4	2	1
First 15 min	Mean number of false reports/15 min	0.2	0.2	0.7	0.8	1.3	1.5
				Short term memory			
Test 1	Week number	6	2	5	4	3	1
	Mean number of line errors/15 min	14.7	18.8	20.1	23.3	23.8	26.1
Test 2	Week number	4	5	3	6	2	1
	Mean number of line errors/15 min	16.5	16.9	17.3	18.2	19.5	26.7
Test 1	Week number	6	5	2	3	4	1
	Mean number of total errors/15 min	27.2	43.2	45.0	49.9	50.0	60.7
Test 2	Week number	6	4	3	5	2	1
	Mean number of total errors/15 min	32.7	33.0	34.8	35.7	37.3	61.1
				Auditory reaction time			
Tests 1 and 2	Week number	2	1	6	4	3	5
	Mean ms	234	237	245	254	256	257
				Visual search			
Tests 1 and 2	Week number	3	1	2	5	4	6
	Mean letters found/15 min	13.5	15.2	16.2	17.0	17.5	19.8
				Tapping			
Tests 1 and 2	Week number	3	4	1	5	2	6
	Mean taps/min	342	349	354	358	360	365
				Digit symbol substitution			
Tests 1 and 2	Week number	1	2	4	3	5	6
	Mean number of substitutions	73.0	76.5	80.3	80.4	81.6	84.1

Table 4—*cont.*

Mean values for twelve subjects obtained on different performance tests each week are shown. Values have been ranked in ascending order and where there was no significant difference ($P > 0.05$) between two or more weeks these have been underlined by a common bar. Performance in weeks not underlined by a common bar are significantly different ($P < 0.05$). Analysis of variance indicated a significant interaction between performance in quarter hour periods and week of testing in both correct detections and false reports in the vigilance test. Values for false reports for quarter hour periods where there were not significant differences between the weeks have been omitted. A significant interaction between week of testing and the two short term memory tests occurred and are shown separately. In all the other tests no significant interaction between week of testing and the first or second test session occurred, and mean values for the two tests are shown.

tests over the 6 weeks. The significance of these findings are considered in the discussion.

Plasma concentrations of the drugs at 3 and 6 h after administration are shown in Table 5. The possibility of a relationship between plasma concentration of drug achieved after four treatments, and the biological effect produced, was examined by ranking the subjects according to plasma level at a given time following each of the four treatments. Subjects were also ranked according to the magnitude of the difference in performance on the preceding test result or score, from the mean value they produced after lactose dummies. The rank order of subjects based on plasma level, was then compared with their rank order in vigilance, reaction time and subjective scores from the alert-drowsy dimension, using Spearman's test. Twenty-four comparisons were, therefore, made (four treatments, three tests, and two times). Of these there was significant correlation between the ranks after diazepam (2.5 mg) at 6 h using subjective drowsiness, and amylobarbitone sodium (50 mg) at 3 h using vigilance correct detections. These correlations could be fortuitous occurring by chance due to multiple comparisons.

Discussion

The results presented indicate that single doses of amylobarbitone sodium and diazepam commonly prescribed when beginning treatment in anxiety states are capable of impairing performance of healthy subjects in various tests of mental function. It has not been possible to find studies of the effect of diazepam on auditory vigilance performance, and in view of the sensitivity of the Wilkinson auditory vigilance test used it was not surprising that significant reduction in correct detections occurred after a dose of only 2.5 mg diazepam. Differences in impairment between the active drugs were not significant but it was unusual to find that mean values for correct detections were lower after the lower doses of the two drugs than after the higher doses. False reports were always infrequent, but significant interaction between treatments, hours and quarter hours indicated that they increased after amylobarbitone sodium (100 mg). Effects on both correct detections and false reports had worn off by 4 hours. Linnoila & Mattila (1973) examined the effects of diazepam (5 mg) given three times daily for 2 weeks on visual attention using a complex test involving scrutiny of four dials for a period of 10 min in twenty subjects. No significant differences occurred after diazepam compared with placebo. Compared with the auditory vigilance test used in the present study this visual attention test was brief and relatively interesting. Similarly, in the present study visual search performance was unaffected by any drug treatment.

Short term memory was impaired by all active drugs in a dose related manner and this was seen most clearly when performance was evaluated by counting line errors. Effects seen 1 h 45 min after the drugs had disappeared at 5 hours. No significant interaction occurred between treatments and performance during the different 5 min periods of the tests. Jäättelä *et al.* (1971) found significant impairment in retention of a digit series recited

Table 5 Mean plasma levels ± s.e. mean of amylobarbitone sodium and diazepam for twelve subjects

Time post drug (h)	*Amylobarbitone sodium*		*Diazepam*	
	100 mg	*50 mg*	*5 mg*	*2.5 mg*
	(ng base/ml plasma)		*(ng base/ml plasma)*	
3	1217 ± 82	775 ± 83	35.2 ± 4.6	22.7 ± 2.9
6	1000 ± 46	700 ± 48	39.3 ± 7.4	19.6 ± 2.9

forward after diazepam (10 mg) in their male medical students (but not in the females) presumably indicating impairment of short term memory. They failed to find drug induced changes following diphenhydramine in this test, a finding consistent with the lack of effect of the antihistamine triprolidine on short term memory reported by Bye, Fowle & Peck (1974).

Jäättelä *et al.* (1971) also found highly significant impairment of digit symbol substitution after diazepam, particularly in males, but not following diphenhydramine. Similarly in the present study digit symbol substitution was impaired after all treatments except diazepam (2.5 mg), whereas it was unaffected by triprolidine (5 mg) as reported by Bye, Dewsbury & Peck (1974). Mental functions involved in digit symbol substitution, while complex, probably involve a short term memory function which appears to be relatively more sensitive to the effects of benzodiazepine and barbiturate drugs than to histamine antagonists, for a given degree of impairment in monotonous tasks of the vigilance type.

Auditory reaction time was examined closely in the present study to see if a test lasting only 15 min was as sensitive to impairment produced by drugs as the auditory vigilance test. Lisper & Kjellberg (1972) showed that a reaction time test with signals presented at 16/min was capable of detecting the effect of sleep deprivation previously only measured using prolonged tests of vigilance and choice serial reaction time (Wilkinson, 1968). Limitations of equipment prevented presentation of signals more frequently than 8.5/min but this was sufficient to detect prolongation after amylobarbitone sodium (100 mg) and diazepam (5 mg) in the morning session. The only significant drug effect measured in the afternoon session in the whole experiment was the prolonged reaction time 5 h 15 min after amylobarbitone sodium (50 mg). No significant interaction occurred between treatments and the mean reaction time in the three 5 min periods of tests. The more complex choice reaction measured by Linnoila & Mattila (1973) was shortened after diazepam (5 and 10 mg) but this achieved significance only at the higher dose. Mistakes did not increase until diazepam (10 mg) was combined with alcohol (0.8 mg/kg).

No significant effects occurred in the visual search task lasting 15 min, and there was no interaction with time on test. This latter test had proved sensitive to artificial changes in time affecting circadian rhythms reported by Preston, Bateman, Short & Wilkinson (1973). Subjects found the test comparatively interesting and obviously had the feed back reward of knowing how well they performed from the number of pages completed. It was also one of the few self paced tasks. The 1 min tapping test failed to show any difference between active drug treatments and lactose.

In this study tests which showed significant impairment after drugs were all either prolonged and monotonous with no feed back of results during the test which resulted in low motivation, or required a short term memory function. Although performance in digit symbol substitution is easily seen by the subject, and the test is brief, performance was impaired possibly due to effects of drugs on short term memory.

Subjective effects (Table 3) were usually dose related following diazepam, the 5 mg dose producing significant mental and motor impairment. Scores after diazepam (2.5 mg), however, rarely differed from those after lactose. Scores after both doses of amylobarbitone sodium never differed though the higher dose frequently gave a lower rating on both mental and motor impairment. All significant effects had disappeared by 6 hours. Lack of a clear cut dose response relationship on subjective measures has been noted before by Malpas (1972) whose subjects could distinguish the difference between amylobarbitone sodium (100 and 200 mg) but not nitrazepam (5 and 10 mg).

Changes in performance over the 6 weeks differed between tests (Table 4). The only test showing no changes over this period was auditory reaction time. Both correct detections and false reports in auditory vigilance tended to fall over the 6 weeks suggesting that the subjects became more cautious with time. By contrast visual search, digit symbol substitution, and short term memory improved significantly over the 6 weeks. Errors in memory were not apparent to the subjects and the improvement probably represents a true practice effect. Performance in visual search and digit symbol substitution was easily apparent to the subjects and improvement might well have resulted from motivation to better a previous performance. With the exception of symbol substitution, in none of the tests was there a clear cut change from either occasion 1 or 2 to a uniformed sustained performance. This suggests that the experimental design would not be improved by either giving more practice in the pre-drug training sessions, or by giving a lactose dummy on one or more of the early occasions before beginning the balanced design for administration of six treatments.

Failure of plasma concentration to correlate with changes in vigilance, reaction time, and subjective rating is not surprising for several reasons. Only two plasma concentrations were obtained due to the experimental design because it was felt that blood sampling during the test battery would unduly disturb the subjects. Tests

were therefore conducted at times often well removed from the 3 and 6 h blood samples. In addition, two samples gave an inadequate guide to the pharmacokinetic disposition in different subjects. While on average amylobarbitone concentration fell between 3 and 6 h, concentrations of diazepam were still rising during this period, but there was considerable inter subject variation.

The authors wish to thank Dr Louis Arenillas of Roche Products Ltd for the preparation and gift of the drugs. Reprint requests should be addressed to A.W.P.

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(Received July 4, 1975)