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COMPARISON OF THE RESIDUAL EFFECTS OF TWO BENZODIAZEPINES (NITRAZEPAM AND FLURAZEPAM HYDROCHLORIDE) AND PENTOBARBITONE SODIUM ON HUMAN PERFORMANCE

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1 The residual effects of two benzodiazepines, nitrazepam (10 mg) and flurazepam hydrochloride (30 mg), and pentobarbitone sodium (200 mg) were studied by adaptive tracking and by reaction time. Performance was measured at 10 h, 13 h, 16 h, 19 h and 34 h after ingestion of each drug. Impaired performance on adaptive tracking was observed at 10 h, 13 h, 16 h and 19 h after nitrazepam and pentobarbitone sodium and at 10 h, 13 h and 16 h after flurazepam hydrochloride. Enhanced performance was observed at 34 h after nitrazepam and pentobarbitone sodium.

2 Increased reaction time persisted to 16 h after nitrazepam, flurazepam hydrochloride and pentobarbitone sodium and reaction time was also increased at 34 h after nitrazepam and pentobarbitone sodium.

3 During the morning immediately after ingestion, the subjects as a group were able to differentiate correctly between placebo and drugs, but they were not able to assess accurately the persistence of the residual effects of nitrazepam and pentobarbitone sodium.

4 Flurazepam hydrochloride would appear to be a more promising benzodiazepine than nitrazepam for use as a hypnotic by persons involved in skilled activity. There was a rapid recovery of performance during the afternoon and, unlike pentobarbitone sodium and nitrazepam, subjects retained the ability to recognize impaired skill.

Introduction

Little is known about the residual effects of hypnotics on the performance of skills essential to certain occupations. Most studies on residual effects have used tests which represent facets of performance, such as perception, attention and computation (Von Felsinger, Lasagna & Beecher, 1953; Kornetsky, Vates & Kessler, 1959; Malpas, Rowan, Joyce & Scott, 1970; Bond & Lader, 1972, 1973), but the relevance of impaired performance on these tests to complex skills has not been defined. In this context the measurement of impaired performance presents a difficult problem and there is a need for studies which provide observations of practical importance on residual effects, though not stimulating completely the skill of a particular occupation.

In a previous study (Borland & Nicholson, 1974) we used an adaptive tracking technique to measure change in performance after drugs. Adaptive tracking provides a continuous measure of performance and is acquired only by considerable practice. The task is related, at least in part, to a skill required of aircrew, though impaired performance on the task is likely to have relevance to other occupations. In the present study we have extended our observations on the residual effects of the barbiturate heptabarbitone to the residual effects of nitrazepam (10 mg) and flurazepam hydrochloride (30 mg). The effects of these benzodiazepines have been compared with those of placebo and pentobarbitone sodium (200 mg).

Methods

Measurement of performance on adaptive tracking

The task required the subject to position a spot inside a randomly moving circle displayed on an oscilloscope. The movement of the spot was controlled by a handheld stick and an error signal, proportional to the square of the distance between the spot and the centre of the circle, controlled

the difficulty of the task by modulating the mean amplitude of the movement of the circle. This technique provided the adaptive component of the task.

The movement of the circle on the oscilloscope was produced by two independent maximum length binary sequences. Low pass filtering smoothed the output of the binary sequences and the movement of the circle was statistically random. Independent x and y signals derived from high grade potentiometers mounted on the control stick were fed via an 'aerodynamic loop' to the inputs of the oscilloscope. The loop avoided an artificial one to one relation between the control stick and spot movement and smoothed out any small steps caused by the potentiometer windings. The oscilloscope (Airmec 383) had a distortion free, medium persistence tube and displayed the task over an area of 20 x 20 cm. It was modified by the addition of x axis beam switching and allowed two independent signals to be displayed in each axis. The distance between the spot and the centre of the target circle was measured and the radial error signal computed. A voltage proportional to the square of the circle radius was subtracted from the square of the radial error signal. The output was fed to a voltage integrator and the output of the integrator, scaled from zero to 10, controlled the mean amplitude of the task.

At the start of each experiment the output from the integrator was set at zero and the circle was stationary. The subject positioned the spot inside the circle and the negative error signal caused the integrator output to increase. The circle tended to move away from the spot and, when the spot could no longer be maintained inside the circle due to the increasing difficulty of the task, the polarity of the voltage to the integrator reversed and the task became less demanding. The integrator had a long time constant which allowed each subject to 'warm up' gradually. With zero error the task required about 25 s to reach maximum difficulty. A constant displacement between the spot and the centre of the circle of 4 cm would reduce the task to zero difficulty within 6 seconds. As the subjects became aware of the penalty of error signals they tried to avoid all errors, but the task did not permit a performance level of 10 to be reached.

An 8-channel pen recorder was used to monitor the equipment and the performance of each subject. The position of circle and spot and the radial error signal were recorded for each axis together with the output from the task integrator. Each tracking run lasted 10 min and the subjects reached a plateau level of performance within the first 100 s of each run. The mean amplitude of the task over the final 500 s was computed using a voltage to frequency convertor and digital counter. This was the performance measure.

Subjective assessment of performance

Each subject was presented after each task with a line 100 mm in length. The question 'What standard of performance did you reach?' was asked and the subject made the assessment by crossing the line with a pencil between the extremes of Zero and Perfect. The assessment was quantified by measuring in mm the displacement of the mark from the Zero extremity.

Measurement of reaction time

Reaction time was measured 2 min after the completion of each tracking run. Subjects were required to press a handheld morse key to cancel a group of red lights switched on at random intervals. The light signal was produced by five light emitting diodes (650 nm: 2.0×10^{-3} cd) arranged within a 5 x 5 cm square. The group of lights was viewed at a distance of 1 m and was illuminated for 1 second. The intertrial time was controlled by a maximum length binary sequence and varied between 1 and 8 seconds. Twenty-five trials were presented to each subject and the mean of the last 20 trials was recorded as the reaction time. Reaction time was measured in 10 ms intervals accurate to the nearest 2 milliseconds.

Experimental procedure

Six healthy male subjects were used. Their ages ranged from 24-39 years (mean 32) and their weights ranged from 67-83 kg (mean 72). Instructions were given to all subjects to avoid alcohol and they were not involved in any other form of therapy. There were no restrictions on the consumption of non-alcoholic beverages. The experiments were carried out in a sound attenuated and air-conditioned room. The subjects were required to reach a plateau level of performance on the task before studies commenced. In subjects familiar with this technique, such as pilots, this level of performance would be reached within a few days, but with scientific personnel a plateau level of performance was usually reached with daily practice after 2-3 weeks. Training sessions were made available to maintain levels of performance.

The assessment of the effect of placebo or of each drug involved 3 days. On day 1 four assessments of each subject's control performance were made at 09.00, 12.00, 15.00 and 18.00 hours. Placebo or drug was given at 23.00 h the same evening and the subjects slept at home.

On day 2 performance was measured at the same times as on day 1, i.e. 09.00 (+10), 12.00 (+13), 15.00 (+16) and 18.00 (+19 h after ingestion of placebo or drug). On day 3 performance was measured at 09.00 h (+34 h) only. Experiments were separated by 4 weeks and each subject completed 4 experimental runs of 3 days. The capsules contained the placebo, nitrazepam (10 mg), flurazepam hydrochloride (30 mg) or pentobarbitone sodium (200 mg) given in a random order. The trial was double blind and placebo and drugs were presented in an identical form. On day 1 of each experiment the subjects were required to report to the laboratory at 08.45 h, but on day 2 of each experiment (after the overnight ingestion of placebo or drug) the subjects were collected from home at 08.15 h to avoid any oversleep.

Results

Performance on adaptive tracking, subjective assessment of performance and change in reaction time were analysed by analysis of variance.

Adaptive tracking

During day 1 performance on adaptive tracking at 09.00 h was lower than performance at 12.00, 15.00 or 18.00 h ($P = 0.01$), but no significant differences were found between performance at 12.00, 15.00 and 18.00 hours. Performance at 09.00 h for the 3 days of each experiment was also analysed. No significant differences could be established between performance at 09.00 h on days 1, 2 and 3 after placebo, but there were significant differences between performance at 09.00 h on day 1 and 09.00 h on day 3 for all drug experiments except after flurazepam hydrochloride. No significant differences could be established between performance at 09.00 h on day 1 for all experiments (placebo and drug). In view of these findings the control value for the 09.00 h performance was taken as the mean of the 09.00 h performance on day 1 and day 3 after placebo and the 09.00 h performance on day 1 for all the drug experiments (mean of 5 values). No significant differences were established between performance at 12.00, 15.00 and 18.00 h on day 1 after placebo and drugs, and the three measures were combined for each subject for comparison with the individual 12.00, 15.00 and 18.00 h

Table 1 Analysis of variance and significance levels for performance change on adaptive tracking (arbitrary units) after drugs

Source	*Degrees of freedom*	*Mean squares*	F	*Significance levels*
Subjects (S)	5	1.151789 (S x D x T)	5.11	***
Drug (D)	3	2.338889 (S x D)	1.07	NS
Time (T)	4	3.688839 (S x T)	16.37	***
S x D	15	2.177089 (S x D x T)	9.66	***
S x T	20	0.383454 (S x D x T)	1.70	(1.75 = *)
D x T	12	0.829653 (S x D x T)	3.68	***
S x D x T	60	0.225353		
Total	119			

	Time after ingestion				
Placebo or drug	*09.00 h Day 2 (+10 h)*	*12.00 h Day 2 (+13 h)*	*15.00 h Day 2 (+16 h)*	*18.00 h Day 2 (+19 h)*	*09.00 h Day 3 (+34 h)*
Placebo	0.17 (NS)	0.16 (NS)	−0.07 (NS)	−0.02 (NS)	
Nitrazepam (10 mg)	−0.43 *	−0.64 **	−0.57 **	−0.52 **	0.77 ***
Flurazepam hydrochloride (30 mg)	−0.63 **	−0.44 *	−0.41 *	0.33 (NS)	0.21 (NS)
Pentobarbitone sodium (200 mg)	−1.35 ***	−0.97 ***	−0.71 ***	−0.49 *	0.51 *

Least significant differences from zero for means of 6 were 5% = 0.39; 1% = 0.52; 0.1% = 0.67.
* = 5%; ** = 1%; *** = 0.1%; NS, not significant.

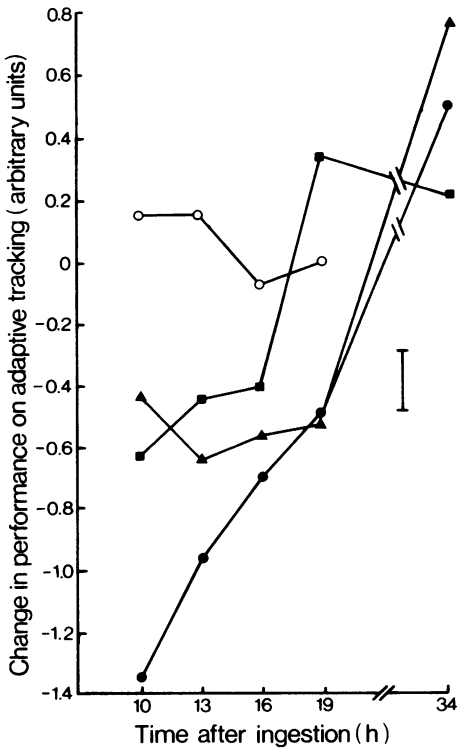

Fig. 1 Change in performance on adaptive tracking (arbitrary units) for all subjects (n = 6) after placebo (o); nitrazepam (10 mg, ▲); flurazepam hydrochloride (30 mg, ■); and pentobarbitone sodium (200 mg, ●). Standard error (0.19 arbitrary units) is given as a vertical bar.

performance measures on day 2 after administration of placebo or drug.

The results of the analysis of performance on adaptive tracking are given in Table 1 and illustrated in Figure 1. There were no significant changes in performance during day 2 after ingestion of placebo. After nitrazepam (10 mg) significant deficits in performance persisted throughout the next day (day 2) and at 09.00 h on the third day there was enhanced performance significant at the 0.1% level. The changes in performance during day 2 after nitrazepam did not differ significantly at the 5% level from each other. After flurazepam hydrochloride (30 mg) impaired performance persisted to 15.00 h (+16 h) on day 2. No change in performance was observed at 18.00 h (+19 h) on day 2 or at 09.00 h (+34 h) the following day (day 3). Performance was impaired throughout the day after the ingestion of pentobarbitone sodium (200 mg), though there was clear evidence of a recovery during the latter part of the day. At 09.00 h (+34 h) the next day (day 3) performance was enhanced.

Subjective assessment of performance

A similar analysis was carried out with subjective assessments of performance. During day 1 performance at 09.00 h was assessed lower by all subjects than performance at 12.00, 15.00 or 18.00 h, but no significant differences were established between the subjective assessments of performance at 12.00, 15.00 and 18.00 hours. Assessments of performance at 09.00 h on each day during the placebo experiment did not differ significantly from the assessments at 09.00 h on day 1 for each of the drug experiments. Assessments of performance at 09.00 h for the 3 days of each drug experiment showed that the subjects assessed performance on day 3 higher than day 1 ($P = 0.05$) and on day 1 higher than on day 2 ($P = 0.001$). In view of these findings the control assessment of performance for 09.00 h was taken as the mean of the 09.00 h assessment on day 1 for each drug experiment for each subject (mean of 5 values). The three assessments at 12.00, 15.00 and 18.00 h on day 1 were combined for comparison with the individual 12.00, 15.00 and 18.00 h assessments for each experiment on the day after the ingestion of placebo or drug (day 2).

The results of the analysis of the assessments of performance are given in Table 2. There were no significant changes in the assessments of performance during day 2 after placebo, but after ingestion of each drug the subjects considered as a group that their performance was impaired. Assessments of impaired performance persisted to the 12.00 h (+13 h) interval after nitrazepam and flurazepam hydrochloride, but the subjects assessed their performance after pentobarbitone sodium as at control level by 12.00 h (+13 hours). After all drugs performance was assessed at control levels by 15.00 h (+16 hours). Enhanced performance was claimed the following day (day 3) only after nitrazepam.

Reaction time

Reaction time at 09.00 h on day 1 of each experiment was significantly different from reaction time at 12.00, 15.00 and 18.00 h ($P = 0.01$), but reaction times at 12.00, 15.00 and 18.00 h did not differ significantly from each other. Reaction times at 09.00 h on day 1, 2 and 3 for the placebo experiment did not differ significantly, but reaction times at 09.00 h on the day after ingestion of the drugs were greater than on day 3 ($P = 0.05$) which were greater than on day 1 ($P = 0.01$). Reaction times at 09.00 h on day 1 of the placebo experiment and on day 1 of each of the drug experiments did not differ significantly from each other, and so for the control reaction

time at 09.00 h the mean of the reaction times at 09.00 h on day 1 and 3 for the placebo experiment and of day 1 for each drug experiment were taken for each subject (mean of 5 values). The mean of the reaction times for 12.00, 15.00 and 18.00 h on day 1 was taken as the control reaction time for each subject at these times on day 2.

The results of the analysis of reaction time are given in Table 3 and illustrated in Figure 2. Reaction times at 09.00 h on day 2 were prolonged after the ingestion of placebo and each drug, but there was no evidence of an increased reaction time at 12.00 h (+13 h) on day 2 after ingestion of placebo. Reaction times after nitrazepam, flurazepam hydrochloride and pentobarbitone sodium were increased until 15.00 h (+16 h) on day 2. Reaction time at 18.00 h (+19 h) was not significantly different from that after ingestion of placebo. On day 3 at 09.00 h there was evidence of an increased reaction time after nitrazepam and pentobarbitone sodium.

Regression analyses

Changes in performance on adaptive tracking were correlated with changes in subjective assessment of performance and with changes in reaction time for the day immediately after ingestion of the drugs.

Significant regression equations between change in performance on adaptive tracking and change in subjective assessment of performance were established for pentobarbitone sodium ($P = 0.001$) and flurazepam hydrochloride ($P = 0.01$), but it was not possible to establish a significant regression equation after nitrazepam. The regresssion equations for change in assessment of performance were (1.22 x change in performance on adaptive tracking – 0.05) for flurazepam hydrochloride and (1.38 x change in performance on adaptive tracking + 0.89) for pentobarbitone sodium. The slopes of these regressions (Fig. 3) did not differ significantly at the 5% level. The regression for flurazepam hydrochloride passed through the origin, but the displacement of the regression for pentobarbitone sodium was significant at the 1% level.

Significant regression equations between change in performance on adaptive tracking and change in reaction time were established for pentobarbitone sodium ($P = 0.01$) and flurazepam hydrochloride ($P = 0.01$), but it was not possible to establish a significant regression equation after nitrazepam. The regression equations for change in reaction

Table 2 Analysis of variance and significance levels for change in assessment of performance (arbitrary units) by subjects after drugs

Source	*Degrees of freedom*	*Mean squares*	F	*Significance levels*
Subjects (S)	5	2.370140 (S x D x T)	6.04	***
Drugs (D)	3	0.866767 (S x D)	2.21	NS
Time (T)	4	4.375325 (S x T)	4.53	**
S x D	15	0.669913 (S x D x T)	1.71	NS
S x T	20	0.966885 (S x D x T)	2.46	**
D x T	12	0.917942 (S x D x T)	2.34	*
S x D x T	60	0.392428		
Total	119			

	Time after ingestion				
Placebo or drug	*09.00 h Day 2 (+10 h)*	*12.00 h Day 2 (+13 h)*	*15.00 h Day 2 (+16 h)*	*18.00 h Day 2 (+19 h)*	*09.00 h Day 3 (+34 h)*
Placebo	0.25 (NS)	−0.12 (NS)	−0.27 (NS)	0.02 (NS)	
Nitrazepam (10 mg)	−1.03 ***	−1.15 ***	−0.22 (NS)	−0.37 (NS)	0.73 **
Flurazepam hydrochloride (30 mg)	−0.88 **	−0.67 *	−0.37 (NS)	0.33 (NS)	0.13 (NS)
Pentobarbitone sodium (200 mg)	−0.95 ***	−0.48 (NS)	−0.07 (NS)	0.22 (NS)	0.45 (NS)

Least significant differences from zero for means of 6 were 5% = 0.51; 1% = 0.68; 0.1% = 0.89.
* = 5%; ** = 1%; *** = 0.1%; NS, not significant.

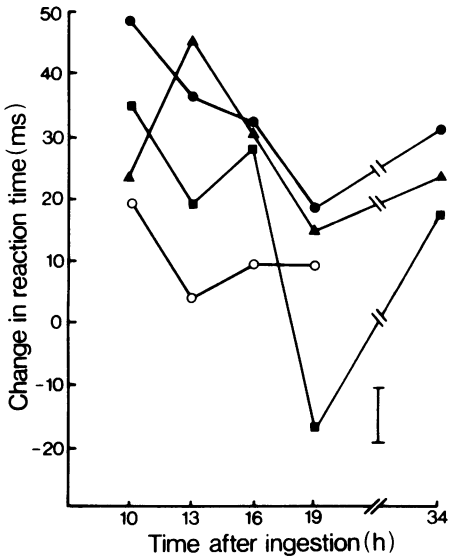

Fig. 2 Change in reaction time (ms) for all subjects ($n = 6$) after placebo (○); nitrazepam (10 mg, ▲); flurazepam hydrochloride (30 mg, ■); and pentobarbitone sodium (200 mg, ●). Standard error (9.4 ms) is given as a vertical bar.

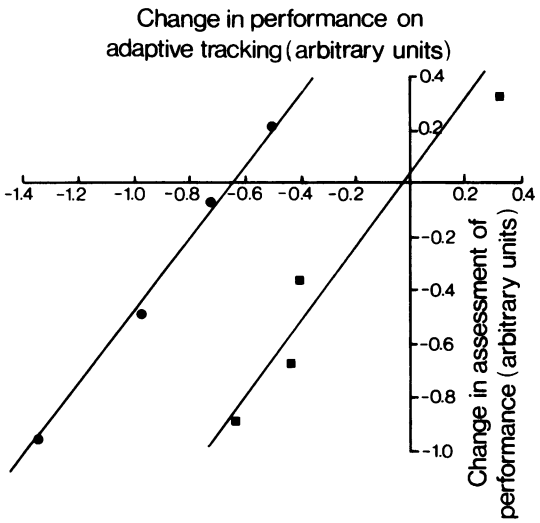

Fig. 3 Regression lines of change in performance on adaptive tracking (arbitrary units) and change in assessment of performance (arbitrary units) during day immediately after ingestion of drug for pentobarbitone sodium (200 mg, ●) and flurazepam hydrochloride (30 mg, ■).

Table 3 Analysis of variance for change in reaction time (ms) after drugs

Source	*Degrees of freedom*	*Mean squares*	F	*Significance levels*
Subjects (S)	5	5817.7099 (S x D x T)	11.0	***
Drug (D)	3	3337.0756 (S x D)	1.22	NS
Time (T)	4	2239.3645 (S x D x T)	4.23	**
S x D	15	2726.2869 (S x D x T)	5.15	***
S x T	20	740.7650 (S x D x T)	1.40	NS
D x T	12	648.7692 (S x D x T)	1.23	NS
S x D x T	60	528.9872		
Total	119			

	Time after ingestion				
Placebo or drug	*09.00 h Day 2 (+10 h)*	*12.00 h Day 2 (+13 h)*	*15.00 h Day 2 (+16 h)*	*18.00 h Day 2 (+19 h)*	*09.00 h Day 3 (+34 h)*
Placebo	19.4 *	3.8 (NS)	9.3 (NS)	9.1 (NS)	
Nitrazepam (10 mg)	23.1 *	45.4 ***	31.4 **	15.0 (NS)	23.3 *
Flurazepam hydrochloride (30 mg)	35.2 ***	19.4 *	28.5 **	−17.5 (NS)	17.1 (NS)
Pentobarbitone sodium (200 mg)	48.7 ***	36.2 ***	32.2 **(*)	18.3 (NS)	31.2 **

Least significant differences from zero for means of 6 were 5% = 18.8; 1% = 25.0; 0.1% = 32.5.
* = 5%; ** = 1%; *** = 0.1%; NS, not significant.

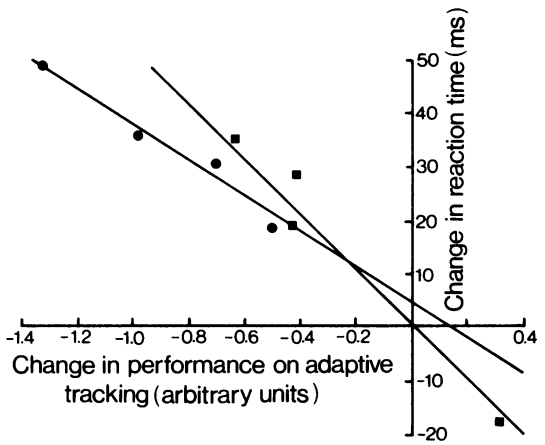

Fig. 4 Regression lines of change in performance on adaptive tracking (arbitrary units) and change in reaction time (ms) during day immediately after ingestion of drug for pentobarbitone sodium (200 mg, •) and flurazepam hydrochloride (30 mg, ▪).

time were (0.7-54.5 x change in performance on adaptive tracking) for flurazepam hydrochloride and (4.8-33.0 x change in performance on adaptive tracking) for pentobarbitone sodium. The slopes of these regressions (Fig. 4) did not differ significantly at the 5% level and the displacements of the regressions from the origin were not significant ($P = 0.05$).

Discussion

In the previous study on the overnight ingestion of heptabarbitone, Borland & Nicholson (1974) showed that the residual effects of this drug on adaptive tracking were related to the dose ingested. Performance was impaired ($P = 0.05$) to 10 h after 200 mg, to 13 h ($P = 0.05$) after 300 mg and to 19 h ($P = 0.01$) after 400 mg heptabarbitone. It would appear from the present studies that the residual effects during the day immediately after ingestion of pentobarbitone sodium (200 mg) do not differ from those observed after heptabarbitone (400 mg), though, unlike heptabarbitone, there is an enhanced performance on the third day.

The similarity of residual effects during the day immediately after ingestion of heptabarbitone (400 mg) and pentobarbitone sodium (200 mg) may be due to the more rapid plasma decay of heptabarbitone, while the rebound in performance on the third day after the ingestion of pentobarbitone sodium may be due to its slower decay. The concentration half time of heptabarbitone is 9.7 h (Clifford, Cookson & Wickham, 1974) compared with 43.2 h for pentobarbitone sodium (Fazekas, Goldbaum, Koppanyi & Shea, 1956), and it is suggested that rebound in performance is delayed until very low plasma levels are reached. After heptabarbitone, even with the higher dose ingested, enhanced performance would have occurred several hours before that of pentobarbitone sodium and would not have been observed in the present experiments.

The benzodiazepines led to consistent, though less severe, deficits in adaptive tracking. Impaired performance after nitrazepam persisted throughout the next day, but with flurazepam hydrochloride a rapid recovery of performance was observed after 16 hours. Unlike nitrazepam, enhanced performance on the third day was not observed after flurazepam hydrochloride and, as with heptabarbitone, it is suggested that this was related to the more rapid metabolism of the drug (Schwartz & Postma, 1970).

The delay in the appearance of enhanced performance indicates that the residual effects of a drug may persist beyond the return of performance to control levels, but changes in performance after hypnotics may also be related to the effects which these drugs have on sleep patterns. Nitrazepam (10 mg) and pentobarbitone sodium (200 mg), which led to enhanced performance on the third day, would have reduced whole night rapid eye movement sleep during the night of ingestion and induced a rebound increase during the next night, whereas flurazepam hydrochloride (30 mg) would have led to very little, if any, changes in rapid eye movement sleep duration during the night of ingestion or during the next night (Lehman & Ban, 1968; Lewis, 1968; Kales, Preston, Tan & Allen, 1970; Kales, Kales, Scharf & Tan, 1970; Haider & Oswald, 1971). But these considerations do not explain the absence of a performance rebound after the barbiturate heptabarbitone, and it is suggested that the relevant factor in the appearance of performance rebound is the excretion pattern of the drug.

The subjects as a group considered that pentobarbitone sodium and nitrazepam were no longer exerting a deleterious effect on their performance 16 h after ingestion, though, at this time and at 19 h after ingestion, their performance on adaptive tracking was impaired. During the morning immediately after ingestion the subjects differentiated correctly between placebo and drugs, but, though they were aware of impaired performance during the early part of the day, they were not always able to assess accurately the

duration of each residual effect. Regression equations between change in performance on adaptive tracking and change in assessment of performance for flurazepam hydrohcloride and pentobarbitone sodium were, at least, highly significant, but only with flurazepam hydrochloride did the regression pass through the origin. It would appear that after flurazepam hydrochloride subjects were able to assess relative changes in performance and identify performance change from control level, but that after pentobarbitone sodium they were able only to assess relative changes in performance. With nitrazepam it was not possible to establish a correlation between change of performance on adaptive tracking and change in assessment of performance. This would suggest an impaired appreciation of even relative change in performance.

The significance levels of impaired adaptive tracking and increased reaction time suggest that reaction time was a less sensitive measure of impaired performance than adaptive tracking, but the regression equations of recovery during the day after ingestion of pentobarbitone sodium and flurazepam hydrochloride were similar and each passed through the origin. There may be differences between change in performance on adaptive tracking and change in reaction time at any particular time interval, but these techniques provided essentially similar information on the residual effects of pentobarbitone sodium and flurazepam hydrochloride, though after nitrazepam it was not possible to establish a relation.

With nitrazepam and pentobarbitone sodium enhanced performance on adaptive tracking on the third day was accompanied by an increase in reaction time. This phenomenon may be due to different levels of performance on these tasks at the same level of central nervous arousal. Performance under control conditions may have been optimum or near optimum for reaction time, but far below optimum for adaptive tracking. Reduced levels of arousal after drugs would have reduced performance on both adaptive tracking and reaction time, but when the effect of the drugs had worn off the rebound increase in nervous arousal would have led to enhanced performance on adaptive tracking and decreased performance on reaction time (i.e. increased reaction time). The model would imply an inverted U relation between performance and central nervous arousal (Hebb, 1955; Malmo, 1962; Broadbent, 1965) with optimum performance on the reaction time curve being at a lower level of arousal than optimum performance on the adaptive tracking curve.

The performance of subjects on a pursuit tracking task may be expressed as a transfer function, though the information recorded from the present experiments did not provide sufficient data to measure the changes brought about by drugs. The basic transfer function may be considered as three linear elements, i.e. a gain term, a term representing delays in the central nervous and neuromuscular systems and a term which matches input demands and the control situation. Differences between performance predicted from this simple linear model and from that obtained by experiment would imply a remnant or noise factor. This would be introduced at the input to the model with the observed error signal. The model would also be complicated by the ability of subjects to predict target movements. In the present experiments the subjects may have used prediction as well as error reduction to optimize their overall performance (McRuer & Krendel, 1974).

If performance decrement resulted solely from an increase in the time delay factors inherent in central nervous and neuromuscular function then a relation between decrement on adaptive tracking and increase in reaction time would be expected. There were significant regressions between change in reaction time and change in adaptive tracking performance for pentobarbitone sodium and flurazepam hydrochloride ($P = 0.001$), but no such relationship was established for nitrazepam. This would suggest that pentobarbitone sodium and flurazepam hydrochloride modified central nervous and neuromuscular delays, but that nitrazepam may have had a more complicated effect. Other studies in man (Malpas *et al.*, 1970; Bond & Lader, 1972) have suggested that nitrazepam leads to greater disturbances in behaviour than barbiturates, and these observations have been supported by studies in the monkey on delayed matching behaviour (Nicholson, Wright & Ferres, 1973; Nicholson & Wright, 1974).

The residual effects of nitrazepam and flurazepam hydrochloride related to an occupation orientated task suggest that performance of complex skills is likely to be impaired throughout most of the working day after maximum doses within the normal therapeutic range of each hypnotic. Decrements in performance are likely to be related to dose and the present studies on flurazepam hydrochloride should be extended to lower doses, as this drug would appear to be a more promising benzodiazepine than nitrazepam for use by persons involved in skilled activity. Performance is impaired only to the early afternoon after overnight ingestion, but, unlike pentobarbitone sodium and nitrazepam, subjects retain the ability to recognize their impaired skill.

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