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BEHAVIOURAL SEQUELAE OF METHAQUALONE IN MAN AND IN THE MONKEY (*Macaca mulatta*)

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1 Residual effects in man of methaqualone hydrochloride (400 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 the overnight ingestion of the drug. There was no evidence of impaired performance on adaptive tracking from 10 h to 19 h, but enhanced performance ($P = 0.001$) was observed 34 h after ingestion. With reaction time an increase ($P = 0.01$) was observed 10 h and a decrease ($P = 0.05$) was observed 19 h after ingestion.

2 Effects in the monkey (*Macaca mulatta*) of methaqualone (20 and 30 mg/kg body weight) were studied by a delayed matching task in which total response time was measured. No consistent effects on matching behaviour or on total response time were observed 2 h after intraperitoneal injection.

3 The studies suggest that methaqualone hydrochloride may be a valuable hypnotic for occasional use by persons involved in skilled activity.

Introduction

Previous studies in man on the residual effects of the overnight ingestion of barbiturates and benzodiazepines have shown that these drugs lead to impaired performance on an adaptive tracking task during most of the next working day (Borland & Nicholson, 1974, 1975). With heptabarbitone (400 mg) and pentobarbitone sodium (200 mg) decrements in performance persist to 19 h after ingestion, and, though performance is less severely affected during the early part of the day after ingestion of benzodiazepines, decrements persist to 16 h after flurazepam hydrochloride (30 mg) and to 19 h after nitrazepam (10 mg). Similar studies have been carried out using tests of perception, attention and computation (Von Felsinger, Lasagna & Beecher, 1953; Kornetsky, Vates & Kessler, 1959; Malpas, Rowan, Joyce & Scott, 1970; Bond & Lader, 1972, 1973), though these tests would appear to be less sensitive to hypnotics than tracking performance.

The behavioural effects of barbiturates and benzodiazepines have also been studied in monkeys using matching tasks (Roberts & Bradley, 1967; Glick, Goldfarb, Robustelli & Jarvik, 1969; Nicholson, Wright & Ferres, 1973; Nicholson & Wright, 1974). Barbiturates and benzodiazepines impair matching behaviour and increase total response time, but it would appear that benzodiazepines, unlike barbiturates, have effects related to the delay between stimuli and to the type of response (GO or NO-GO) demanded. Benzodiazepines may possess the property of disinhibition and nitrazepam, in particular, has considerable potential for disturbing established behaviour in the monkey (Nicholson & Wright, 1974).

These studies show that both barbiturates and benzodiazepines have important residual effects on performance in man and that complex patterns of behaviour in the monkey are disrupted. The present study is concerned with methaqualone hydrochloride. We have been unable to establish any consistent residual effects of this hypnotic on performance in man, and, in view of this observation, we have carried out additional studies on delayed matching behaviour in the monkey. These support the observation in man that methaqualone hydrochloride has limited effects on behaviour compared with other commonly used hypnotics.

Methods

Studies in man

Performance was measured using an adaptive tracking task. 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. An error signal, proportional to 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 and 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. A voltage proportional to the distance between the spot and the centre of the target circle was generated and the radial error signal was computed. A voltage proportional to the square of the circle radius was subtracted from the square of the radial error signal. The output from the scoring circuit 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 made the integrator output increase. The circle tended to move away from the spot and, when the spot could no longer be maintained inside the target 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 monitored the tracking equipment and the performance of each subject.

Assessment of performance on adaptive tracking 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 on adaptive tracking 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 pressed 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} candela) 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 inter-trial time varied between 1 and 8 seconds. Twenty-five trials were presented to each subject and the mean of the last twenty trials was recorded as the reaction time. Reaction time was measured in 10 ms intervals accurate to the nearest 2 mseconds.

Experimental procedure Six healthy male subjects were used. Their ages ranged from 24-39 (mean 32) years and their weights ranged from 67-83 (mean 72) kg. Instructions were given to all subjects to avoid alcohol for the three days of the experiment and they were not involved in any other form of drug 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 tracking performance before studies commenced, and in subjects familiar with the technique, such as pilots, this level of performance would have been reached within a few days, but with laboratory personnel a plateau level of performance was reached with daily practice only after 2-3 weeks. Practice sessions were made available between experiments to maintain levels of performance reached after training.

The assessment of the effect of placebo or 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 h. 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. at 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. In any one subject, experiments were separated by 4 weeks and each subject completed three experimental runs of 3 days. The capsules contained methaqualone hydrochloride (400 mg), pentobarbitone sodium (200 mg) or placebo given in a random order. The trial was double blind and placebo and drugs were presented in an identical capsule. On day 1 of each experiment the subjects were required to report to the laboratory at 08 h 45 min, but on day 2 of each experiment (after the overnight ingestion of placebo or drug) the subjects were collected from home at 08 h 15 min to avoid any oversleep.

Studies in the monkey

A delayed matching task (Nicholson *et al.*, 1973) was used to study the effect of methaqualone in the monkey. The stimuli for the matching task were white illuminated patterns (cross or square) on dark backgrounds and were displayed on two vertical panels (5 x 5 cm) mounted on the wall of the testing box. A lever below the stimulus panels was depressed for GO responses and the rewards for correct GO and NO-GO responses (Purina chow pellets) were delivered through a chute. The testing box was situated in a sound-attenuated room with a constant background noise.

The initial stimulus of each trial was presented at 20 s intervals on the right hand panel. It was either a cross or a square of 2 s duration presented in random order. After the initial right hand stimulus there was a delay before the left hand panel was illuminated. The left hand stimulus was also a square or a cross of 2 s duration. The delay between stimuli was fixed for each session at either 2, 4 or 8 seconds. The cross and square sequence of each panel and the like or unlike sequence of each trial were both in random order. Each sequence consisted of fifty trials with twenty-five squares and twenty-five crosses on each panel. If the stimuli were like (cross followed by cross or square followed by square) the animal was required to depress the lever (GO response) during the 2 s presentation of the left hand stimulus. If the stimuli were unlike (cross followed by square or square followed by cross) the animal was required to refrain from pressing the lever (NO-GO response). In the event of an error the trial was repeated until a correct response was made, but only the result of the initial trial was used in the assessment of performance.

Details of training are given in a previous paper (Nicholson *et al.*, 1973). One of the five monkeys failed consistently to reach criterion performance on the 8 s delay (i.e. 80% correct on accuracy of matching), but was included for studies on the 2 and 4 s delays. Monkeys were maintained on a slightly restricted food intake, but records of body weight showed a steady increase. The animals weighed between 5.4 and 7.1 kg at the beginning and between 8.9 and 14.6 kg at the end of the experiments.

Each experiment consisted of ten sessions of fifty trials spread over 5 days. Two sessions were held each day at approximately 11.00 and 15.00 hours. Days 1 and 2 were control sessions, but injection of solvent for the drug (polyethylene glycol) on day 2 was not used because the previous study (Nicholson *et al.*, 1973) showed that it had no effect on behaviour. On day 3 the drug was given at approximately 09.00 h and testing sessions were held exactly 2 and 6 h later. Days 4 and 5 consisted of two sessions, each held at approximately 11.00 and 15.00 h, to assess any residual effects. The second session of each day was always held 4 h after the first session of that day. The data, which were recorded on paper tape, gave the number of the trial, the response required (GO or NO-GO), the total response time for GO responses (from onset of the left hand stimulus to the pressing of the lever) and whether the response was correct. Methaqualone (3,4-dihydro-2-methyl-4-oxo-3-*O*-tolylquinazoline) was given at 20 and 30 mg/kg body weight by i.p. injection in 5 ml polyethylene glycol. At least 7 days and usually 14 days separated drug injections at the lower dose, but with the higher dose 14 days always separated each injection.

Results

Studies in man

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

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 for placebo, but there were significant differences between performance at 09.00 h on day 1 and 09.00 h on day 3 after methaqualone hydrochloride and pentobarbitone sodium. No

significant differences could be established between performance at 09.00 h on day 1 before the ingestion of placebo or drugs. 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 for placebo and the 09.00 h performance on day 1 for the two drug experiments (mean of 4 values). And as no significant differences were established between performance at 12.00, 15.00 and 18.00 h on day 1 for placebo or drugs these three measures were combined for each subject for comparison with the individual 12.00, 15.00 and 18.00 h performance measures on the day immediately 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 on day 2 after ingestion of placebo. After methaqualone hydrochloride (400 mg) no significant deficits were observed in performance from 10 h to 19 h after ingestion, but the next morning at 09.00 h (34 h after ingestion) performance was enhanced. The change was significant at the 0.1% level. With pentobarbitone sodium performance was impaired from 10 h to 19 h after ingestion and there was evidence of enhanced performance the next day at 09.00 h (34 h after ingestion).

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 for placebo did not differ significantly from each other and these assessments did not differ significantly from the assessment at 09.00 h on day 1 for each drug. Assessment of performance at 09.00 h for the 3 days of each drug showed that the subjects assessed performance on day 3 higher than day 1 ($P = 0.05$) and day 1 higher than day 2 ($P = 0.001$). In view of these findings the control for assessment of performance at 09.00 h was taken as the mean of the 09.00 h assessment on day 1 and 3 for the placebo and the 09.00 h assessments on day 1 for each drug (mean of 4 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 on the day after (day 2) the ingestion of placebo or drug.

The results of the analysis of the assessments of performance are given in Table 2. There were no significant differences between the assessments of performance after placebo. After ingestion of

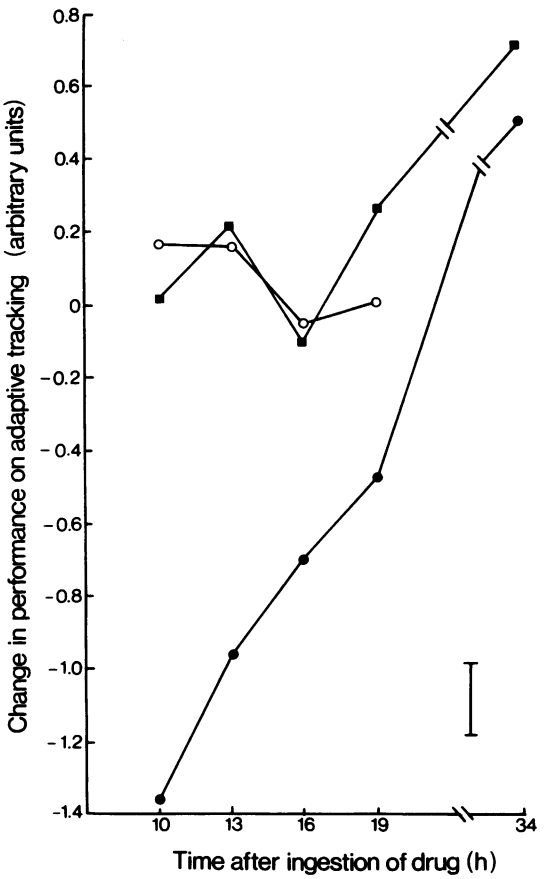

Figure 1 Mean change ($n = 6$) in performance on adaptive tracking (arbitrary units) for all subjects after overnight ingestion of methaqualone hydrochloride (400 mg, ▪), pentobarbitone sodium (200 mg, •) and placebo (○). The standard error is given as a vertical bar (0.19 arbitrary units).

methaqualone hydrochloride the subjects assessed their performance as impaired at 09.00 h (10 h after ingestion), but they assessed their performance as equal to that of the day before ingestion of drug during the rest of the day. Performance was assessed as enhanced at 09.00 h on the third day (34 h after ingestion) and this was significant at the 5% level. With pentobarbitone sodium performance was assessed as impaired at 10 and 13 h, but the subjects as a group considered their performance to be unimpaired 16 and 19 h after ingestion. Essentially the group detected the enhanced performance on adaptive tracking the next morning, though this was just not statistically significant at the 5% level.

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

Source	*Degrees of freedom*	*Mean squares*	F	*Significance levels*
Subjects (S)	5	1.372512	6.37	***
Drug (D)	2	5.690333 (SxD)	2.36	
Time (T)	4	1.911741	8.87	***
SxD	10	2.407933	11.17	***
SxT	20	0.269739	1.25	
DxT	8	0.811723	3.77	**
SxDxT	40	0.215489		
Total	89			

	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)	–
Methaqualone hydrochloride (400 mg)	0.02 (NS)	0.21 (NS)	−0.11 (NS)	0.24 (NS)	0.69 ***
Pentobarbitone sodium (200 mg)	−1.35 ***	−0.97 ***	−0.71 ***	−0.49 *	0.51 **

Least significant difference from zero for means of 6 were 5% = 0.38; 1% = 0.51; 0.1% = 0.67.
NS = not significant; * = 5%; ** = 1%; *** = 0.1%.

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	1.203140	3.95	**
Drug (D)	2	0.308750	1.01	
Time (T)	4	1.931775 (SxT)	3.12	*
SxD	10	0.605970	1.99	(2.08 = *)
SxT	20	0.619405	2.03	*
DxT	8	0.807163	2.65	*
SxDxT	40	0.304488		
Total	89			

	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)	
Methaqualone hydrochloride (400 mg)	−0.72 **	0.07 (NS)	−0.15 (NS)	0.42 (NS)	0.50 *
Pentobarbitone sodium (200 mg)	−0.95 ***	−0.48 *	−0.07 (NS)	0.22 (NS)	0.45 (*)

Least significant difference from zero for means of 6 were 5% = 0.46; 1% = 0.61; 0.1% = 0.80.
NS = not significant; * = 5%; ** = 1%; *** = 0.1%.
Change in assessment of performance at 09.00 h on day 3 after pentobarbitone sodium was only 0.01 below the value required for significance at the 5% level.

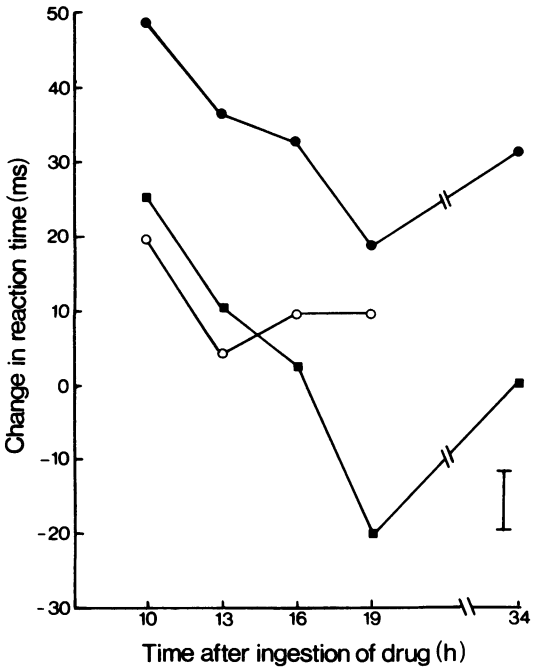

Figure 2 Mean change ($n = 6$) in performance on reaction time (ms) for all subjects after overnight ingestion of methaqualone hydrochloride (400 mg, ▪), pentobarbitone sodium (200 mg, •) and placebo (○). The standard error is given as the vertical bar (8.3 ms).

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 and 2 did not differ significantly for the placebo assessment, but reaction times at 09.00 h on the day after ingestion of the drugs were greater than on day 3 ($P = 0.05$) and these were greater than on day 1 ($P = 0.01$). Reaction times at 09.00 h on day 1 for placebo and 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 placebo and of day 1 for each drug were taken for each subject (mean of 4 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 time was prolonged 10 h after the ingestion of placebo and methaqualone hydrochloride and all day after pentobarbitone sodium. There was a decrease in reaction time 19 h after ingestion of methaqualone hydrochloride. Increased reaction time was observed the next morning (34 h after ingestion) after pentobarbitone sodium, but no change in reaction time

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

Source	*Degrees of freedom*	*Mean squares*	F	*Significance levels*
Subjects (S)	5	3157.7882	8.00	***
Drug (D)	2	7288.1688 (SxD)	2.95	
Time (T)	4	1875.8434	4.75	**
SxD	10	2470.5448	6.26	***
SxT	20	699.1234	1.77	(1.84 = *)
DxT	8	323.5452	1.00	
SxDxT	40	394.5728		
Total	89			

Placebo or drug	*Time after ingestion* 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	9.3	9.1	–
	*	NS	NS	NS	
Methaqualone hydrochloride (400 mg)	24.7	10.9	2.4	–20.2	0.6
	**	NS	NS	*	NS
Pentobarbitone sodium (200 mg)	48.7	36.2	32.2	18.3	31.2
	***	***	***	*	***

Least significant difference from zero for means of 6 were 5% = 16.4; 1% = 21.9; 0.1% = 28.8.
NS = not significant; * = 5%; ** = 1%; *** = 0.1%.

Table 4 Analysis of variance and significance levels for change in total response time (ms) for the monkey after methaqualone

Source	Degrees of freedom	Mean squares	F	Significance levels
		Four monkey analysis		
Monkeys (M)	3	143538.555556	11.10	**
Delays (D)	2	19493.347223	1.51	
Dose level (L)	1	6050.000000		
MxD	6	28891.569445	2.23	
MxL	3	49212.851852	3.81	
DxL	2	2121.291667		
MxDxL	6	12933.254628		
T	2	1965.097223	1.79	
MxT	6	1539.208334	1.40	
DxT	4	602.993055		
LxT	2	276.291666		
MxDxT	12	602.576388		
MxLxT	6	2700.476851	2.46	
DxLxT	4	393.270834		
MxDxLxT	12	1098.983798		
		Five monkey analysis		
M	4	50962.566667	30.15	**
D	1	6848.016667		
L	1	9907.350000	5.86	
MxD	4	19068.683334	11.28	*
MxL	4	6524.933334	3.86	
DxL	1	2.016668		
MxDxL	4	1690.349997		

* = 5%; ** = 1%.

was detected at this time after methaqualone hydrochloride.

No significant correlations could be established between performance on adaptive tracking, assessments of performance and reaction time after methaqualone hydrochloride and this was due, presumably, to the minimal residual changes in performance after ingestion of the drug. The correlations between performance on adaptive tracking, assessments of performance and reaction time after pentobarbitone sodium are described elsewhere (Borland & Nicholson, 1975).

Studies in the monkey

The analysis of the studies in the monkey was concerned with total response time for GO responses and accuracy of response on the matching task. These measures were related to the performance of individual monkeys, delay between stimuli, dose levels and time after injection. The morning and afternoon sessions of the 5 days of each experiment provided ten assessments and gave nine degrees of freedom. This allowed the following comparisons to be made. The morning assessments (at 11.00 h) of all non-drug days (1, 2, 4 and 5) were compared with the afternoon assessments (at 15.00 h) of all non-drug days (1, 2, 4 and 5). The morning (at 11.00 h) and afternoon (at 15.00 h) assessments of the 2 days (1 and 2) before the administration of the drug were compared with morning (11.00 h) and afternoon (15.00 h) assessments of the 2 days (4 and 5) after the administration of the drug. No differences were established between morning and afternoon assessments of the non-drug days (1, 2, 4 and 5) or between the days before the drug (1 and 2) and the days after the drug (4 and 5). The morning and afternoon assessments of days 1, 2, 4 and 5 were combined to give the control value for a particular week and this value was compared with the morning and afternoon assessments of the drug (day 3) of the same week.

Two separate analyses were carried out on the data because one of the monkeys failed to reach criterion level of performance at the 8 s delay. The first analysis was on the effects of the three treatments on total response time and on accuracy of response on matching of four monkeys trained to carry out the task at all three delays. The

Table 5 Analysis of variance and significance levels for change in accuracy on GO responses for the monkey after methaqualone

Source	Degrees of freedom	Mean squares	F	Significance levels
		Four monkey analysis		
Monkeys (M)	3	4.504666	6.75	*
Delays (D)	2	10.726888	16.08	**
Dose level (L)	1	2.815429 (MxL)		
MxD	6	2.039822	3.06	
MxL	3	3.182618	4.77	*
DxL	2	2.920899	4.38	
MxDxL	6	0.666993		
T	1	0.719075	1.66	
MxT	3	0.692167	1.60	
DxT	2	2.336263	5.40	*
LxT	1	0.002930		
MxDxT	6	1.128364	2.61	
MxLxT	3	0.703448	1.63	
DxLxT	2	1.374023	3.18	
MxDxLxT	6	0.432617		
		Five monkey analysis		
M	4	34.879883	9.12	***
D	1	2.626562		
L	1	1.139062		
MxD				
MxL		3.824219		
DxL				
MxDxL				

* = 5%; ** = 1%; *** = 0.1%.

second analysis, which included the fifth monkey, was on the effects of the three treatments on total response time and accuracy of matching at two delays (2 and 4 s). The analysis of variance and significance levels for changes in total response time are given in Table 4. No significant effects were observed after methaqualone except that the responses of individual monkeys were variable ($P = 0.01$). The analysis of variance and significance levels for changes in response on matching on GO and on NO-GO responses are given in Tables 5 and 6. There were no significant effects of the drug on GO responses, but the tendency of the animals as a group to respond to NO-GO situations was reduced after methaqualone. Examination of the effects after the low (20 mg/kg) and high dose (30 mg/kg) suggested that the reduced tendency to respond to NO-GO situations was associated with the low dose only. This was significant at the 5% level, but the behaviour of individual monkeys was variable.

Discussion

The present studies on the overnight ingestion of methaqualone hydrochloride (400 mg) have revealed little, if any, residual effects on performance in man. Performance on adaptive tracking from 10 h to 19 h after ingestion was not impaired and, though reaction time was increased at 10 h, the change was not significantly different from that observed at this time after ingestion of placebo. The minimal residual effects of methaqualone hydrochloride are in contrast with those observed after barbiturates and benzodiazepines (Borland & Nicholson, 1974, 1975). With the overnight ingestion of heptabarbitone (400 mg) and pentobarbitone sodium (200 mg) decrements in performance on adaptive tracking persist to 19 h, and with flurazepam hydrochloride (30 mg) and nitrazepam (10 mg), though decrements on adaptive tracking are not as severe as those observed after barbiturates, they persist to 16 h and 19 h respectively.

After methaqualone hydrochloride the changes in performance on adaptive tracking and on reaction time did not correlate with each other. This phenomenon was also observed after barbiturates and benzodiazepines (Borland & Nicholson, 1975). With pentobarbitone sodium and nitrazepam, though deficits in performance on both

Table 6 Analysis of variance and significance levels for change in accuracy of matching on NO-GO responses for the monkey after methaqualone

Source	Degrees of freedom	Mean squares	F	Significance levels
		Four monkey analysis		
Monkeys (M)	3	1.192274		
Delays (D)	2	3.440430	2.88	
Dose level (L)	1	1.171874		
MxD	6	1.524631	1.28	
MxL	3	1.807293	1.51	
DxL	2	0.838868		
MxDxL	6	1.195639		
T	1	2.636719	6.47	*
MxT	3	0.983941	2.41	
DxT	2	0.159179		
LxT	1	0.421876	1.04	
MxDxT	6	1.118382	2.74	
MxLxT	3	1.196178	2.94	
DxLxT	2	0.745117	1.83	
MxDxLxT	6	0.407443		

Least significant difference between means of 24 were 5% = 0.4509; 1% = 0.6831.

		Five monkey analysis		
M	4	9.104492	6.02	**
	1	1.269140		
L	1	0.112890		
error	13	1.512831		
T	1	2.956640	17.07	*
MxT	4	0.410742	2.37	
DxT	1	0.244142	1.41	
LxT	1	0.087892		
MxDxT	4	0.563478	3.25	
MxLxT	4	1.555665	8.98	*
DxLxT	1	0.047262		
MxDxLxT	4	0.173240		

Least significant difference between means of 20 were 5% = 0.3654; 1% = 0.6060
* = 5%; ** = 1%.

adaptive tracking and reaction time were parallel throughout the next working day, there was an enhanced performance on adaptive tracking with an increase in reaction time 34 h after ingestion. It was suggested that the impaired performance after ingestion of an hypnotic may be associated with the reduced level of arousal, but that changes in performance after the effect of the drugs had worn off may be related to a rebound increase in arousal. It was also proposed that, with the inverted U relation which may exist between performance on a task and nervous arousal (Hebb, 1955; Malmo, 1962; Broadbent, 1965), optimum performance on reaction time may be attained at a lower level of arousal than optimum performance on adaptive tracking, and so a rebound increase in arousal could lead to a dissociation between the performance reached on these tasks.

With methaqualone hydrochloride there were several dissociations between performance on adaptive tracking and on reaction time. At 19 h after ingestion there was a decrease in reaction time without significant change in performance on adaptive tracking. This may have been due to the rebound increase in arousal being of sufficient magnitude to shift performance significantly to the optimum point of the reaction time curve, but of insufficient magnitude to modify significantly performance on the adaptive tracking curve. On the other hand enhanced performance on adaptive tracking without significant change in reaction time observed 34 h after ingestion may have been

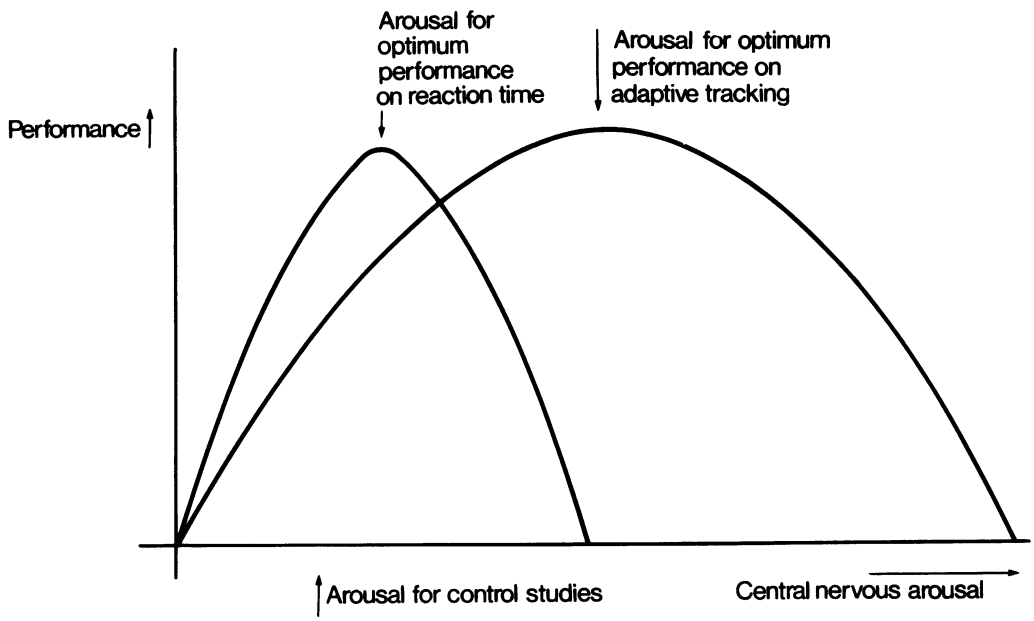

Figure 3 Model to explain differential changes in performance on adaptive tracking and on reaction time after hypnotics. It is suggested that optimum performance on reaction time is reached at a lower level of arousal than optimum performance on adaptive tracking and that the curve relating performance and central nervous arousal for reaction time has less spread than the curve for adaptive tracking. It is also suggested that nervous arousal under the control conditions for the present experiments was below the optimum for performance on both adaptive tracking and reaction time. Reduced arousal after hypnotics leads to a decrease in performance on both adaptive tracking and reaction time (increased reaction time) and rebound increase in arousal, after the effect of the drugs wears off, leads initially to improved performance on each task as arousal approaches that for optimum performance. A further increase in arousal leads to reduced performance. In this way the separate curves for adaptive tracking and reaction time may lead to differential effects on performance as the level of central nervous arousal changes.

due to a further increase in arousal, in which performance on reaction time moved beyond the optimum point on the curve and down the descending limb where it was equivalent to that attained under control conditions. This model, which is illustrated in Figure 3, not only implies that optimum performance on reaction time and adaptive tracking are at different levels of arousal, but that the spread of the reaction time curve is much less than the spread of the adaptive tracking curve. Further, that nervous arousal may have been below optimum for the assessment of control performance.

Changes in nervous arousal after ingestion of drugs are likely to be related to their excretion. The concentration half times of pentobarbitone sodium and nitrazepam are much longer than those for heptabarbitone and flurazepam hydrochloride (Fazekas, Goldbaum, Koppanyi & Shea, 1956; Schwartz & Postma, 1970; Clifford, Cookson & Wickham, 1974), and so the more persistent plasma levels of pentobarbitone sodium and nitrazepam would be associated with a rebound enhancement in performance during the morning of the third day. But with heptabarbitone and flurazepam hydrochloride, with their shorter concentration half times, enhanced performance would have occurred before the morning of the third day and would not have been detected as performance was not tested from 19 h to 34 h after ingestion to avoid any complications from sleep disturbances.

The excretion pattern of methaqualone hydrochloride involves an initial fast concentration half time followed by a slow decay (Alvan, Lindgren, Bogentoft & Ericsson, 1973; Clifford *et al.*, 1974). It is considered that the absence of performance decrements during the day immediately after ingestion of methaqualone hydrochloride was due to the initial rapid fall in plasma concentration and

that the delay in the appearance of enhanced performance until the morning of the third day was related to the slower secondary decay curve. A separate configuration of each performance curve with nervous arousal would explain the decreased reaction time 19 h after ingestion when there was no significant change in adaptive tracking, and the absence of a significant change in reaction time on the third morning when there was an enhancement of performance on adaptive tracking.

The limited effect which methaqualone hydrochloride has on performance in man is supported by the studies on methaqualone in the monkey. No definite effects on total response time were observed even 2 h after the intraperitoneal injection of 30 mg/kg methaqualone, and the drug had little, if any, effect on matching behaviour compared with both barbiturates (Nicholson *et al.*, 1973) and benzodiazepines (Nicholson & Wright, 1974). It is possible that methaqualone may reduce the tendency to respond to NO-GO situations, but the variation in behaviour observed between monkeys allows little confidence to be placed in this observation at present.

The studies suggest that methaqualone hydrochloride may prove to be a valuable hypnotic for occasional use by persons involved in skilled activity. Experiments in man have failed to provide definite evidence that this drug, even at a dose which is the maximum of the normal therapeutic range (400 mg), has residual effects on performance from 10 h after ingestion. The observation that methaqualone hydrochloride has limited effects in man is supported by the studies in the monkey (*Macaca mulatta*). Doses comparable to those used in the previous studies on barbiturates and benzodiazepines, when related to their use as hypnotics in man, do not increase total response time or effectively disturb matching behaviour in the monkey.

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