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INHIBITORY AND DISINHIBITORY EFFECTS OF NITRAZEPAM, DIAZEPAM AN--ETC(U)
NOV 75 A N NICHOLSON, C M WRIGHT

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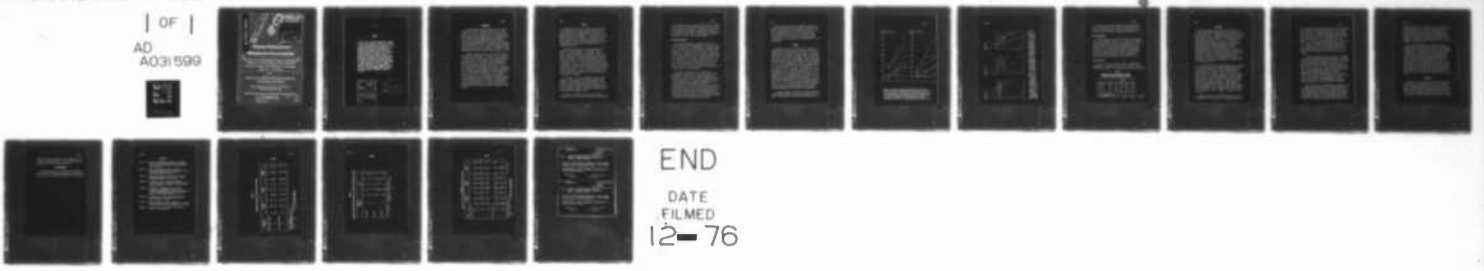

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Inhibitory and Disinhibitory Effects of Nitrazepam, Diazepam and Flurazepam Hydrochloride on Delayed Matching Behaviour in Monkeys (Macaca - mulatta)

by

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ABSTRACT

The effect of three benzodiazepines, nitrazepam (0.15, 0.45 and 0.75 mg/kg), diazepam (0.6, 1.8 and 3.0 mg/kg) and flurazepam (0.45, 1.35 and 2.25 mg/kg) on total response time and on the accuracy of response on a delayed matching task has been studied in monkeys (Macaca mulatta). Increased total response time was observed after all three doses of diazepam and particularly nitrazepam, but after flurazepam increased total response time was limited to the highest dose (2.25 mg/kg). Accuracy of response on delayed matching was impaired by all three drugs. The effect of diazepam and flurazepam was limited to the highest dose in each case, but with nitrazepam performance was impaired also after 0.45 mg/kg. The effect of the three benzodiazepines on delayed matching was related in a complex way to the delay between stimuli and to the response demanded (GO OR NO-GO). It is suggested that the effect of the benzodiazepines depended on a complex interaction between the differential response of two systems leading to inhibited or disinhibited behaviour.

INTRODUCTION

Delayed matching has been used by several workers to study the effects of drugs (Roberts and Bradley, 1967; Glick et al., 1969; Nicholson et al., 1973). The task usually involves delays of a few seconds between stimuli and though drugs, such as chlorpromazine and pentobarbitone sodium, may impair the accuracy of response, there is little evidence of delay dependent effects with these drugs in monkeys with well established behaviour. Impaired delayed matching with the simultaneous presentation of stimuli may be due to decreased motor responsiveness (Glick et al., 1969), while the higher performance reached on short delays may be less sensitive to drugs than the lower performance usually attained on longer delays (Nicholson et al., 1973).

Some delayed matching tasks involve both GO and NO-GO responses. These introduce the possibility of two types of incorrect response. The animal may fail to respond to a GO situation which would suggest behavioural inhibition or may respond to a NO-GO situation which would suggest the release of inhibitory behaviour (disinhibition). There is no evidence that barbiturates have a selective effect on NO-GO responses (Roberts and Bradley, 1967: Nicholson et al., 1973), but recent studies on chlordiazepoxide suggest that the benzodiazepine group of drugs may possess the property of disinhibition (Margules and Stein, 1968; Wedeking, 1969; Heise et al., 1970; Schallek et al., 1972; Hasegawa et al., 1973). Within this context the present studies on the effect of three benzodiazepines (nitrazepam, diazepam and flurazepam hydrochloride) were carried out. Performance on the task has been related to the type of response demanded (GO/NO-GO), to the delay between stimuli and to dose. Total response time was measured to provide information on the effect of these drugs on motor activity.

METHODS

Five male rhesus monkeys (Macaca mulatta) trained on delayed matching (Nicholson et al., 1973) were used. 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 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-sec intervals on the right hand panel. It was either a cross or a square of 2 sec 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 sec duration. The delay between stimuli was fixed for each session at either 2, 4 or 8 sec. The cross and square sequence of each panel and the like or unlike sequence of each trial were both in random order. Each sequence of trials consisted of 25 squares and 25 crosses on each panel. A total of 50 trials was presented in each session. In the event of an error, the trial was repeated until a correct response was made, though only the initial trial was used in the assessment of performance.

If the stimuli were like (cross followed by cross or square followed by square), the animal was required to depress the lever during the 2 sec 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. A correct response (GO response if like stimuli or NO-GO response if unlike stimuli) was rewarded by a pellet.

The details of training are given in the previous paper (Nicholson et al., 1973). One of the five monkeys failed consistently

to reach criterion performance (ie 80% correct on accuracy of matching) on the 8 sec delay, but was included for atudiea on the 2 and 4 sec delaya. 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 of the experiments and between 8.9 and 14.6 kg at the end of the experimenta.

Experiments with Drugs

Each experiment consisted of 10 sessions of 50 triala. Two sessions were held each day at approximately 1100 and 1500 hr. Daya 1 and 2 each coneisted of two control sessions. Injections of solvent only on day 2 were not used in this study because the previous etudy (Nicholson et al., 1973) did not reveal any effects. On day 3, the drug waa given at approximately 0900 hr and testing aessions were held exactly 2 and 6 hr later. Days 4 and 5 consisted of 2 sessions, each held at approximately 1100 and 1500 hr. The second aession of each day waa alwaya held 4 hr after the first aession of that day. The data, recorded on paper tape, gave the number of the trial and the response required (GO or NO-GO), the total response time for GO responsea (from onset of the left hand stimulus to the pressing of the lever) and whether the reaponse was correct.

Nitrazepam (1.2-dihydro-7-nitro-2-oxo-5-phenyl-3H-1,4-benzodiazepine) was given at 0.15, 0.45 and 0.75 mg/kg body weight and diazepam (7-chloro-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1, 4-benzodiazepine) was given at 0.6, 1.8 and 3.0 mg/kg body weight both in 5 ml polyethylene glycol. Flurazepam hydrochloride (7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one dihydrochloride) was given at 0.45, 1.35 and 2.25 mg/kg body weight in 5 ml of saline. Each drug was adminietered by intraperitoneal injection and was studied at the three dose levels with each of the three delays except in the one monkey which failed to reach criterion at the 8 eec delay. At least seven daye and usually fourteen daye separated drug injections at the lowest dose, but in all other experiments 14 days separated each drug injection.

The lowest dose for each drug was determined in relation to the maximum dose of the normal therapeutic range for man assuming a body weight of approximately 70 kg, ie 0.15 mg/kg for nitrazepam (10 mg for man), 0.6 mg/kg for diazepam (40 mg for man) and 0.45 mg/kg for flurazepam hydrochloride (30 mg for man). The middle and highest doses represented factors of three and five times the lowest dose. A similar regime was used in the previous study (Nicholson et al., 1973) on barbiturates.

RESULTS

The analysis was concerned with change in total response for GO responses and with change in accuracy of matching, but excluding the repeated responses if the initial trial was incorrect. 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 10 assessments and gave 9 degrees of freedom. This allowed the following comparisons to be made. The morning assessment (at 1100 hr) of all non-drug days (1, 2, 4 and 5) were compared with the afternoon assessments (at 1500 hr) of all non-drug days (1, 2, 4 and 5). The morning (at 1100 hr) and afternoon (at 1500 hr) assessments of the 2 days (1 and 2) before the administration of the drug were compared with morning (1100 hr) and afternoon (1500 hr) 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). For this reason the morning and afternoon assessments of days 1, 2, 4 and 5 were combined to give the control values for a particular week and this value was compared with the morning and afternoon assessments of the drug day (day 3) of that 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 sec delay. The first analysis was on the effects of the three drugs on

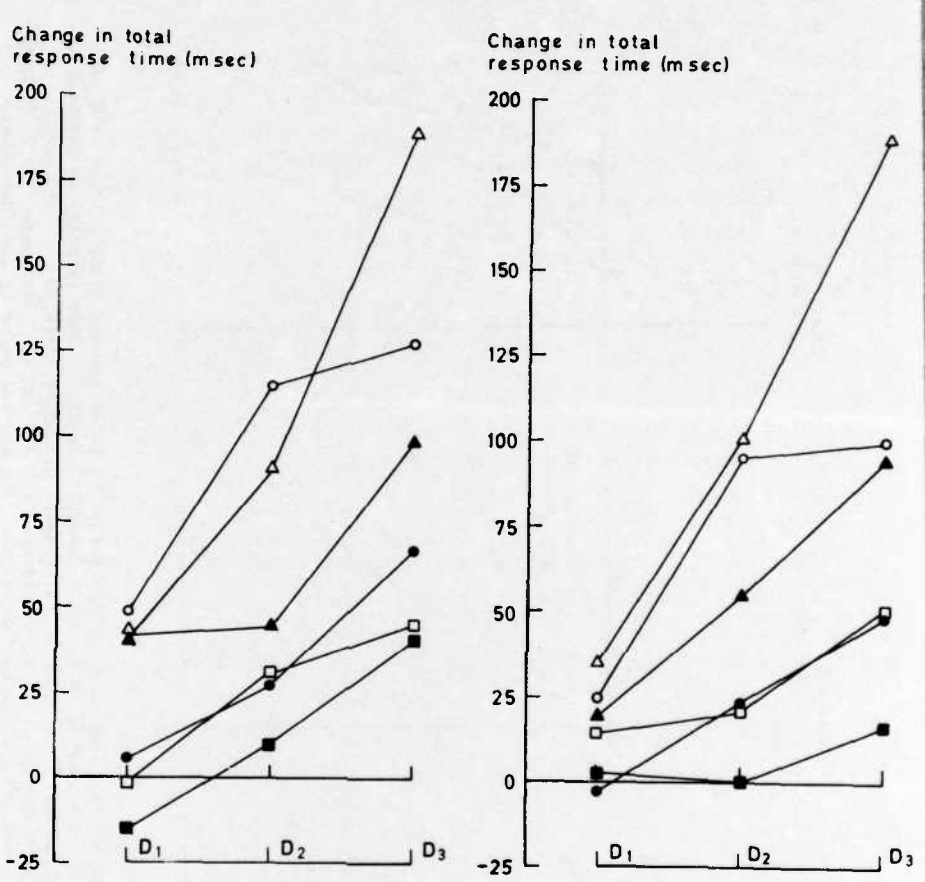

Fig. 1. Change in total response time (msec) after nitrazepam (triangle), diazepam (circle) and flurazepam (square). Open symbols: 2 hr after injection; closed symbols: 6 hr after injection. D1: 0.15 mg/kg nitrazepam, 0.6 mg/kg diazepam and 0.45 mg/kg flurazepam. D2: 0.45 mg/kg nitrazepam, 1.8 mg/kg diazepam and 1.35 mg/kg flurazepam. D3: 0.75 mg/kg nitrazepam, 3.0 mg/kg diazepam and 2.25 mg/kg flurazepam. Left-hand figure refers to five-monkey analysis and right-hand figure refers to four-monkey analysis (see Annex A, Table 1).

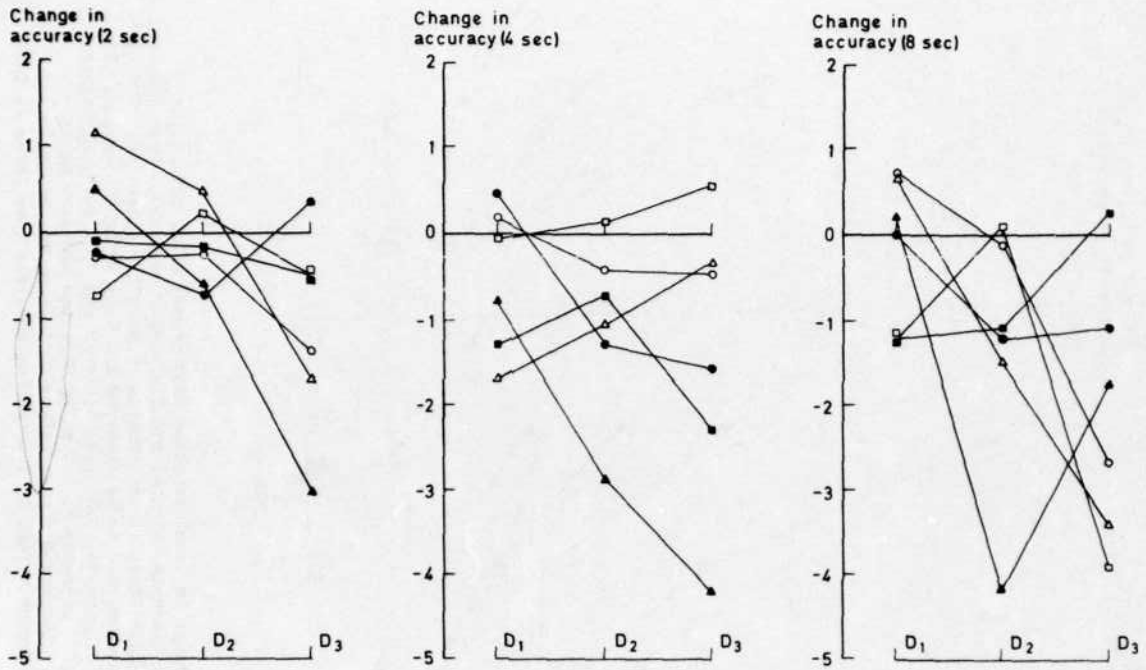

Fig. 2. Change in accuracy of response on matching related to delay between stimuli (2, 4 or 8 sec) after nitrazepam (triangle), diazepam (circle) and flurazepam (square). Open symbols: GO responses: closed symbols: NO-GO responses. D1: 0.15 mg/kg nitrazepam, 0.6 mg/kg diazepam and 0.45 mg/kg flurazepam. D2: 0.45 mg/kg nitrazepam, 1.8 mg/kg diazepam and 1.35 mg/kg flurazepam. D3: 0.75 mg/kg nitrazepam, 3.0 mg/kg diazepam and 2.25 mg/kg flurazepam. The figures refer to the four-monkey analysis only (Table 7).

total response time and accuracy of matching of four monkeys trained to carry out the task at all three delays. The second analysis, which included the fifth monkey, was on the effects of the three drugs on total response time and accuracy of matching at two delays (2 and 4 sec).

Total Response Time

Very highly significant effects were observed on total response time (Tables 1 and 2 (Annexes A and B) and Fig 1). The effect of nitrazepam was significantly greater than the effect of diazepam (P = 0.01) and the effect of diazepam was significantly greater than the effect of flurazepam (P = 0.01). Though there were interactions between drugs, dose levels and time (2 and 6 hr after injection) it was not possible to establish a relationship between the effect of the drugs and the delay between stimuli. The analysis of total response time was restricted to the dose injected and to the time after injection.

Delayed Matching

Analysis of GO and NO-GO responses revealed a complex pattern of effects related to dose and delay (Table 3 (Annex C), Table 4 and Fig 2). The effects were limited to the 2 hr interval after injection of each drug.

Table 4

Change in Accuracy of Response on Delayed Matching for Individual Monkeys after Drugs

	Monkey 1	2	3	4	5
Nitrazepam	-0.08 NS	-1.97 ***	-2.38 ***	-0.01 NS	-1.98 ***
Diazepam	-0.14 NS	-0.44 NS	-0.72 NS	-0.54 NS	0.22 NS
Flurazepam	-0.51 NS	-1.03 *	-0.15 NS	-0.32 NS	-0.17 NS

NS: Not significant.
Least significant differences. *P = 0.05: 0.98 **P = 0.01: 1.30 ***P = 0.001. 1.69

DISCUSSION

The present studies have shown that the three benzodiazepines, nitrazepam, diazepam and flurazepam, impaired the accuracy of response on a delayed matching task. Diazepam and flurazepam impaired performance only after injection of the highest dose of each drug and so the effect of these drugs was similar to that of the three barbiturates studied in the previous paper (Nicholson et al., 1973). With nitrazepam, performance was impaired after 0.45 mg/kg and this drug had a much greater potential than diazepam and flurazepam for disturbing established behaviour. But unlike barbiturates, the three benzodiazepines had effects on delayed matching which were related to the delay between stimuli. Impaired performance after the highest dose of diazepam (3.0 mg/kg) and flurazepam (2.25 mg/kg) was observed only with the 4 and 8 sec delays. With nitrazepam, though impaired performance was observed on all three delays after an equivalent dose (0.75 mg/kg), performance was also impaired after 0.45 mg/kg, but only with the 4 and 8 sec delays.

A further difference between the benzodiazepines and the barbiturates was that the benzodiazepines had effects on delayed matching related to the type of response demanded. Impaired performance after 0.45 mg/kg nitrazepam was due solely to incorrect responses to NO-GO situations (ie errors of commission), but after 0.75 mg/kg nitrazepam deficits at 2 and 4 sec were due predominantly to incorrect responses to NO-GO situations, while impaired behaviour at the 8 sec delay was due predominantly to failure to respond to GO situations (ie errors of omission). After 1.8 mg/kg diazepam and 1.35 mg/kg flurazepam, delayed matching behaviour was unaffected, but at the highest dose of each drug, corresponding with 0.75 mg/kg nitrazepam, impaired matching was due predominantly to incorrect responses to the NO-GO situation at the 4 sec delay and to failure to respond to GO situations at the 8 sec delay.

Impaired performance on GO and NO-GO situations was observed at the highest dose of each benzodiazepine, though impaired performance

on NO-GO situations only was also observed at a lower dose of nitrazepam. The complex effects of benzodiazepines on tasks involving GO and NO-GO responses suggest that these drugs possess properties in addition to their hypnotic action. Response to NO-GO situations after drugs has been discussed elsewhere in terms of disinhibition (Margules and Stein 1968; Wedeking 1969; Heise et al., 1970; Schallek et al., 1972; Hasegawa et al., 1973), but, though such a behavioural concept may have some value, it must be appreciated that it does not imply a neurological process. The mechanisms of disinhibited behaviour are not clear. Many factors could be involved including altered tendencies to make responses or regression to forms of behaviour, such as GO behaviour, which were appropriate at earlier stages of the animal's training.

Increased total response time was observed after all three doses of nitrazepam and diazepam, though consistent changes in total response time after the lowest dose was observed only in the case of nitrazepam. With flurazepam increased total response time was limited to the highest dose (2.25 mg/kg). The effects of diazepam on total response timewere similar to the effects of the barbiturates (Nicholson et al., 1973). Very highly significant increases in total response time were observed after the highest dose of diazepam (3.0 mg/kg), pentobarbitone sodium and quinalbarbitone sodium (15 mg/kg) and heptabarbitone (30 mg/kg) which persisted to the 6 hr interval, while after 1.8 mg/kg diazepam, 10 mg/kg pentobarbitone sodium and quinalbarbitone sodium and 20 mg/kg heptabarbitone total response times were increased, but were restricted to the 2 hr interval.

The overall effects of the benzodiazepines on the behaviour of the five monkeys have been discussed so far, but the responses of individual monkeys on both total response time and delayed matching varied. After flurazepam there were significant increases in total response time in only three monkeys. All three drugs modified the behaviour of three monkeys, but the behaviour of one monkey was modified only by nitrazepam. The duration of drug effects on total response time also

varied between animals. It would appear that drugs with profound behavioural effects, such as nitrazepam, tended to affect all monkeys, whereas drugs with less severe effects, such as flurazepam, had a more variable effect. But it must be appreciated that, though the effect of a drug may fail to reach a level of significance in some monkeys, the effect may still contribute to the significance level reached for the group. Similar considerations apply to the results on performance on delayed matching.

It is evident that increased total response time and impaired responses on delayed matching are effects common to both barbiturates and benzodiazepines, but the magnitude of the effects vary considerably between the drugs. Impaired matching is observed particularly after nitrazepam and total response time is increased particularly after nitrazepam, diazepam and the barbiturates. Flurazepam has similar effects, but unlike the other benzodiazepines and the barbiturates, they are restricted to the highest dose given (2.25 mg/kg). The behavioural effects of the benzodiazepines were related also to the delay between stimuli and to the response situation. Benzodiazepines impaired both GO and NO-GO responses and these effects increased with dose. Disinhibited behaviour predominated at lower doses and reached its maximum effect at short delays, while inhibited behaviour was seen only at higher doses and reached its maximum effect only at longer delays.

CONCLUSIONS

The manner in which the same drug can exert different behavioural effects depending on dose and delay is not clear from the present studies. The mechanisms controlling GO and NO-GO behaviour would appear to respond differentially according to the delay between stimuli and this pattern of response is dose related. Inhibition or disinhibition tends to dominate at particular combinations of dose and delay and will reverse at the same dose from one delay to another, or at the

same delay from one dose to another. This would suggest that the behaviour of the animal depends on a complex interaction between the differential response of two systems to the drug.

ACKNOWLEDGEMENTS

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TABLE 1

Change in Total Response time (msec) after Drugs

Time after injection (hr)	Nitrazepam mg/kg 0.15	0.45	0.75	Diazepam mg/kg 0.6	1.8	3.0	Flurazepam mg/kg 0.45	1.35	2.25
Four-monkey analysis									
+2	36 **	102 ***	190 ***	24 NS	94 ***	99 ***	15 NS	20 NS	50 ***
+6	19 NS	55 ***	95 ***	-04 NS	23 NS	49 ***	02 NS	00 NS	15 NS
Five-monkey analysis									
+2	41 *	88 ***	189 ***	49 **	115 ***	128 ***	-02 NS	32 NS	46 **
+6	41 *	46 **	100 ***	05 NS	27 NS	61 ***	-16 NS	10 NS	38 *

NS: Not significant.
Least significant differences.
*P = 0.05: **P = 0.01: ***P = 0.001.

26	35	46 for four-monkey analysis
34	46	61 for five-monkey analysis.

TABLE 2

Change in Total Response Time (msec) for Individual Monkeys after Drugs

	Time after injection (hr)	Monkey 1	2	3	4	5
Nitrazepam	+2	61 •••	87 •••	176 •••	84 •••	122 •••
	+6	35 ••	47 ••	81 •••	59 •••	88 •••
Diazepam	+2	82 •••	21 NS	114 •••	44 ••	225 •••
	+6	00 NS	-06 NS	58 •••	24 NS	79 •••
Flurazepam	+2	31 •	-20 NS	73 •••	09 NS	34 •
	+6	-06 NS	-05 NS	35 ••	08 NS	21 NS

NS: Not significant. Least significant differences.
•P = 0.05: 25 • P = 0.01: 35 •••P = 0.001. 49

TABLE 3

Change in Accuracy of Response on Delayed Matching after Drugs

Delay (sec)	Response	Nitrazepam (mg/kg) 0.15	0.45	0.75	Diazepam (mg/kg) 0.6	1.8	3.0	Flurazepam (mg/kg) 0.45	1.35	2.25
Four-monkey analysis										
2	GO	1.16	0.47	-1.69	-0.28	-0.25	-1.38	-0.72	0.22	0.50
		NS	NS	•	NS	NS	NS	NS	NS	NS
	NO-GO	0.50	-0.59	-3.03	-0.22	-0.72	0.36	-0.09	-0.16	-0.50
		NS	NS	•••	NS	NS	NS	NS	NS	NS
4	GO	-1.69	-1.06	-0.34	0.19	-0.44	-0.47	-0.06	0.12	0.56
		•	NS	NS	NS	NS	NS	NS	NS	NS
	NO-GO	-0.78	-2.84	-4.16	0.47	-1.28	-1.56	-1.28	-0.72	-2.28
		NS	•••	•••	NS	NS	(•)	NS	NS	••
8	GO	0.66	-1.46	-3.31	0.69	-0.13	-2.66	-1.22	0.09	-3.91
		NS	NS	•••	NS	NS	••	NS	NS	•••
	NO-GO	0.19	-4.14	-1.75	0.00	-1.22	-1.09	-1.22	-1.09	0.25
		NS	•••	•	NS	NS	NS	NS	NS	NS
Five-monkey analysis										
2	GO	0.72	0.22	-1.43	-0.68	0.17	-0.50	-0.25	-0.07	-0.10
		NS	NS	NS	NS	NS	NS	NS	NS	NS
	NO-GO	-0.25	-1.20	-2.70	-0.35	-0.35	-0.63	-0.13	-0.65	-0.55
		NS	NS	••	NS	NS	NS	NS	NS	NS
4	GO	-1.20	0.00	-0.38	0.30	0.62	0.30	-0.00	-0.58	1.60
		NS	NS	NS	NS	NS	NS	NS	NS	•
	NO-GO	-1.05	-3.58	-5.17	1.02	-1.25	-2.63	-1.38	-0.45	-2.33
		NS	•••	•••	NS	NS	••	NS	NS	••

Least significant differences. NS: Not significant.

•P = 0.05; ••P = 0.01; •••P = 0.001.

1.64 2.17 2.82 for the four-monkey analysis.

1.58 2.11 2.76 for the five-monkey analysis.

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Ministry of Defence, London.
Flying Personnel Research Committee.

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