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Effects of Diazepam and Nitrazepam on Psychophysiological Functions in Normal Humans

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Abstract The influence of diazepam and nitrazepam on arousal level, muscle strength, psychomotor performance and memory function using the photopalpebral reflex (PPR), critical flicker frequency (CFF), tapping test, pursuit rotor test (PRT), choice reaction test (CRT) and memory drum test (MDT) were investigated in the present study. Ten healthy male university students were given diazepam 5 mg and 10 mg, nitrazepam 5 mg and 10 mg, and placebo in a double-blind, cross-over design. The tests and subjective assessments were performed before and after drug administration. All drugs produced a prolongation of PPR latencies and a decrease of CFF, and diazepam 10 mg and nitrazepam 10 mg were the most efficacious in producing these phenomena. Tapping rate increased after administration of all agents, and then decreased to control levels. PRT and CRT improved after all drugs and performance on these tasks was most improved by diazepam 10 mg. Memory tasks were impaired following administration of all drugs. No significant changes were observed in the assessments of the subjects. These results suggest that the physiological and psychological tests employed in this study are useful tools for assessing the residual effects of benzodiazepines in normal humans, and that small doses of benzodiazepines lower arousal level, impair memory, but improve motor and psychomotor performance.

Key Words : Residual effects, Diazepam, Nitrazepam, Psychophysiological tools, Normal humans

Introduction

A number of benzodiazepine derivatives have been developed and applied to the clinical field. In general, they have anxiolytic, hypnotic, anticonvulsant, and muscle-relaxant effects. These are effective agents and side effects associated with their use are relatively uncommon[1]. However, some adverse effects have recently been noted. Benzodiazepine intoxication or withdrawal may cause confusion, cognitive impairment, poor memory and judgement, emotional lability, and reduced muscle strength[2]. Moreover, it has become apparent that patients taking normal therapeutic doses of benzodiazepines for long time periods are likely to encounter these symptoms. Therefore, side effects of benzodiazepines can conceivably lead to dire social consequences

such as traffic or occupational accidents. The residual impairment of performance following ingestion of benzodiazepines is thus of particular interest.

The present study was undertaken to investigate the influence of diazepam and nitrazepam on arousal level, memory function, muscle strength and psychomotor performance in normal human subjects using physiological and psychological tests.

Materials and Methods

Subjects

Ten healthy male university students aged 21 to 24 years (mean age of 22.6 years) were used in the present study.

Drugs

Two doses of diazepam, 5 mg and 10 mg ; similar doses of nitrazepam, 5 mg and 10 mg ; and placebo were used. Capsules containing each dose of the drug or placebo were prepared identically. Drug doses were determined by reference to the data in human studies[3].

Physiological and Psychological Tests

Photopalpebral reflex (PPR), critical flicker frequency (CFF), tapping test, pursuit rotor test (PRT), choice reaction test (CRT) and memory drum test (MDT) were employed to measure the subjects' arousal level, muscle strength, psychomotor performance, and memory function. All tests were performed in a randomized order in each examination.

PPR represents the mean of summed reflex contractions of the orbicularis oculi muscle in response to periodic photic stimuli. The subjects lay in the supine position with eyes closed. One disc electrode was placed on the nasal part of the right lower eyelid (Grid 1) and the another on the center of the right upper eyelid (Grid 2). Single flash stimuli were applied 100 times, at a frequency of 1/sec, from a distance of 10 cm in front of the eyes of the subject, and the potential changes thereby evoked in the orbicularis oculi muscle were conveyed via an EEG amplifier to the analog computer, which averaged the sum of individual responses. The analysis time of the record was 100 msec. Both P_1 and P_2 latencies of PPR (Fig. 1) were measured.

CFF is assessed by holding the intensity of a flickering light source constant and progressively increasing (upward) or decreasing (downward) the frequency until the subject reports a change in his perception of flicker.

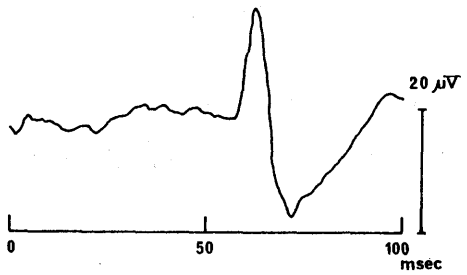

Fig. 1 Schematic representation of PPR. The first upward deflection with latency around 57 msec is designated as Peak 1 (P_1) and the downward deflection at about 73 msec as Peak 2 (P_2). The latencies of peak effects after the photic stimuli (0 msec) are defined as P_1 latency and P_2 latency.

Tapping rate was calculated by tapping the second finger as quickly as possible for 30 sec. The total number of taps of both hands was recorded.

PRT consisted of a turntable 30 cm in diameter that revolved clockwise at 60 rpm. The target was 1.5 cm in diameter, 10 cm from the center. The task involved trying to keep an articulated metal stylus on the target for a 30 sec test period. When the stylus was in contact with the target it activated a counter. A mean of two experimental trials was calculated.

The CRT was obtained using a console containing 5 colored lights (white, blue, green, red and yellow) presented in a randomized order, with 5 colored buttons under the console. Using the subjects' preferred hand, correct responses, defined as pressing the corresponding colored button under the light following a delay of 0.8 sec, were recorded.

Memory function was measured by using a memory drum which consisted of a panel with a window. One simple word was shown every 10 sec in the window. There were seven simple words which were unrelated to each other. The subjects responded by providing the next word which was to appear in the window. The number of trials required for an error-free word series was recorded.

Subjective Assessments

A seven-point (−3~0~3) rating scale derived in our department was used in order to measure the subjective responses following drug administration. The rating scale consisted of 10 items (clear-headed or distorted, alert or drowsy, feel well or feel bad, strong or feeble muscle tone, vivid or dull volition, calm or restless, concentrated or distracted, good or poor memory, good or poor eye-sight, and quick or slow response to stimuli). The subject was requested to fill out the scale regarding 0 as the value prior to drug administration.

Experimental Procedure

After recording the control physiological or psychological tests and scoring the control subjective assessments at 1200 hr, the subjects were given lunch at 1300 hr. This was followed by one of the drugs or placebo by oral administration in a double-blind, cross-over (Latin square) design at 1330 hr. Following drug or placebo ingestion, the tests were repeated 30, 60, 90, 120, 180, and 240 min after medication. The subjects were also requested to fill out a questionnaire for subjective assessments at 60, 120, 180 and 240 min after the drug administration. Seven days were employed as the wash-out period for the residual effects of the previous drug.

Statistical Analysis

Analysis of variance was employed for statistical analysis, as well as Tukey's multiple comparison statistic for post-hoc analysis. The Kruskal-Wallis H test and Dunn's procedure were used for analysis of the subjective assessments.

Results

PPR Changes

P_1 latency was prolonged by all the drugs as shown in Table 1. Both doses of diazepam prolonged P_1 latency in a dose-dependent manner. When diazepam 10 mg was given, prolongation of the latency occurred within 30 min of drug administration, and was maintained at the same level for 240 min. The prolongation of P_1 latency by diazepam 10 mg was significantly different from diazepam 5 mg at all times except 240 min following drug administration. When diazepam 5 mg was given, the P_1 latency was shortened 30 min after administration, and then gradually prolonged. When nitrazepam 5 mg and 10 mg were given, prolongation of the P_1 latency occurred after 60 min, and was maintained at the same level from 90 min to 180 min after administration. However, nitrazepam 5 mg kept the same level until 240 min after administration, while nitrazepam 10 mg further prolonged the P_1 latency at this time period.

Both doses of diazepam also prolonged P_2 latency in a dose-dependent manner (Table 1). When diazepam 10 mg was given, prolongation of the latency occurred within 30 min after administration, and was maintained at the same level for 240 min. The prolongation of P_2 latency by diazepam 10 mg was the strongest of all drug treatments. When diazepam 5 mg was given, the P_2 latency was shortened at 30 min after ingestion, and then slightly prolonged. When both doses of nitrazepam were given, prolongation of the latency occurred after 60 min, and was maintained at the same level for the next 180 min. The P_2 latencies induced by both doses of nitrazepam were between those of diazepam 5 mg and 10 mg.

CFF Changes

In the upward change of CFF, the frequency was virtually unaltered by placebo from 30 min to 90 min after administration but decreased slightly from 120 min (Table 2). Both doses of diazepam decreased the frequency in a dose-dependent manner. The decrease in CFF induced by diazepam 5 mg was similar to that of placebo. A decrease in CFF by diazepam 10 mg occurred within 30 min, and was then gradually and significantly intensified. The significant decrease in CFF induced by diazepam 10 mg was equivalent to that of nitrazepam 10 mg from 30 min to 120 min following drug treatment. Both doses of nitrazepam also decreased CFF in a dose-dependent manner. A decrease in CFF by nitrazepam 5 mg occurred after 60 min, was gradually intensified, and was between that produced by diazepam 5 mg and 10 mg. A decrease in CFF by nitrazepam 10 mg occurred after 30 min, and was the strongest from 120 min to 240 min.

Table 1 Effects of diazepam and nitrazepam on PPR (Mean±S. D.)

P_1 latency of PPR

	Control	30 min	60min	90min	120min	180min	240min
P	60.70±3.43	0.57±2.15	1.85±2.33	1.32±2.11	0.85±1.13	0.95±2.25	0.67±1.39
D5	62.22±3.94	−0.57±2.10	0.07±1.96	1.52±2.27	0.97±2.53	1.38±2.97	2.65±6.18
D10	62.00±3.15	1.92±2.65b	2.38±3.18b	2.27±2.42	2.67±2.47	2.67±3.29	2.50±3.15
N5	61.15±3.03	1.22±1.88a	1.20±1.50	2.05±1.88	1.75±2.54	2.38±3.76	2.10±2.32
N10	62.10±3.41	0.97±1.45	0.95±2.56	2.42±2.82	2.05±3.26	2.05±3.75	3.60±3.31A

P_2 Latency of PPR

	Control	30 min	60min	90min	120min	180min	240min
P	79.47±4.46	1.20±2.29	1.38±2.51	0.65±1.37	1.17±1.95	1.20±2.41	1.10±1.76
D5	81.90±4.58	−1.10±2.10B	−0.42±3.08	0.35±2.14	0.13±1.68	0.20±2.64	−0.35±1.94
D10	78.15±3.64	2.72±3.17c	2.85±3.44c	2.13±2.08Ab	3.13±3.15b	3.50±3.53b	3.05±3.94b
N5	80.97±4.51	1.10±1.59b	0.60±2.20α	2.50±2.32Bb	2.22±3.06a	2.47±3.74	1.82±3.17
N10	80.88±3.73	1.45±1.81b	1.10±1.70	2.00±1.61a	2.27±2.86a	1.97±3.47	2.13±4.92

The control values were shown by the value of actual measurement, and the values of 30 min, 60 min, 90 min, 120 min, 180 min and 240 min were obtained by subtracting the value before the drug administration (control value) from that after medication, respectively. P : placebo ; D5 : diazepam 5 mg ; D10 : diazepam 10 mg ; N5 : nitrazepam 5 mg ; N10 : nitrazepam 10 mg. A : significantly different from placebo $P<0.10$; B : significantly different from placebo $P<0.05$; C : significantly different from placebo $P<0.01$. a : significantly different from diazepam 5 mg $P<0.10$; b : significantly different from diazepam 5 mg $P<0.05$; c : significantly different from diazepam 5 mg $P<0.01$. α : significantly different from diazepam 10 mg $P<0.10$; β : significantly different from diazepam 10 mg $P<0.05$. I : significantly different from nitrazepam 5 mg $P<0.10$.

Table 2 Effects of diazepam and nitrazepam on CFF (Mean±S. D.)

The upward change of CFF

	Control	30 min	60min	90min	120min	180min	240min
P	36.61±3.03	−0.13±1.43	0.04±1.43	−0.02±0.91	−0.29±0.89	−0.73±1.87	−0.68±1.93
D5	35.44±3.68	0.10±1.52	0.09±1.54	0.15±1.14	−0.28±1.34	−0.43±1.47	−0.76±1.09
D10	36.55±3.95	−0.57±2.55	−0.21±1.86	−1.01±2.02a	−0.70±1.67	−1.33±2.28	−1.73±2.60
N5	36.57±2.10	0.29±1.37	0.27±1.88	−0.47±1.52	−0.56±1.30	−0.90±1.70	−1.25±1.57
N10	36.22±4.49	−0.04±0.76	−0.93±1.22	−0.73±1.60	−0.72±1.11	−2.10±1.47Ab	−2.49±1.47Bb

The downward change of CFF

	Control	30min	60min	90min	120min	180min	240min
P	35.13±3.32	0.01±1.12	−0.27±0.82	−0.25±0.72	−0.87±1.17	−0.93±1.51	−0.82±1.45
D5	34.35±3.83	−0.16±0.93	−0.72±0.82	−0.95±0.55	−0.64±1.34	−0.99±0.75	−1.21±0.73
D10	35.23±3.50	−0.72±1.60	−0.51±1.63	−0.92±1.26	−1.24±1.11	−1.63±1.68	−1.41±1.81
N5	36.23±2.97	−0.35±0.94	−0.97±1.17	−1.17±1.02A	−1.42±1.16	−1.58±1.46	−1.64±1.57
N10	35.38±4.28	−0.90±1.46	−1.35±1.29B	−1.77±1.46Caα	−1.80±1.49b	−2.06±1.74A	−3.00±1.90CbβI

The details are in the legend for Table 1.

Table 3 Effects of diazepam and nitrazepam on tapping test and PRT (Mean±S. D.)

Tapping test

	Control	30 min	60min	90min	120min	180min	240min
P	270.50±40.17	2.70±23.19	14.10±21.58	15.90±29.42	19.60±28.02	5.40±27.31	7.20±15.53
D5	268.20±34.92	−1.50±26.21	6.80±29.74	18.90±30.37	11.00±30.65	4.30±31.89	−2.70±29.20
D10	272.10±44.28	2.70±24.72	11.20±25.51	11.80±21.25	7.30±21.61	3.30±21.06	−7.10±25.37
N5	260.50±32.45	8.60±18.55	14.00±21.49	17.20±21.03	13.20±15.53	6.10±21.93	10.50±11.82α
N10	261.40±38.02	5.40±23.42	20.40±24.78	17.00±25.38	12.80±25.87	0.30±23.29	1.10±24.97

Pursuit rotor test

	Control	30min	60min	90min	120min	180min	240min
P	73.30±20.02	3.45± 8.35	4.05±18.98	3.40±11.99	7.50±19.50	2.60±16.33	12.55±16.89
D5	80.35±26.51	−1.75±17.18	−0.55±14.56	4.20±12.39	−0.15±16.79	−0.65±12.31	6.40±19.24
D10	71.25±15.52	3.50±12.38	14.00±15.19b	13.75± 8.28	6.90±12.82	13.20±15.56a	4.80±14.84
N5	76.75±21.97	7.85±12.03	5.35±14.30	8.60±22.81	7.85±12.78	8.50±17.27	13.80±15.84
N10	72.50±23.45	7.45±22.37	6.90±15.06	5.25±16.47	2.10±16.68	3.65±19.94	4.55±18.59

The details are in the legend for Table 1.

Table 4 Effects of diazepam and nitrazepam on CRT and MDT (Mean±S. D.)

Choice reaction test

	Control	30min	60min	90min	120min	180min	240min
P	219.20± 6.00	1.90±3.87	−0.60±4.14	−0.90± 4.15	0.40±4.55	−0.90± 7.39	1.20± 4.08
D5	211.80±13.53	2.80±7.79	0.30±9.89	−0.20±17.21	2.50±6.59	1.30±15.06	4.60±11.18
D10	215.80± 9.38	2.60±5.76	2.20±5.01	2.80± 6.21	3.20±5.73	2.70± 7.21	1.40± 4.99
N5	217.70± 6.82	0.10±5.65	1.00±3.68	0.40± 4.33	1.60±2.17	2.20± 2.70	2.80± 3.94
N10	216.90± 5.00	2.00±3.59	2.30±3.62	0.80± 3.88	1.80±4.69	1.20± 4.34	1.90± 5.45

Memory drum test

	Control	30min	60min	90min	120min	180min	240min
P	3.00±1.89	0.70±2.41	0.20±2.10	0.40±2.59	−0.50±3.06	−0.20±1.75	1.20±2.97
D5	3.10±1.66	0.40±2.27	0.70±3.02	1.00±2.31	0.20±2.44	−0.60±1.07	0.60±4.01
D10	3.30±1.89	1.10±3.00	−0.50±1.65	−0.30±2.11	0.70±2.71	0.90±3.25	2.40±2.27
N5	2.80±1.40	0.40±1.71	1.70±2.50β	0.80±2.04	0.80±2.62	0.20±2.30	1.30±2.67
N10	3.10±1.66	−0.10±1.52	0.20±1.55	1.00±1.83	0.70±2.45	0.10±2.56	0.50±2.12

The details are in the legend for Table 1.

In the downward change of CFF, alterations similar to those in the upward change, were shown by placebo administration (Table 2). Both doses of diazepam decreased the frequency but not in a dose-dependent manner. A decrease in CFF produced by diazepam 10 mg occurred after 60 min, and then gradually intensified. A decrease in CFF produced by diazepam 5 mg occurred after 30 min, gradually intensified until 90 min, and then showed a similar change to that induced by placebo. Both doses of nitrazepam decreased CFF in a dose-dependent manner. A decrease in CFF by nitrazepam 5 mg occurred after 30 min, and then showed a similar change to that induced by diazepam 10 mg. A decrease in CFF by nitrazepam 10 mg occurred within 30 min, and then gradually intensified. The decrease in CFF by nitrazepam 10 mg was the largest of all drug treatments.

Tapping Rate

All drugs increased tapping rate after administration, followed by a decrease to the control level (Table 3). Placebo increased tapping rate which peaked at 120 min after administration, and then decreased to the level seen 30 min after admin-

istration. Tapping rate increased and peaked at 90 min, 90 min, 90 min and 60 min after administration of diazepam 5 mg, diazepam 10 mg, nitrazepam 5 mg and nitrazepam 10 mg, respectively. Tapping rate then gradually decreased in all drug conditions, however, diazepam 10 mg decreased tapping rate more than all other drugs. The overall effect of diazepam on tapping rate was stronger than that of nitrazepam.

Pursuit Rotor Task

All drugs with the exception of diazepam 5 mg, increased the performed tasks following their administration (Table 3). Placebo slightly increased performance immediately after administration, and then maintained it at the same level, except at 120 min and 240 min after administration, at which times, performance increased. Diazepam 5 mg slightly decreased performance at 30 min, 60 min, 120 min, and 180 min after ingestion. Diazepam 10 mg significantly increased performance except at 120 min and 240 min after administration. Both doses of nitrazepam increased task performance and reached comparable levels 30 min after their administration. Nitrazepam 5 mg gradually increased performance while nitrazepam 10 mg gradually decreased performance over time.

Choice Reaction Test

Placebo increased the number of correct responses 30 min after administration, however, placebo also decreased correct responding from 60 min to 240 min after administration (Table 4). Diazepam 5 mg increased the number of correct responses 30 min after administration, decreased them at 90 min, and then increased them following 90 min. Diazepam 10 mg increased the number of correct responses 30 min after administration, and then maintained correct responding at the same level until 180 min following administration. The number of correct responses by diazepam 10 mg was the highest of all drugs at all times with the exception of 240 min after administration. Nitrazepam 5 mg gradually increased the number of responses from 30 min after its administration. Nitrazepam 10 mg increased correct responses 30 min and 60 min after administration, then decreased them slightly from 60 min following treatment. However, there were no significant differences between the drugs in terms of CRT.

Memory Drum Test

Placebo slightly increased the number of trials at 30 min after its administration, decreased the number of trials at 120 min, and then increased them at the longer time interval (Table 4). Diazepam 10 mg increased the number of trials 30 min after treatment, decreased them at 60 min and 90 min, and then markedly increased them at 240 min after administration. Diazepam 5 mg gradually increased the number of trials until 90 min after drug treatment, and then decreased them significantly at 180 min. Nitrazepam 10 mg increased the number of trials 90 min after treatment, and then gradually decreased them. Nitrazepam 5 mg markedly increased the number of trials 60 min after treatment, and then gradually decreased them. The effects of nitrazepam 5 mg on memory trials were the strongest until 120 min after treatment, while the effects of diazepam 10 mg were the most efficacious following 120 min after drug administration.

Subjective Assessments

In the item concerning quick or slow responses at 60 min after drug administration, diazepam 10 mg produced more evidence of slower responses as compared with nitrazepam 10 mg ($P<0.05$). There were no significant differences between the drugs at any times in the remaining items of subjective assessments.

Discussion

Diazepam and nitrazepam are the most commonly prescribed benzodiazepines in the world. Diazepam has a relatively short duration of action, however, its major metabolite, desmethyldiazepam, has a much longer half-life[3]. Nitrazepam, a hypnotic sedative, has a relatively long duration of action[3]. It is reported that diazepam pro-

longs reaction times in tasks requiring rapid reaction[4], impairs saccadic and smooth pursuit eye movements[5,6], judgement and memory[7,8], and psychomotor and cognitive performance[9,10]. It is also reported that nitrazepam primarily impairs memory function and reduces a muscle strength[11]. None of these studies, however, has objectively described the effects of benzodiazepines on arousal levels in humans.

In the present study, PPR and CFF were used as indices to assess the arousal level of subjects ; the tapping test, PRT and CRT were employed as indices to measure muscle strength, psychomotor and cognitive functions ; and MDT was used as an index of memory function. Tanaka et al. reported that the latencies of PPR are prolonged in conditions of lowered arousal level and shortened in a more aroused state[12]. Smith and Misiak noted that psychostimulant drugs significantly increase CFF but that hypnotics decrease it[13]. It thus seems that PPR and CFF are useful, objective indices of arousal level in humans.

All the drugs used in the present study showed a prolongation of PPR latencies and a decrease of CFF. The effects of diazepam 10 mg and nitrazepam 10 mg on these indices were the strongest of all drug treatments. It has been reported that benzodiazepines prolong the latencies of PPR[12,14], and that hypnotics produce a decrease in CFF[13] while anxiolytics produce either a decrease in CFF or no significant changes[13]. The present results suggest that benzodiazepines lower the arousal level of humans, and that anxiolytics produce this effect soon after administration, while hypnotics lower arousal level much later following their administration. This interpretation is also supported by the results of pharmacokinetic studies of benzodiazepines[15].

Muscle strength, measured by the tapping test, increased gradually after all drugs, and then decreased to control levels. Both doses of diazepam were the most efficacious at reducing muscle strength. Psychomotor performance, measured by the PRT and CRT, improved after all drugs and was most improved by diazepam 10 mg. These results are inconsistent with previous reports[9-11], however, Saletu et al.[16] noted that lower doses of benzodiazepines improve motor or psychomotor performance and reaction time, and that these effects of anxiolytics are stronger than those of hypnotics. Similar results were also presented by Bond and Lader[17]. A possible reason for this phenomenon is that the benzodiazepines have muscle-relaxant effects, and subjects may be differentially sensitive to the central motor effects of these drugs. Another possibility is that diazepam may relieve subjects of anxiety created by the experimental situation, due its tranquilizing effects.

Memory functions required by the MDT were impaired after all drugs used in this study. Nitrazepam 5 mg produced the strongest impairment of memory function soon after its administration, while diazepam 10 mg produced this effect much later. However, no dose-dependent relationships were observed for either diazepam or nitrazepam. These results suggest that benzodiazepines produce poor memory, however, a decrease in arousal level occurs simultaneously with the memory deficits. Therefore, caution must be used in concluding that these drugs disturb memory function.

No significant changes were observed in the subjective assessments, and only diazepam 10 mg produced a subjective assessment of slower responses. The item of quick or slow responses may reflect overall motor function of the subjects. Saletu et al.[16] reported that benzodiazepines produce improvements in mood and affect at low doses, no significant changes at medium doses, and a deterioration at high doses. Therefore, the subjects might have regarded the doses of diazepam and nitrazepam used in the present study as a medium dosage.

In summary, the present results suggest that the physiological and psychological tests used in this study are useful tools for assessing the residual effects of benzodiazepines in normal humans. In addition, the

present data suggest that small or medium doses of benzodiazepines lower arousal level and impair memory, but improve motor and psychomotor performance.

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