

## STUDIES ON PSYCHOMOTOR PERFORMANCE IN HEALTHY VOLUNTEERS AFTER DIAZEPAM, PROPRANOLOL AND ALCOHOL GIVEN ALONE OR IN COMBINATION

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**Abstract:** The effects of diazepam, propranolol or alcohol alone or in combination with each other were examined in ten normal healthy volunteers on tests of psychomotor function. Results showed impaired psychomotor performance persisting upto 4-5 h when the aforementioned agents given singly were tested on simple reaction time (SRT), multiple choice reaction time (MCRT) and critical flicker fusion frequency (CFFF) tasks. Digit cancellation task (DCT) was similarly affected by diazepam and alcohol only.

No summation of adverse effects on psychomotor performance was noted when a combination of diazepam and alcohol, diazepam-propranolol or alcohol plus propranolol were tested on SRT and MCRT. An additive impairment of CFFF was observed with alcohol - propranolol combination only. No summation of pharmacodynamic effects on DCT were noted when different combinations were used.

**Key words:** psychomotor performance                      CNS depressants  
diazepam    propranolol    alcohol

### INTRODUCTION

Diazepam is extensively used as an anxiolytic agent and propranolol is favourite drug for a variety of cardiovascular ailments. Both these agents are known to cause central depressant effects including impairment of psychomotor performance (1, 2). The detrimental effects on cognitive and psychomotor performance induced by the aforementioned drugs are generally thought to be qualitatively similar to those produced by alcohol (2, 3). It has been known for long that alcohol enhances the sedative effects of other CNS depressants. Reports on clinical importance of such interactions, in particular an increase in accident risk in traffic are not adequately supported by valid experimental data (4, 5, 6).

The present study was therefore undertaken to investigate the problem. Accordingly the effects due to pharmacodynamic interaction of

alcohol with diazepam, alcohol with propranolol and diazepam plus propranolol on human psychomotor performance was studied by employing a battery of tests in healthy subjects.

### METHODS

Ten male volunteers (28-35 y; 55-63 kg) were admitted to the study after obtaining their voluntary consent. All the subjects were in normal physical health with no history of cardiovascular, gastric, renal, hepatic or psychiatric disorder and had laboratory/biochemical values within normal range. The subjects were non-smokers and abstained from alcohol and drugs for one week prior to experimentation. On the day of experimentation, caffeinated drinks and drugs other than those used in the study were withheld.

**Materials:** Alcohol 60 ml (Standard Whiskey 40%) and tablets diazepam (5 mg) and propranolol (80 mg).

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**Experimental design:** Each subject acted as his own control and received one of the six treatments given in Table I in the morning according to a randomised crossover design with a washout period of 7 days between different test sessions. Postdrug administration assessment was conducted for 6h. Prior to entry in the study, the subject were familiarized with the test procedure to obtain stable values. Placebo control could not be applied to the study because of characteristic smell and taste of alcohol which was found difficult to mask:

#### Assessment

**Simple reaction time:** Visual reaction time was determined by measuring the latency between presenting a visual stimulus and the response (pressing a key) (7). The means of five measurements to each stimulus were recorded in two sessions and the results of the sessions averaged.

**Multiple choice reaction time:** Light stimuli of red, green and yellow colours were presented on a panel in front of the subject. The subject was required to extinguish the coloured stimulus by pressing appropriate key (8) within a period of 0.5 sec (CR). Longer latency response of 0.5-0.8 sec (DR) and pressing an inappropriate key was designated as wrong response (WR). Out of the 100 such responses, missed responses (MR) were calculated as  $100 - (CR + DR + WR)$  and Error index (EI) was determined as per the method described by Allain and Coworkers (9).

**Critical flicker fusion threshold:** Subjects were required to discriminate flicker fusion in a set of 4 light emitting diodes placed a foveal distance of 1m. Individual thresholds in Hz were determined on five ascending and five descending frequencies as per the method described by Hindmarch (10).

**Digit cancellation task:** In a matrix of 400 arithmetic digits a particular digit was distributed randomly 40 times and the subject was required to cancel the digit as fast as he could. The number of digits cancelled per minute was recorded (11).

## RESULTS

The data obtained with each drug and the drug combinations in different psychomotor tasks has been summarised in Table I. The change in performance relative to the basal value at different time intervals has been analysed by paired 't' test and incorporated in the table. In addition the alteration in the performance induced by a drug combination in comparison to that due to either of its constituents was analysed by unpaired students 't' test.

Significant increase in SRT was observed within 1h of administration of diazepam or propranolol and the effect lasted for 4-5 h. Alcohol administration failed to significantly alter the visual reaction time relative to baseline value at any time interval.

In comparison to basal values, a significant increase in EI was noted after alcohol, diazepam or propranolol and this impairment continued for 4 hours with all the drugs.

CFFF threshold relative to baseline values was observed to be decreased for 3-4 hours after administration of all the pharmacological agents. However, the decrement in the threshold was significantly more after diazepam.

Less number of digits were cancelled by the volunteers after ingestion of alcohol or diazepam, and the effect lasted for the two hours. On the contrary, propranolol failed to modify the predrug score.

When the results were analyzed to explore the pharmacodynamic interaction as a result of use of combination of alcohol with diazepam or propranolol and diazepam with propranolol, no significant alterations in the performance levels from the levels obtained by the aforementioned agents when given alone were observed. However, the only exception noted was the effect of the combination of alcohol and propranolol on CFFF threshold. The effect of the combination on the threshold was significantly more than the effect produced by either drug alone.

TABLE I : Effect of diazepam, propranolol and alcohol alone or in combination on human psychomotor performance

Tasks	Drug(s)	Basal value	Values after drug administration					
			1 hour	2 hour	3 hour	4 hour	5 hour	6 hour
SRT	A	580 ± 44.1	590 ± 43.4	5865 ± 41.8	588 ± 40.5	586.6 ± 40.5	580 ± 44.1	580 ± 44.1
	B	566.6 ± 46.4	636.6 ± 45.6**	641.6 ± 45.8**	623.3 ± 39.5**	606.6 ± 37.3*	583.3 ± 47.3	565 ± 45.7
	C	571.6 ± 44.3	645.0 ± 36.6**	625 ± 42.2*	616.6 ± 42.5*	600 ± 38*	588.3 ± 37.2	576.6 ± 45.6
	A+B	570 ± 45.7	646.6 ± 43.1**	651.6 ± 44.4***	621.5 ± 40**	600 ± 47.4*	591.6 ± 48.6	588.3 ± 49.3
	A+C	570 ± 46.4	643.3 ± 46.4**	616.6 ± 48.8*	595 ± 46.2	583.3 ± 44.8	578.3 ± 44.7	573.3 ± 42.7
	B+C	466.6 ± 39.3	638.3 ± 52.2*	658.3 ± 55.1**	630 ± 48.6*	606.6 ± 45.9*	586.6 ± 39.1*	576.6 ± 38
MCRT (Error index)	A	99.5 ± 17.76	119.66 ± 17.28**	114.5 ± 17.15*	110.66 ± 17.41	106.83 ± 17.09*	104.55 ± 17.18	100.3 ± 17.96
	B	99 ± 17.29	120 ± 16.47*	122.6 ± 16.06*	115.8 ± 15.61*	115.5 ± 15.80*	112.10 ± 15.5	109.65 ± 16.1
	C	99.6 ± 16.80	108.6 ± 15.75	111.6 ± 15.05	107.6 ± 15.31*	106 ± 15.5*	100.5 ± 16.59	100.3 ± 16.59
	A+B	96.16 ± 16.25	120.83 ± 17.7*	127 ± 15.8**	116.83 ± 18.44*	113 ± 18.92	108.66 ± 18.72	104.6 ± 19.10
	A+C	99.6 ± 16.80	109.6 ± 15.25	109.3 ± 15.84*	107.6 ± 16	106 ± 16.29	102 ± 16.62	100.3 ± 16.90
	B+C	100.5 ± 17.57	117 ± 16.28*	119.5 ± 16.85	115 ± 17.27*	111.0 ± 17.45	103.6 ± 16.7	100.8 ± 17.11
CFFF threshold (Hertz)	A	34.75 ± 1.34	33.51 ± 1.09	33 ± 1.22*	33.50 ± 1.24	33.72 ± 1.22	34.03 ± 1.17	34.33 ± 1.22
	B	34.52 ± 1.27	32.59 ± 1.31**	31.81 ± 1.33***	32.38 ± 1.31***	32.82 ± 1.29**	33.18 ± 1.17**	33.64 ± 1.14*
	C	34.63 ± 1.23	33.35 ± 0.98	32.69 ± 0.98*	33.17 ± 1.01	33.35 ± 1.02	33.69 ± 1.02	33.84 ± 1.10
	A+B	34.72 ± 1.33	32.18 ± 1.21**	31.36 ± 1.33***	32.58 ± 1.19***	32.79 ± 1.21***	33.26 ± 1.18**	33.87 ± 1.16**
	A+C	34.80 ± 1.31	32.30 ± 1.37	31.80 ± 1.37***	32.30 ± 1.31***	32.82 ± 1.38**	33.47 ± 1.43**	34.26 ± 1.42*
	B+C	34.66 ± 1.34	32.13 ± 1.08**	31.7 ± 1.15***	32.34 ± 1.26**	32.77 ± 1.33**	32.42 ± 1.38**	33.61 ± 1.29**
DCT c/min	A	37 ± 0.85	35.66 ± 1.12*	36.0 ± 1.0	36.8 ± 0.98	37 ± 0.85	37 ± 0.85	37 ± 0.85
	B	37 ± 0.85	34.83 ± 0.75***	35.16 ± 1.01**	36.33 ± 0.99	36.5 ± 0.88	36.66 ± 0.80	37 ± 0.85
	C	37 ± 0.85	36.5 ± 0.99	36.83 ± 0.98	36.83 ± 0.98	36.83 ± 0.98	36.83 ± 0.98	37 ± 0.85
	A+B	37 ± 0.85	35 ± 0.73***	34.83 ± 0.79***	36.33 ± 0.99	36.33 ± 0.99	36.50 ± 0.88	36.66 ± 0.80
	A+C	37 ± 0.85	36.5 ± 1.08*	36 ± 1.06*	36.5 ± 0.92	37 ± 0.85	37 ± 0.85	37 ± 0.85
	B+C	37 ± 0.85	34.83 ± 0.75***	35 ± 0.81**	36.16 ± 1.11	36.5 ± 0.92	37 ± 0.85	37 ± 0.85

Abbreviations : A = Alcohol; B = Diazepam; C = Propranolol; msec = milli seconds; c/min = digits cancelled per minute

Values obtained after drug administration were compared with corresponding basal values and analyzed by student t test

\* = P &lt; 0.05; \*\* = P &lt; 0.01; \*\*\* = P &lt; 0.001

## DISCUSSION

Benzodiazepines and alcohol have been reported not to cause any appreciable impairment of simple tasks like SRT in doses comparable to those employed in the present study (12). Our results confirm the aforementioned findings to the extent that alcohol failed to impair SRT. Both diazepam and propranolol, however, caused an impairment of this task.

More complex tasks like MCRT and CFFF that measure that ability to distinguish discrete units of sensory data, the level of sensorimotor integration and coordination of sensorimotor response were uniformly effected by all the three agents in the present study. Similar results on MCRT and CFFF have been previously reported for alcohol, benzodiazepines and  $\beta$ -adrenoceptor antagonists (1, 7, 12, 13, 14).

There is considerable degree of similarity in central effects of alcohol and diazepam. Both are anxiolytic in small doses and an increase in dose induces sleep with ataxia and nystagmus at still higher doses. It is, therefore anticipated that concomitant ingestion of the two will potentiate their adverse effects on psychomotor performance. However, in the doses employed in the present investigation

no such pharmacodynamic interaction was observed.

Diazepam and propranolol are often prescribed together in various cardiovascular ailments and propranolol is known to produce central depressant effects. The results of this study do not suggest any significant pharmacodynamic potentiation of psychomotor impairment due to the concomitant administration of the aforementioned drugs.

Alcohol plus propranolol combination was not, however, seen to produce uniform results in all the task. While as concomitant administration did not produce psychomotor impairment different than that produced by individual components in SRT, MCRT and DCT; there was summation of adverse effect on performance in CFFF task.

The conclusions therefore are that the combination of various central depressants used in the present study did not in general terms produce any significant pharmacodynamic interaction on psychomotor performance.

However, the present observations with alcohol have to be viewed in context to the limitation that the beverage in this investigation was administered in a mode different than social drinking wherein the ingestion is gradual and is spread over a long duration.

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