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Propranolol and Skilled Human Performance

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LANDAUER, A. A., L. B. JELLETT AND J. KIRK. *Propranolol and skilled human performance.* PHARMAC. BIOCHEM. BEHAV. 4(3) 283–287, 1976. – In a double-blind crossover experiment 18 young men received on one occasion 6 doses of 40 mg propranolol and on the other placebo. Medication was given at 6 hour intervals. One hr after the last capsule was ingested subjects were measured with various physiological and behavioral tests. At the conclusion of testing mean plasma propranolol concentration was 67.6 ng/ml. Propranolol significantly reduced systolic blood pressure and heart rate. There was an increased variability on one behavioral measure but the results of other tests were not affected. The findings are discussed in terms of therapeutic use of this and other β-adrenergic receptor blocking agents.

Behavioral effects Cognitive tests Drug action Performance tests Propranolol
β-adrenergic receptor blocking agents

PROPRANOLOL is a β-adrenergic blocking agent which has been used extensively in the treatment of angina pectoris, hypertension and various cardiac arrhythmias [4]. It has also been employed in the management of transient anxiety states [5,17]. The use of propranolol and other β-adrenergic receptor blocking agents in psychiatry has recently been reviewed by Whitlock and Price [18]. However, the definite central method of action of these drugs has not yet been fully characterized.

A central effect of propranolol should be reflected by changes in perceptual and cognitive functions. This hypothesis has already been examined [1] in a double-blind, crossover experiment in which a single dose of propranolol was administered to 6 normal subjects. The results showed a decrease in heart rate, an increase in simple visual reaction time, and a performance decrement in complex hand-eye coordination. No significant changes were found in various ophthalmological measures.

However, other investigations employing single doses of β-adrenergic receptor blocking drugs have failed to show behavioral changes. For example, in two studies [7,15] no decrement in performance was found when single oral doses of propranolol (120 mg), sotalol (240 mg), or oxprenolol (80 mg) were administered.

A criticism of such single-dose studies is that the pharmacological responses obtained do not relate to the general therapeutic situation in which a drug is administered regularly. Accordingly, the present study was designed to investigate the effects of repeated doses of propranolol on various behavioral parameters.

METHOD

Subjects and Experimental Medication

A total of 18 young men took part in the study. They were healthy undergraduate students, who had not taken any medication for at least the past two months and who had volunteered to participate in this experiment. Their mean age was 20.5 y (range 18–31), and their mean weight was 72.7 kg (SD = 8.26). They attended 2 testing sessions which were held on 2 consecutive Sundays. Each subject was tested at the same time in the forenoon on both occasions.

Subjects were instructed to take one capsule at 6 hr intervals on 6 occasions, the last being ingested 1 hr before their arrival at the laboratory. The plasma half-life of oral propranolol is 3.5 to 6 hr [3], so that the dosage schedule employed was similar to the therapeutic situation of regular

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[1] This investigation was approved by the Senate Committee for Human Rights of the University of Western Australia and was financed by a University Research Grant. Propranolol was supplied by ICI Australia Limited, Melbourne.

drug dosage [11,13]. On one occasion each capsule contained 40 mg of propranolol and on the other occasion it consisted of placebo. The entire experiment was conducted under double-blind conditions and a simple crossover design was used.

Procedure

On arrival at the laboratory subjects completed the Profile of Mood States questionnaire [10] and after 5 min rest blood pressure and heart rate were recorded in the seated position: 3 measures, by the indirect auscultatory method with a mercury sphygmomanometer, were taken at 1 min interval by the same investigator (L. B. J.).

After being weighed the subjects were tested in random order with the motor and cognitive skill tests listed below. Earlier investigations showed that these tests are relatively independent of each other and that they measure some of the abilities used by car drivers [8,9]. Before they left the laboratory, approximately 2 hr after the last capsule was taken, heparinized blood samples were collected. Plasma propranolol levels were assayed by a fluorometric procedure which measures only unchanged drug [12].

Letter Substitution Test. This test is similar to the Digit Substitution test developed by Wechsler [16] except that various consonants had to be substituted for digits. The score is the number of correct substitutions made in 90 sec.

Kinetic Visual Acuity Test. This test and its apparatus was developed by Suzumura [14] and is designed to examine the subject's ability to recognize the gap in a Landolt ring which approaches him at an optic speed of 30 km/hr. The subject depresses a pedal the moment he recognizes the position of the gap in the display. Each subject made 8 judgments and the mean recognition distance in meters is reported.

Serial Reaction Time Test. The apparatus used for this test consists of 5 lights each of which can be extinguished by pressing a separate lever. When the correct lever is touched that light is extinguished and another light is illuminated. The score is the total number of lights extinguished in 1 min.

Dot Tracking Task. For this performance measure the subject is required to draw a continuous line between dots spaced approximately 5 mm apart in an irregular spiral pattern. These dots are on a slowly rotating disk and become visible through a slot on the lid of the apparatus. Since the dots are tracked from the center to the periphery, they appear at an ever increasing speed. The score is the number of dots successfully tracked.

Steadiness Test. This apparatus consists of a horizontal platform which moves freely in lateral directions. The subject, who wears ear protectors and is blindfolded, is instructed to stand perfectly still for 60 sec. Whenever a slight movement occurs microswitches are activated and the event is recorded on a counter. The total number of microswitch movements serves as the score.

Martin Driving Simulator. In this test the person being assessed turns a steering wheel so that a pointer follows a moving track which is projected from the rear onto a screen. The seated subject controls the speed of the display by means of a pedal. Simultaneously with the tracking task he is required to pay attention to digits which are presented binaurally through headphones. The signal consists of 3 consecutive odd numbers which are embedded in a series presented at the rate of 50 per min. The test lasts for 5 min and 2 scores are obtained from this test. The first is the driving score which is a function of the time the subject is on target, and distance travelled and the number of instances the pointer is off-track. The second score is a converted auditory score which accounts for both the reaction time to the appropriate digits and to missed signals.

Choice Reaction Time Apparatus. This apparatus gives two time measures in a visual choice reaction time task; (1) the time it takes to identify a stimulus and (2) the time to execute the appropriate manual response. The seated subject is required to depress one of 10 buttons corresponding to the number which is presented on a display panel in front of him. One timer records the elapsed time from the appearance of the number till he lifts his finger from the rest position (decision time) and the other timer starts from the beginning of the response movement and operates until the correct button is depressed (response time). Each subject completed 30 trials and the standard deviation of the scores on the two time intervals as well as the two mean reaction times serve as measures on this particular test.

RESULTS

The mean plasma propranolol level was 67.6 ng/ml (SD = 29.1).

Responses to the Profile of Mood States questionnaire were converted into factor scores and the mood states between the two testing days (drug or placebo) were then compared. On none of the factors measured by this personality scale was a significant difference found between the testing days.

Table 1 shows the means and the standard error of the mean differences in the blood pressure and heart rate measures. Following a suggestion by Chassan [2] *t*-tests rather than analyses of variance were made to determine the statistical significance of the observed differences. It can be seen that propranolol significantly reduced systolic blood pressure and heart rate.

The means and the standard error of the mean differences of the motor and cognitive skill tests are presented in Table 2. The only significant effect due to experimental medication was an increase in the variance (expressed in terms of standard deviations) of the response time on the Choice Reaction Time test. No other behavioral measure was significantly affected by propranolol.

All experimental results were correlated but no significant relationship was observed between plasma propranolol levels and any of the physiological or psychological measures. Since only 10 correlations in a matrix of 20 variables measured in this study were statistically significant, the results tend to confirm the independence of the tests used.

DISCUSSION

The results suggest that motor performance is mildly affected by repeated doses of propranolol and confirms the findings of a previous single dose study [1]. The significant increase in the variance of response time denotes that subjects are at times slower in making some movements. This performance irregularity can be disabling since the subject is unaware when it occurs and is therefore unable to compensate for it. Significant increases in response times variance on the CRT apparatus are typically found in

TABLE 1

EFFECT OF PROPRANOLOL ON BLOOD PRESSURE AND HEART RATE OF 18 YOUNG MEN

	Propranolol		Placebo
Systolic Blood Pressure			
Mean	115.4		126.6
Standard Error of the Mean Difference		2.53	
t*		3.246	
p		< 0.01	
Diastolic Blood Pressure			
Mean	70.6		71.7
Standard Error of the Mean Difference		2.05	
t		0.570	
p		N.S.	
Mean Arterial Blood Pressure			
(Diastolic BP + 1/3 [Systolic BP − Diastolic BP]			
Mean	85.6		89.0
Standard Error of the Mean Difference		1.95	
t		1.739	
p		N.S.	
Heart Rate			
Mean	57.2		74.3
Standard Error of the Mean Difference		1.57	
t		10.918	
p		< 0.001	

*df = 17 for all t tests

intoxicated subjects [9]. Increase in the variance of response time on this apparatus may well prove to be a reliable measure of a person's behavioral impairment, whether the latter is due to alcohol consumption, sleep deprivation or drug action. From this finding it can be implied that care should be exercised by ambulant patients for whom β-adrenergic receptor blocking agents are prescribed.

Determination of plasma levels of propranolol was undertaken in an attempt to relate drug concentrations to behavioral and physiological effects. In view of the lack of correlation between these propranolol values and measured performance, it was not possible to further examine this concept in the present study. The plasma levels obtained indicate that subjects were cooperative in taking the drug as instructed.

There have been considerable differences in the methods employed by different investigators in their efforts to determine the behavioral effect which a drug may have upon a person. The relative independence of the performance measures used in this investigation ensured that perceptual, cognitive and motor skills were drawn from a very wide area.

Ideally, every drug should be tested to determine its psychological and behavioral effects in humans, particularly if it is used by ambulant patients. Tests should include measurement of psychomotor skill performance, perceptual tasks and the effect of the numerous cognitive judgments which are required by the environment in which a drug is taken.

TABLE 2

EFFECT OF PROPRANOLOL ON MOTOR AND COGNITIVE SKILLS PERFORMANCE OF 18 YOUNG MEN

	Propranolol		Placebo
Letter Substitution Test*			
Mean	60.1		62.1
Standard Error of the Mean Difference		1.57	
t‡		1.578	
p		N.S.	
Kinetic Visual Acuity Test*			
Mean	16.0		16.6
Standard Error of the Mean Difference		0.887	
t		0.639	
p		N.S.	
Serial Reaction Time Test*			
Mean	94.1		97.5
Standard Error of the Mean Difference		2.68	
t		1.265	
p		N.S.	
Dot Tracking Test*			
Mean	173.9		172.7
Standard Error of the Mean Difference		5.64	
t		0.217	
p		N.S.	
Steadiness Test†			
Mean	47.3		43.6
Standard Error of the Mean Difference		14.82	
t		0.248	
p		N.S.	
Martin Simulator, Drive Score*			
Mean	181.1		190.8
Standard Error of the Mean Difference		12.22	
t		0.800	
p		N.S.	
Martin Simulator, Auditory Score† Mean	84.9		116.4
Standard Error of the Mean Difference		28.88	
t		1.093	
p		N.S.	
C.R.T. Apparatus, Decision Time†			
Mean	614		597
Standard Error of the Mean Difference		18.80	
t		0.916	
p		N.S.	
C.R.T. Apparatus, Within Subjects Decision Time Variance (SD)†			
Mean	97		102
Standard Error of the Mean Difference		26.55	
t		0.207	
p		N.S.	
C.R.T. Apparatus, Response Time†			
Mean	381		358
Standard Error of the Mean Difference		15.96	
t		1.442	
p		N.S.	
C.R.T. Apparatus, Within Subjects Response Time Variance (SD)†			
Mean	206		163
Standard Error of the Mean Difference		17.38	
t		2.481	
p		< 0.05	

*Higher score denotes better performance †Lower score denotes better performance ‡$df = 17$ for all t tests

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