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Central effects of single oral doses of propranolol in man

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1 The central effects of propranolol, a lipophilic β-adrenoceptor antagonist, were investigated in six healthy male volunteers using two flash fusion threshold (2FFT), simple reaction time (SRT), digital copying test (DCT), symbol digit modalities test (SDMT), Gibson spiral maze test (GSMT) and mood rating scales for tension, alertness, depression, detachment and anxiety.

2 Compared to placebo, 2FFT was prolonged by propranolol 40, 80 and 160 mg at one or more times tested but not by propranolol 320 mg: the largest effect was seen at 3 h after 40 mg, and the effects of 40, 80 and 160 mg were significantly greater than 320 mg at 2 h.

3 SRTs were significantly prolonged by all doses of propranolol at 2 and 3 h and by 40 and 80 mg doses at 5 h. DCT was lowered by 40 and 80 mg at 2 and 3 h by 80 mg at 5 h, and by 320 mg at 2 h, but the 160 mg dose had no effect.

4 Propranolol impaired the expected retest gain of the SDMT with all doses except 320 mg and at 2 h after 40, 80 and 160 mg, performance was actually worsened.

5 Mood rating scales showed increased detachment with 40 mg and decreased alertness with 80 and 320 mg.

6 The results show that propranolol has central effects in man: the effects appeared to be greater with lower doses, 40 and 80 mg, than with higher doses, 160 and 320 mg.

Keywords propranolol CNS effects

Introduction

β-adrenoceptor blocking drugs are widely prescribed for hypertension and angina pectoris in patients who are ambulant and at work. Therefore, the question of whether they affect human performance could be important in the context of common everyday skills such as car driving and operating industrial machinery. In a previous study (Salem & McDevitt, 1983), we have reported central effects of the cardioselective β-adrenoceptor antagonist, atenolol, in normal subjects after single oral doses. Since atenolol has relatively low lipid solubility and is thought to penetrate the brain only poorly (Neil-Dwyer *et al.*, 1981), it was considered possible that a lipophilic β-adrenoceptor blocking drug might demonstrate even greater effects than atenolol.

This study was designed to measure the effects of increasing doses of propranolol, a β-adrenoceptor antagonist with high lipid solubility, on psychomotor function in normal subjects after oral administration.

Methods

Six healthy male volunteers, whose age ranged from 22–34 years, were studied after informed consent. Clinical examination revealed no evidence of psychiatric or organic disease and biochemical tests for hepatic and renal function were normal. No other medication was taken during the study, and subjects abstained from alcohol for 24 h before each experiment.

After an overnight fast, each subject took propranolol 40, 80, 160 and 320 mg and placebo tablets orally at 09.00 h on separate occasions with at least 1 week between each. The order of treatments was randomised and double-blind,

and the tablets were identical in number, shape and colour on each occasion. Immediately before the treatment was given and at 2, 3, 5 and 8 h after administration, each subject performed a battery of tests in the following order—two flash fusion threshold (2FFT), simple reaction time (SRT), digital copying test (DCT), symbol digit modalities test (SDMT), Gibson's spiral maze test (GSMT) and mood rating scales for tension, alertness, depression, detachment and anxiety: these tests were completed within 10 min. Through a cannula, inserted into a forearm vein in the arm which the subject was not using to perform tests, 10 ml blood samples were obtained at 0, 2, 3, 5 and 8 h. The samples were heparinised and centrifuged and the plasma stored at −20°C until assayed for plasma propranolol concentration by the fluorometric method (Shand *et al.*, 1970).

Tests of psychomotor function

Two flash fusion threshold (2FFT) is the point at which two flashes of light (square wave pulse of 5 ms) projected as a spot, appear to separate or fuse when the time interval between them is increased or decreased respectively. The flashes were square waves of an essentially white source of light of 5 ms duration. Associated timing equipment made possible the presentation of two flashes of light whose durations were constant at 5 ms whilst the interflash interval was continuously varied between 1 and 250 ms. The spot was viewed monocularly and subjects were told that they would see and should identify verbally either one or two flashes of light. Subjects were adapted to constant room illumination, no artificial pupil was used, and readings were the mean of two ascending thresholds. Subjects practised until preliminary responses were reproducible.

Simple reaction time (SRT), was measured as the mean of 15 simple reaction times to light.

Digital copying test (DCT), the time taken to copy 100 digits (in seconds), was used to calculate the DCT score from the formula

$$\text{DCT score} = \frac{100}{\text{time in s}} \times 100$$

Symbol digit modalities test (SDMT) (Smith, 1973). This test was repeated and the extent of improvement compared to zero time (retest gain) was used to indicate the learning ability. The retest gain was calculated as follows:

$$\text{Retest gain} = \frac{\text{score of trial} - \text{score at time zero}}{\text{score at time zero}} \times 100$$

Gibson spiral maze test (GSMT) was performed by the method of Gibson (1965) with the subjects stressed after 15 and 30 s. The time taken to complete the test and the number of errors were recorded. Visual analogue *mood rating scales* (Ashton *et al.*, 1978) were completed for tension, alertness, depression, detachment and anxiety.

Statistical methods

Results are expressed as the mean ± s.e. mean. Statistical analyses were performed using analysis of variance and Duncan's new multiple range test. P values of less than 0.05 were considered to be statistically significant.

Results

The mean plasma propranolol concentrations achieved with the differing propranolol doses are shown in Table 1. The mean peak propranolol level occurred between 2 and 3 h with each dose and ranged from 37.8 ± 7.4 ng/ml with 40 mg to 314.0 ± 54.8 ng/ml with 320 mg, demonstrating at each time the expected graded relationship between dose and plasma concentration.

Psychomotor function tests

2FFT The effects of propranolol on 2FFT are summarised in Table 2. It can be seen that the threshold was reproducible both from the different times tested with placebo and from the zero time readings with all doses: no significant differences occurred between any of these. The large reproducible standard error represents wide inter-individual variation. Compared to placebo, propranolol prolonged the 2FFT at 2, 3, and 5 h after 40 mg, at 3, 5 and 8 h after 80 mg and at 3 h

Table 1 Relationship between propranolol dose and plasma propranolol level achieved (ng/ml).

	Time (h)			
Dose(mg)	*2*	*3*	*5*	*8*
40	37.8 ± 7.4	30.2 ± 10.3	16.3 ± 4.0	9.2 ± 4.0
80	65.2 ± 16.7	66.7 ± 14.6	42.2 ± 6.6	25.8 ± 5.7
160	195.0 ± 32.5	159.7 ± 28.9	108.0 ± 15.5	49.8 ± 3.8
320	297.8 ± 68.7	314.0 ± 54.8	231.0 ± 35.1	108.3 ± 7.6

(mean of six subjects ± s.e. mean)

Table 2 Relationship between the dose of propranolol and the effect on 2 flash fusion threshold (ms).

	Time (h)				
Dose (mg)	*0*	*2*	*3*	*5*	*8*
Placebo	58.3 ± 19	61.8 ± 20	62.0 ± 20	60.6 ± 20	59.7 ± 21
40	61.7 ± 20	69.8* ± 22	74.0*† ± 21	68.6* ± 21	62.5 ± 17
80	57.3 ± 18	67.8 ± 20	72.2*† ± 20	68.8* ± 21	66.8* ± 20
160	57.5 ± 20	65.5 ± 23	69.0*† ± 22	64.8 ± 23	62.7 ± 23
320	57.5 ± 19	63.6 ± 21	60.6 ± 20	62.5 ± 19	62.5 ± 18

(mean of six subjects ± s.e. mean)

*Significant difference compared to placebo

†Significantly greater than 320 mg at 3 h

after 160 mg: the 320 mg dose had no significant effect. The largest effect was seen at 3 h after 40 mg and the effects of 40, 80 and 160 mg were significantly greater than those of 320 mg at 3 h.

SRT SRT was reproducible both at the various times tested and before the different doses (Table 3). Compared to placebo, SRTs were significantly prolonged by all doses of propranolol at both 2 and 3 h and by 40 and 80 mg doses at 5 h. Propranolol 40 mg significantly prolonged SRT more than 160 and 320 mg at both 2 and 3 h.

DCT The DCT score was reproducible at zero time and with placebo (Table 4). It was significantly lowered by 40, 80 and 320 mg at 2 h, by 40 and 80 mg at 3 h and by 80 mg at 5 h. The 160 mg dose had no effect.

SDMT As demonstrated by the placebo response, the retest gain of the SDMT improves with each subsequent testing compared to zero time up to about 5 h (Table 5). Propranolol not only impaired the expected improvement with all doses except 320 mg but at 2 h after 40, 80 and 160 mg the subjects showed an actual worsening

Table 3 Effects of propranolol dosage on simple reaction time (ms)

	Time (h)				
Dose (mg)	*0*	*2*	*3*	*5*	*8*
Placebo	210 ± 8	207 ± 11	192 ± 8	200 ± 12	203 ± 9
40	227 ± 13	280*† ± 24	268*† ± 10	235* ± 11	218 ± 8
80	213 ± 8	250* ± 11	247* ± 12	242* ± 15	228 ± 17
160	212 ± 16	245* ± 12	232* ± 15	218 ± 12	207 ± 13
320	212 ± 12	247* ± 13	235* ± 12	222 ± 11	228 ± 16

(mean of six subjects ± s.e. mean)

*Significant difference compared to placebo

†Significantly greater than 160 mg and 320 mg at same times

Table 4 Effects of propranolol dosage on digital copying test score

	Time (h)				
Dose (mg)	0	2	3	5	8
Placebo	259 ± 18	259 ± 17	257 ± 16	258 ± 17	260 ± 16
40	257 ± 19	237* ± 7	243* ± 17	255 ± 18	251 ± 15
80	260 ± 16	243* ± 17	244* ± 16	244* ± 15	249 ± 16
160	262 ± 16	248 ± 19	256 ± 16	254 ± 18	262 ± 16
320	259 ± 16	239* ± 16	247 ± 14	250 ± 14	253 ± 17

(mean of six subjects ± s.e. mean)
* Significant difference compared to placebo

of performance compared to zero time. The effects were greatest with 40 mg, after which mean baseline performances did not return until 5 h. In general, at any particular time, the greatest effects were seen with the lowest doses. There was a correlation between the retest gain and the plasma propranolol concentration at 2 h ($r = 0.62$; $P < 0.01$), indicating that the greatest effects occurred at the lowest plasma levels (Figure 1).

GSMT Neither the time taken to complete the GSMT nor the number of errors were significantly altered at any propranolol dosage.

Table 5 Effects of propranolol dosage on retest gain

	Time (h)			
Dose (mg)	2	3	5	8
Placebo	7.1 ± 2.2	12.4 ± 4.9	16.2 ± 6.9	14.7 ± 7.2
40	− 5.8* ± 3.9	− 3.2* ± 2.8	0.5* ± 2.8	4.6 ± 3.1
80	− 2.5 ± 2.6	1.7 ± 2.2	3.3* ± 2.7	9.6 ± 4.3
160	− 0.4 ± 3.1	2.1 ± 3.8	6.7 ± 6.1	7.2 ± 7.8
320	5.3 ± 5.2	11.4 ± 7.0	12.7 ± 8.4	19.6 ± 11.4

(mean of six subjects ± s.e. mean)
*Significant difference compared to placebo

Mood rating scales Detachment was significantly increased at 2 and 3 h after 40 mg (Table 6) and alertness was significantly decreased 3 h after 80 and 320 mg and 5 h after 80 mg (Table 7). There were no significant changes in the other mood rating scales (anxiety, depression, detachment and tension).

Discussion

These results suggest that propranolol does have central effects in man. 2FFT, SRT, DCT and SDMT were all affected by some doses of propranolol, suggesting impairment of level of arousal or integration performance, sensorimotor performance, perception and recognition respect-

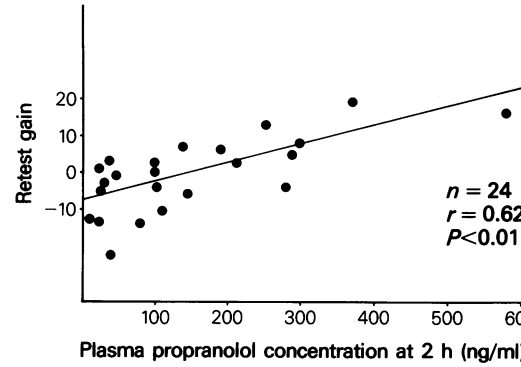

Figure 1 Relationship between retest gain of the symbol digit modalities test and plasma propranolol concentration 2 h after multiple dosing in six subjects.

Table 6 Effects of propranolol dosage on mood rating scale for detachment

	Time (h)				
Dose (mg)	*0*	*2*	*3*	*5*	*8*
Placebo	100 ± 0	103 ± 3	103 ± 3	105 ± 5	104 ± 3
40	101 ± 7	116* ± 8	114* ± 8	113 ± 6	105 ± 5
80	100 ± 0	107 ± 4	108 ± 4	103 ± 3	101 ± 2
160	96 ± 4	105 ± 3	104 ± 3	101 ± 2	98 ± 2
320	100 ± 0	100 ± 5	99 ± 7	100 ± 0	99 ± 1

(mean of six subjects ± s.e. mean)

* Significant difference compared to placebo

ively (Hindmarch, 1980). Previous studies with propranolol have yielded conflicting results. Propranolol 80 mg was found to increase variability of a choice reaction-time task significantly (Laudauer *et al.*, 1979), whereas SRT was prolonged by 80 mg in one study (Bryan *et al.*, 1971) but not by 240 or 320 mg in another (Ogle & Turner, 1974). Critical flicker fusion was not altered by propranolol (Ogle & Turner, 1974; Ogle *et al.*, 1976; Laudauer *et al.*, 1979). However, in none of these studies were dose-response relationships examined with an acceptable dose range. The results from this present study may help to explain some of these anomalies. In general, it was found that lower doses of propranolol produced effects of greater magnitude than higher doses (see 2FFT, SRT, DCT, SDMT). Thus studies of 240 or 320 mg (Ogle *et al.*, 1976) might be expected to produce very few effects.

Secondly, although direct comparisons are not possible, the extent and duration of effects of propranolol on psychomotor function in this study appeared to be similar to but not obviously greater than those demonstrated for atenolol in a study of identical design (Salem & McDevitt, 1983). Thus the expectation that propranolol, a highly lipid soluble drug with a much greater brain/plasma ratio than atenolol (Neil-Dwyer *et al.*, 1981), would produce markedly greater

Table 6 Effects of propranolol dosage on mood rating scale for alertness

	Time (h)				
Dose (mg)	*0*	*2*	*3*	*5*	*8*
Placebo	104 ± 4	101 ± 2	103 ± 5	104 ± 5	105 ± 4
40	109 ± 6	96 ± 9	93 ± 9	95 ± 8	95 ± 5
80	103 ± 2	93 ± 9	85* ± 5	89* ± 5	99 ± 2
160	96 ± 7	96 ± 6	93 ± 7	96 ± 6	103 ± 4
320	101 ± 8	96 ± 4	92* ± 5	99 ± 5	96 ± 4

(mean of six subjects ± s.e. mean)

* Significant difference compared to placebo

central effects than atenolol does not appear to have been realised.

The unexpected finding was that propranolol appeared to affect tests of psychomotor function more at lower doses than at higher doses, indeed the 320 mg dose had least effect. This contrasts with atenolol which has previously been shown to have dose-dependent effects, particularly on 2FFT, DCT and SDMT—the higher the dose, the greater the effect (Salem & McDevitt, 1983). This observation requires confirmation. If it is a real effect, could it be related to the membrane stabilising activity which propranolol possesses but atenolol does not (McDevitt, 1979)? Thus it could be postulated that at high doses, propranolol's membrane stabilising effects might diminish the effects of β-adrenoceptor blockade on psychomotor function.

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