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Central effects of β-adrenoceptor antagonists I – Performance and subjective assessments of mood

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1 Central effects of the β-adrenoceptor antagonists, propranolol (40, 80 and 160 mg) and atenolol (50 and 100 mg) were studied in 12 healthy male subjects. Two placebo ingestions and an active control (oxazepam 15 mg) were included. Single doses were administered double-blind at 11.00 h, and assessments of performance and subjective feelings were made before, 2 h and 4 h after ingestion.

2 Performance was measured using letter cancellation, digit symbol substitution, continuous attention, choice reaction time, finger tapping, short term and immediate memory, critical flicker fusion and two flash fusion. Subjective feelings were assessed using twelve visual-analogue scales.

3 Oxazepam impaired performance at letter cancellation ($P < 0.001$), digit symbol substitution ($P < 0.05$), continuous attention ($P < 0.001$), immediate recall ($P < 0.05$) and finger tapping ($P < 0.05$), but neither of the β-adrenoceptor antagonists affected these measures. Propranolol (40 and 160 mg) also impaired short term memory ($P < 0.05$), though it was not possible to establish this effect with atenolol.

4 Subjective alertness was reduced by oxazepam ($P < 0.01$) and atenolol ($P < 0.05$), while propranolol (40 mg) reduced anxiety ($P < 0.01$) and propranolol (80 mg) impaired ability to concentrate ($P < 0.05$).

5 The results suggest that both lipophilic and hydrophilic antagonists modify the central nervous system, though impairment may be difficult to establish with conventional tests. The observations on memory and alertness suggest that the central effect of β-adrenoceptor antagonists may be subtle.

Keywords β-adrenoceptor antagonists propranolol atenolol performance

Introduction

There is uncertainty concerning the nature of the possible central effects of β-adrenoceptor antagonists, but, though it is likely that these drugs have such effects, their severity may be minimal compared with the benzodiazepines. Indeed, light-headedness, visual and auditory hallucinations, sleep disturbances, vivid dreams and changes in mood and affect have been related to long-term treatment (Greenblatt & Shader, 1972; Fleming, 1978). However, presently available information is difficult to evaluate. Impaired performance has been reported after single doses (Bryan *et al.*, 1974; Glaister *et al.*, 1973; Landauer *et al.*, 1979; Salem & McDevitt, 1983), while other studies have failed to show such effects (Ogle *et al.*, 1976; Turner & Hedges, 1973; Tyrer & Lader, 1974).

The question of central effects with β-

adrenoceptor antagonists is an important one as these drugs are commonly prescribed in hypertension and ischaemic heart disease when the patients continue to work. In such cases impairment of alertness and co-ordination could be significant. It is in this context that we have carried out a dose-response study in healthy volunteers on the effects of a hydrophilic (atenolol) and a lipophilic (propranolol) antagonist in which an active control (oxazepam) has been included.

In this paper we report the observations on various aspects of performance as well as subjective assessments of well being and mood, and in the following paper we deal with the findings on the electroencephalogram and body sway.

Methods

Experimental design

Twelve healthy male volunteers, aged between 19 and 29 years, participated in the study which was approved by the Hospital Ethics Committee. None was taking any concurrent medication and each was required to abstain from alcohol for 24 h before each study period. No caffeine-containing beverages were permitted during the study days.

Performance was tested in individual, sound-proofed cubicles. The intensity of lighting could be adjusted to permit dark adaptation before measurement of critical flicker fusion and two-flash fusion thresholds. Each subject spent at least 1 day in the laboratory before beginning the study to familiarise himself with the schedule and the physiological procedures. Subjects were trained to plateau levels of performance before the effect of drugs was studied.

Each subject took single doses of propranolol (40, 80 and 160 mg), atenolol (50 and 100 mg), an active placebo (oxazepam 15 mg) and two inactive placebos. Treatments were separated by at least 1 week. The drugs were administered in a randomised, double-blind manner, except that one placebo was included in each half of the study. On each of the study days drugs were taken orally at 11.00 h with 100 ml of water. Performance was measured at 1 h before (10.00 h) and 2 (13.00 h) and 4 h (15.00 h) after ingestion.

In each session several aspects of performance were tested together with subjective assessments of mood and well-being and recordings of the electroencephalogram and body sway (*q.v.* Nicholson *et al.*, 1988). The techniques to measure performance have been used previously by the authors in studies on antihistamines (Nicholson & Stone, 1984) and analgesics (Bradley & Nicholson, 1987), and are believed to be particularly useful in the detection of drug effects. In addition, the extent of β-adrenoceptor blockade was estimated 4 h after ingestion by measuring the reduction in exercise-induced tachycardia during a modified step test. Venous blood was taken for the measurement of plasma concentrations using high performance liquid chromatography (h.p.l.c.) techniques (Walle 1974; Winkler *et al.*, 1982).

Performance tests

Six letter cancellation Subjects were presented with one of a series of 50 sheets with 1200 randomised letters arranged in 40 columns, with 6 target letters printed at the top. They were given 5 min to cancel as many target letters as possible working down each column in turn. The number of letters correctly cancelled and number attempted were recorded.

Digit symbol substitution Two sheets, from a series of 50, each containing 200 randomised digits and a code relating each digit to a symbol, were presented to the subjects who were required to complete as many substitutions as possible. Two minutes were allowed for each sheet, and the total number of substitutions was recorded.

Continuous attention Randomised series of letters were generated by a BBC microcomputer and presented on individual monitors at a rate of one per second. A 'critical stimulus' of two letters was displayed at the top of the screen and subjects were required to respond within 750 ms by pressing a key whenever the second letter followed the first in the series of presentations. The test lasted for 10 min and the number of correct responses, together with the number of errors, were recorded.

Choice reaction time (CRT) Subjects were required to press a key adjacent to each of four light emitting diodes which were illuminated in a random sequence of 30 presentations. The mean reaction time to the last 20 responses was recorded.

Finger tapping Subjects were required to tap a pressure-sensitive transducer as rapidly as possible. The total number of taps per minute, and number of involuntary rest pauses exceeding 250 ms were recorded.

Short term memory During the first session of each study day the subjects were presented with a set of ten photographs of miscellaneous, unrelated objects, and given 1 min to examine them. Each subject was then given 45 s to recall and write down as many objects as possible 4 h after presentation.

Immediate memory During the second session (2 h after ingestion) immediate memory was tested using a modified version of the Williams Word Memory Task (Williams, 1966). The subjects were presented with a list of 16 disassociated words generated by a microcomputer and displayed on individual monitors at a rate of one word every 3 s. The words were two syllable nouns used with a frequency of greater than 15 per million in general usage. Immediately after the presentations the subjects were given 45 s to write down all words recalled from the list.

Physiological measurements

Critical flicker fusion Flicker fusion threshold was assessed using a central flickering background, with presentations at optical infinity. The field was viewed monocularly through an artificial pupil. For each stimulus the flickering source was presented for 2 s. The first flicker frequency was chosen randomly between 15 and 20 Hz and was thereafter altered in a stepwise manner according to the pattern of response. Initially, frequency increased or decreased by 4 Hz depending on whether the subject perceived the field as flickering or fused. Thereafter, each change in response caused the stepsize to be halved until steps of 0.25 Hz were reached. The fusion threshold was defined as the mean of the last 20 presentations varying by 0.25 Hz.

Two flash fusion The subjects viewed a central background through an artificial pupil and were presented with pairs of 10 ms flashes of light separated by a period varying between 12 and 120 ms. Initially, the separation was selected randomly between 50 and 63 ms, and then increased or decreased by 8 ms depending on the subject's response. Thereafter, each change in response caused the stepsize to be halved until steps of 1 ms were reached. The subjects were required to report when the light sources appeared as two separate flashes. The flash fusion point was defined as the mean of the last 20 responses of 1 ms stepsize.

Subjective assessments

Subjects assessed their mood on a series of twelve 100 mm visual analogue scales. All scales were presented on a single sheet of paper. Scales were scored by measuring the distance from the subject's mark to the end of the line corresponding to absence of symptom.

The assessments were:- A: I am, extremely sleepy (0) – extremely wide awake (100); B: I am, extremely tense (0) – absolutely relaxed (100); C: I am, extremely agitated (0) – absolutely calm (100); D: I am, extremely lethargic (0) – extremely energetic (100); E: I am, mentally very dulled (0) – extremely alert (100); F: I have, no ability to concentrate (0) – complete ability to concentrate (100); G: with regard to carrying out general duties I feel that I am, absolutely useless (0) – extremely efficient (100); H: I am, extremely irritable (0) – not at all irritable (100); I: I am, extremely aggressive (0) – extremely passive (100); J: I feel, extremely withdrawn (0) – extremely sociable (100); K: I am, in the depths of depression (0) – ecstatically happy (100); L: I feel, extremely anxious (0) – absolutely carefree (100).

Statistical analysis

All data were analysed using analysis of variance (ANOVA). Three factors were identified (drugs, times and subjects) of which drugs and time were fixed effects, and subjects was a random effect. Homogeneity of variance, normality and independence were examined for each variable, and transformations of the raw data applied according to the method of maximum likelihood of Box & Cox (1964). Each variable was tested for the presence of sequence effects using analysis of covariance.

Two possible methods of estimating drug effects were investigated for each variable. The pre-ingestion sessions were screened for homogeneity, and where these eight mean values were homogeneous direct comparisons of drug means with the placebo mean for each post-ingestion session were made. However, where significant differences occurred among the pre-ingestion values the difference between pre- and post-ingestion means were calculated, and these differences used to compare drug responses with the placebo value at each post-ingestion time. Based on this criterion the direct test was subsequently used for all comparisons in this part of the study.

The significance levels for all comparisons between mean placebo and drug responses were based on the appropriate Bonferroni inequality (Miller, 1966) to allow for the number of simultaneous comparisons. The effect of each of the three drugs (meaned over dose and post-ingestion sessions) and of individual doses of the drugs

(meaned over post-ingestion times) were determined. Responses for each dose at individual times were also examined.

For the visual analogue scales, principal components analysis was used to reduce the number of variables required to explain drug effects. Analyses of individual assessments for mood are reported only where additional information is provided.

Results

All subjects completed the study and none experienced any significant side effect.

Performance tests

Oxazepam impaired performance at letter cancellation ($P < 0.001$), digit symbol substitution ($P < 0.05$), continuous attention ($P < 0.001$), immediate recall ($P < 0.05$) and finger tapping ($P < 0.05$). It did not affect choice reaction time, short term memory, critical flicker fusion threshold or two-flash fusion threshold (Table 1).

Analysis of variance identified a drug effect related to short-term memory, and this was related to propranolol. Propranolol (40 and 160 mg) reduced the mean number of photographs recalled ($P < 0.05$), while no changes in memory were observed with atenolol (Table 1). Neither of the β-adrenoceptor blockers had any effect on the other tests of performance.

Subjective assessments

Two principal components were derived from the 12 assessments. The first component comprised B, C, H, I, J, K and L and reflected feelings associated with mood. None of the treatments affected this component. Analysis of individual assessments showed that propranolol (40 mg) reduced anxiety 4 h after ingestion ($P < 0.01$) (Table 2).

Assessments A, D, E, F and G were related to perceived levels of alertness. This component was changed by oxazepam ($P < 0.01$) and atenolol ($P < 0.05$) indicating a reduction in alertness. Analysis of individual assessments showed that propranolol (80 mg) reduced ability to concentrate ($P < 0.05$) 4 h after ingestion (Table 2).

Heart rate

All doses of both β-adrenoceptor antagonists produced a decrease ($P < 0.01$) in exercise-induced heart rate (Table 3).

Plasma concentrations

Plasma concentrations of atenolol and propranolol 2 and 4 h after ingestion are given in Table 4.

Discussion

Before considering the present results it is useful to review other broadly comparable studies in healthy subjects in which the possibility of central effects was investigated over a similar dose range (propranolol 40–160 mg: atenolol 50–100 mg) and in which performance was observed between 2 and 4 h after acute ingestion. Within such constraints several authors have reported impaired performance (Bryan *et al.*, 1974; Broadhurst, 1980; Broadhurst & Monaghan, 1984; Salem & McDevitt, 1983, 1984; File & Lister, 1985) while several others have not observed any drug effects (Lader & Tyrer, 1972; Tyrer & Lader, 1974; Ogle & Turner, 1974; Bayliss & Duncan, 1975; Harvey *et al.*, 1977; Wagner *et al.*, 1981; Levander & Gillner, 1982; Harms, 1985). Nevertheless, there is a fair degree of commonality between these studies in terms of choice of tests as many include motor skills and skills which are dependent on alertness.

However, examination of the papers suggests several reasons why contradictory results may have been obtained. In particular, the sensitivity of the test situation has often not been established by the use of an active control, and the statistical analyses may not have allowed adequately for variation between control values, learning effects and multiple comparisons. Even so, though contradictory results have been obtained from several centres, the suspicion remains that these drugs are not entirely free of central effects.

The present studies in which oxazepam was used as an active control failed to establish effects of propranolol and atenolol on a wide range of skills, but it does appear that central effects of the β-adrenoceptor antagonists cannot be entirely excluded. Analysis of variance revealed a drug effect on short term memory identified with propranolol and, in a similar way, analysis of subjective assessments suggested changes in mood with propranolol and in alertness with atenolol. These observations, together with the evidence obtained in the same study that both atenolol and propranolol modify the electrical activity of the brain (Nicholson *et al.*, 1988), suggest that, though the β-adrenoceptor antagonists may not lead to central effects similar to drugs like the benzodiazepines, they may, nevertheless, modify central activity. The well

Table 1 Effects of β-adrenoceptor antagonists on performance – means over post-ingestion times (means for 12 subjects)

Measure	*Trans-formation*	*Placebo*	*Oxazepam 15 mg*	*Propranolol 40 mg*	*Propranolol 80 mg*	*Propranolol 160 mg*	*Atenolol 50 mg*	*Atenolol 100 mg*	*†Standard error*
Cancellation (number correct)	–	87.9	78.5***	87.2	93.5	85.9	88.1	87.5	2.97
DSST	–	169.9	163.6*	171.1	174.7	171.1	170.9	170.4	2.85
Attention (% correct)	–	97.3	93.3***	97.1	96.2	97.6	97.8	95.1	1.23
Attention (number of errors)	log x	0.95	1.43*	0.81	1.02	0.91	0.72	1.30	0.13
CRT (ms)	–	396.5	398.3	385.8	412.9	415.2	404.3	388.8	12.18
Short term memory	–	7.4	7.8	6.3*	8.2	6.3*	7.5	6.5	0.42
Immediate recall	–	10.3	8.5*	9.7	9.9	9.8	9.9	10.1	0.50
Tapping (number)	–	396.1	395.0	402.5	396.8	398.5	397.1	401.0	7.29
Tapping (involuntary rest pauses)	x^3	154.2	160.0*	152.5	159.2	157.6	157.2	158.5	18.3×10^5
Critical flicker fusion	–	41.4	41.0	44.0	41.2	39.8	40.2	40.8	1.54
Two flash fusion	x^2	31.7	32.8	28.3	32.5	30.1	30.7	32.1	69.69

Significance levels: * $P < 0.05$; *** $P < 0.001$.
† The standard errors shown are a pooled estimate taken from the analysis of variance based on all treatments. Where the data have been transformed prior to analysis, the standard errors relate to transformed data.

Table 2 Effect of β-adrenoceptor antagonists on subjective assessments (means for 12 subjects)

Measure	*Time after ingestion (h)*	*Placebo*	*Oxazepam 15 mg*	*Propranolol 40 mg*	*Propranolol 80 mg*	*Propranolol 160 mg*	*Atenolol 50 mg*	*Atenolol 100 mg*
+ PC1	Mean over 2 + 4	0.0334	–0.2502	–0.0557	0.0341	0.0623	–0.0037	0.1430
+ PC2	2	0.0546	–0.8037**	0.1566	–0.0722	0.0884	–0.8565*	–0.2948
	4	0.5699	0.0675	0.5435	0.2067	0.2235	0.1534	0.2042
	Mean over 2 + 4	0.3107	–0.3681**	0.3500	0.0672	0.1599	–0.3516*	–0.0453
Concentration (F)	2	50.3	44.3	51.5	52.3	54.0	43.8	48.3
	4	58.0	51.4	55.9	48.8*	51.6	53.0	54.8
Anxiety (L)	2	58.6	59.0	56.8	54.6	56.7	55.7	55.3
	4	56.6	59.5	63.9**	60.0	59.4	56.5	57.4

				Propranolol 40–160 mg	*Atenolol 50–100 mg*
PC1	Mean over 2 + 4	0.0334	–0.2502	–0.0279	0.0697
PC2	Mean over 2 + 4	0.3107	–0.3681**	0.1911 †	–0.1984*

+ PC1 = score on component representing assessments B, C, H, I, J, K and L (mood).
+ PC2 = score on component representing assessments A, D, E, F and G (alertness).
Significance levels: * $P < 0.05$; ** $P < 0.01$.
†indicates that the value for atenolol differs from propranolol, meaned over dose for each drug ($P < 0.05$).
The pooled standard error estimates for the variables in this table are PC1 = 0.1738; PC2 = 0.2675; Concentration (F) = 2.93; Anxiety (L) = 1.96.

Table 3 Effect of β-adrenoceptor antagonists on post-exercise heart rate in beats min^{-1} (means for 12 subjects)

		Time after ingestion (h) 2	4
Placebo		139.3	137.4
Oxazepam (mg)	15	140.1	135.7
Propranolol (mg)	40	109.7**	113.0**
	80	107.3**	107.7**
	160	104.6**	105.1**
Atenolol (mg)	50	109.3**	109.1**
	100	101.9**	102.7**

Significance levels: ** $P < 0.01$.
Prior to analysis, a square root transformation was applied, and the pooled standard error this scale was 0.352.

Table 4 Plasma levels (ng ml^{-1}) of β-adrenoceptor antagonists (means for 12 subjects)

		Time after ingestion (h) 2	4
Propranolol (mg)	40	41.6	29.3
	80	113.7	71.8
	160	207.1	143.1
Atenolol (mg)	50	212.7	177.8
	100	545.8	423.3

being of the individual may be degraded in a way not easily appreciated with impairment of alertness and memory.

In view of the marginal effects on mood it is of interest that some workers have reported subjective changes including decreased alertness (Lader & Tyrer, 1972; Salem & McDevitt, 1983, 1984) while others have failed to obtain feelings of sedation (Bayliss & Duncan, 1975, Levander & Gillner, 1982; File & Lister, 1985). In the present studies an anxiolytic effect of propranolol (40 mg) and reduced ability to concentrate with propranolol (80 mg) were found, and the subjects reported reduced alertness with atenolol. Clearly subjective appreciation of marginal central effects is difficult, and so positive reports cannot easily be ignored as elsewhere we have evidence of changes in the electroencephalogram consistent with modulation of wakefulness.

The only objective finding in the present study was impairment of memory. This was related to propranolol, but the subsequent analysis which allowed for multiple comparisons indicated only a reduction with 40 and 160 mg. The data do not permit any firm conclusions to be drawn with respect to the apparent non-linearity of the effect across dose, but clearly a dose-related response was not present and this would suggest a marginal effect. It is, therefore, appropriate to consider the effect on memory likely to be applicable over the dose range 40–160 mg. In this context, impaired memory was not observed by Landauer *et al.* (1979) and Levander & Gillner (1982) using a digit span test in healthy volunteers, though studies with hypertensive patients have suggested disturbances in short-term memory with both propranolol (Solomon *et al.*, 1983) and atenolol (Lichter *et al.*, 1986). We observed a memory deficit using similar tests and this, together with changes in the electroencephalogram, would suggest that central effects of these drugs may involve skills of a more subtle nature than those usually observed.

In summary, the present study suggests that the β-adrenoceptor antagonists are likely to have central effects, and that these may occur with both lipophilic and hydrophilic drugs. However, clear dose-response effects are difficult to establish, subjective awareness of central effects is poor, and the most usual skills tested are unlikely to be impaired. However, impairment of short term memory together with changes in the electroencephalogram suggest that the β-adrenoceptor drugs may have subtle effects on central function and that these may be difficult to appreciate.

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