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The effect of acute β-adrenoceptor blockade on examination performance

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1 Simple tests of verbal reasoning and mental arithmetic, taken under mildly stressful conditions, have been shown to give a reproducible test of intellectual function within groups of normal subjects.
2 Using these tests, in two separate examinations, a double-blind cross-over study was performed on 35 medical students to assess the effects of acute β-adrenoceptor blockade with propranolol on intellectual function.
3 With placebo treatment, students recorded an average total score of 231.3 marks, with average scores of 108.9 marks on the mental arithmetic paper and 122.4 marks on the verbal reasoning paper. Treatment with propranolol was associated with an improvement in total score of 9.2 ± 3.9 marks ($P < 0.05$), an improvement in mental arithmetic score of 5.6 ± 2.3 marks ($P < 0.05$) and an improvement in verbal reasoning score of 3.6 ± 2.4 marks (NS).
4 Eighteen out of the 35 students said that they were mildly anxious before one examination and 13 students said they were anxious before both examinations. Those students who admitted anxiety seemed to benefit the most, in terms of improved examination performance, from treatment with propranolol.

Keywords anxiety β-adrenoceptor blockade examinations propranolol

Introduction

β-adrenoceptor blocking drugs reduce the tremor induced by anxiety and have been used to improve musical performance under stress (James *et al.*, 1977, 1983). They are also used as anxiolytic agents during intellectual tests of a less practical nature (Brewer, 1972) although there has been no satisfactory assessment of the effects of these drugs on higher cerebal function in such circumstances; indeed the available information from the chronic use of β-adrenoceptor blocking drugs in patients is that these treatments can cause unwanted central side effects which are likely to impair performance (Bai *et al.*, 1982). We have devised a precise method of estimating performance in mental arithmetic and verbal reasoning under conditions of mild stress and applied it to a double-blind, placebo controlled, cross-over study, designed to assess the effects of β-adrenoceptor blockade with propranolol.

Methods

The pilot study

This was designed to assess the reproducibility of the method and was performed on nine junior doctors (aged 23–33 years). Each sat two examinations, taken 1 week apart, testing powers of mental arithmetic and verbal reasoning. Examination questions were selected from 'Mental Arithmetic 4', published by Schofield & Sims (Goddard, 1982) and from 'More Verbal

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Reasoning Tests' by Haydn Richards (1982). The questions are considered suitable material for 11 year old children. Examination candidates were given sample questions to complete several days before the first examination and the questions in the two examinations were completely different although extracted from the same source. Each examination lasted for 1 h 20 min; 40 min was devoted to arithmetic and 40 min to verbal reasoning. Candidates were encouraged to complete as many questions as possible during this time and were told that they would be marked on the number of correct answers; errors would be noted but not penalised. Each examination paper contained more questions than could be answered within the time limit. The verbal reasoning tests were always completed first and the examinations were taken at the same time of day with all candidates seated in close proximity. Each examination was marked by one examiner. Competition was encouraged by peer review (results were publicised) and the award of prizes for the best performance. At the beginning of the second examination more prizes were offered for the best improvements as well as the best performance.

Using this technique we found that subjects showed an average improvement between examinations of 29.6% ± 1.7% (mean ± s.e. mean). The mean score in the first examination was 189.2 ± 8.4 marks and in the second examination it was 244.7 ± 9.7 marks. This information suggested that the paired examination design could be used in a cross-over study to assess the effects of two different treatments and if conducted in 30 subjects would have a 90% chance of showing a real difference in performance between treatments of 5% to be statistically significant ($P < 0.05$).

The study of propranolol vs *placebo*

A double-blind, placebo controlled, cross-over study was designed to assess the effects of propranolol on examination performance in at least 30 student volunteers. Each student underwent two examinations, the details of which were exactly as described in the pilot study with the exception that 4.5 h before each test candidates were given either 120 mg of propranolol or a matching placebo. Candidates were randomised in blocks of 4 for the order in which they received the treatments. After each examination candidates were asked to pass a specimen of urine for thin layer chromatographic analysis for propranolol (Jack *et al.*, 1980). After the second examination a questionnaire was sent to each student asking for details of any side effects with the treatments, an assessment of the blindness of the study and an indication of the level of anxiety produced before each examination (none, mild, moderate, severe).

The statistical analysis of the study employed a paired t test and followed the guidelines outlined by Hills & Armitage (1979). The data were of interval scale and showed an approximately Gaussian distribution of residuals with no evidence of heteroscedasticity. Effects of treatment on total score, mental arithmetic score and verbal reasoning score were calculated and the possibility of period effects and treatment-period effects investigated. A P value of less than 0.05 (two-tailed) was considered significant. In the presentation of results all scores have been given as the mean ± s.e. mean.

This study was approved by The London Hospital Ethics Committee.

Results

Forty-one students (26 men and 15 women aged between 20 and 28 years) entered the study and 35 completed all aspects. Compliance with the propranolol treatment was confirmed in these subjects by thin layer chromatography of urine. All the subjects who dropped out were male; five did not turn up for the second examination because they were playing cricket and one subject had entered a drug trial sponsored by a commercial drug testing centre before he attended for the second examination, and was therefore excluded from the rest of the study. Three of the subjects who dropped out had received propranolol as their first treatment and three had received placebo; none had suffered side effects.

Of the 35 subjects who completed the study, 18 were randomised to receive propranolol before the first examination (Group A) and 17 were allocated to receive placebo (Group B). Treatment with propranolol was associated with an improvement in total score of 9.2 ± 3.9 marks ($P < 0.05$) and in mental arithmetic score of 5.6 ± 2.3 marks ($P < 0.05$). An improvement of 3.6 ± 2.4 marks in verbal reasoning score was not statistically significant and there were no differences in the number of errors made by each group (Table 1).

Period effects, with an improvement in verbal reasoning score and a deterioration in mental arithmetic score on the second examination were very highly statistically significant although there was no significant period effect for total score. There was no evidence of any treatment-period interactions.

Table 1 The effect of propranolol treatment on total score, mental arithmetic score, verbal reasoning score and the number of mistakes made during each examination. Results are given as means ± s.e. mean and statistical significance indicated by either one asterisk ($P < 0.05$) two asterisks ($P < 0.02$) or three asterisks ($P < 0.001$)

	Group A ($n = 18$)		*Group B* ($n = 17$)				
Score	*1st exam (Propranolol)*	*2nd exam (Placebo)*	*1st exam (Placebo)*	*2nd exam (Propranolol)*	*Period effect*	*Treatment/ period interaction*	*Propranolol effect*
Total score	228.7 ± 12.7	226.7 ± 14.3	236.1 ± 14.6	252.5 ± 18.0	+7.2 ± 3.9	−16.6 ± 20.9	+9.2 ± 3.9*
Maths score	120.3 ± 9.0	95.3 ± 9.4	123.3 ± 9.1	109.5 ± 11.7	−19.4 ± 2.3***	−8.6 ± 13.8	+5.6 ± 2.3*
Verbal reasoning score	108.4 ± 5.9	131.4 ± 6.7	112.8 ± 7.1	143.1 ± 8.5	+26.6 ± 2.4***	−8.01 ± 9.8	+3.6 ± 2.4
Number of mistakes	22.1 ± 1.6	26.8 ± 2.4	21.3 ± 2.2	23.5 ± 2.7	+3.5 ± 1.4**	+2.0 ± 2.8	−1.2 ± 1.4

Unwanted effects of treatment were experienced by 19 subjects; 15 cases occurred on propranolol and 4 cases on placebo. Some subjects complained of more than 1 symptom. Unwanted effects on propranolol included nausea (5), headache (3), weak legs (3), tiredness (2), postural dizziness (2), bradycardia (1), 'light headedness' (1), poor concentration (1), indigestion (1) and 'excess relaxation' (1). Unwanted effects on placebo included headache (1), tiredness (3) and poor concentration (1). Sixteen subjects had no unwanted effects with treatment but only six of these felt confident enough to identify their treatments; two were wrong. When all subjects who developed symptoms on one or other treatment were excluded from the analysis an effect of propranolol treatment was still apparent although it was no longer statistically significant. Thus eight subjects remained in Group A and recorded a total score of 245.0 ± 20.0 marks on examination 1 and 244.7 ± 20.9 marks on examination 2, whilst the eight subjects remaining in Group B recorded scores of 264.1 ± 13.4 marks and 277.6 ± 20.5 marks respectively. Propranolol treatment improved scores by 6.9 ± 5.8 marks (NS).

Eighteen subjects said they were anxious (11 mild, seven moderate) before one or other examination and 13 experienced anxiety before both examinations. Of these 18 subjects, five were in Group A and 13 were in Group B. Those in Group A scored 184.4 ± 9.5 marks in Examination 1 and 170.8 ± 7.3 marks in Examination 2 whilst those in Group B scored 227.5 ± 17.3 and 244.4 ± 19.2 marks respectively. The apparent improvement with propranolol was 15.2 ± 5.2 marks ($P < 0.01$).

Students were ranked in order of performance in both examinations; the position attained by students in the examination taken on treatment with propranolol was slightly lower than the position attained in the examination taken on treatment with placebo (0.3 ± 1.1 of a place, NS).

Discussion

This study has shown that propranolol treatment is associated with a small, but statistically significant, improvement in performance of simple tests of verbal reasoning and mental arithmetic, conducted in an atmosphere of mild stress. The study was specifically designed to reveal such a small effect and systematic errors were reduced by the randomised, double-blind, placebo controlled design.

We were surprised to find an improvement in performance with the dose of propranolol used, which caused an appreciable incidence of unwanted effects, but which was considered, from known pharmacokinetics, to be the smallest dose capable of maintaining substantial peripheral β-adrenoceptor blockade in all subjects throughout the examination (Johnsson & Regardh, 1976; Coltart & Shand, 1970). It is possible that the development of unwanted effects may have had some subtle effect on student performance although deterioration would have seemed the more likely response. However, even when the results of those students who had experienced unwanted effects were removed from the analysis the trend towards an improvement with propranolol remained. An analysis of sub-groups is fraught with hazards especially if treatment order is unevenly distributed and there is a significant period effect. Nevertheless, our data shows that the major benefit of treatment with propranolol was experienced by the group which suffered symptoms of anxiety, and presumably it is the anxiolytic effects of the drug which conferred benefit.

One other possibility which needs to be considered is a treatment-period interaction which camouflaged either a null-effect or deleterious effect of propranolol treatment. Such would be the case if propranolol in some way interfered with the capacity to learn from the experience of the first examination and it is noticeable that those subjects in Group A, who received propranolol first, showed no improvement between the examinations. We found no significant treatment-period effect but recognise that any test for such an interaction is relatively insensitive.

The apparent improvement in examination performance which we have demonstrated with propranolol is small when compared to the innate differences between individuals and this is reflected by the lack of change in ranked performance with treatment. It should also be noted that our effects have been documented with a single dose of a lipid soluble β-adrenoceptor blocker and any extrapolation to β-adrenoceptor blockers in general or to the chronic use of these drugs should be avoided.

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References

Bai, T. R., Webb, D. & Hamilton, M. (1982). Treatment of hypertension with β-adrenoceptor blocking drugs. *J. Roy. Coll. Phys.*, **16**, 239–241.

Brewer, C. (1972). Beneficial effect of β-adrenergic blockade on exam nerves. *Lancet*, **ii**, 435 (C).

Coltart, D. J. & Shand, D. G. (1970). Plasma propranolol levels in the quantitative assessment of β-adrenergic blockade in man. *Br. med. J.*, **3**, 731–734.

Goddard, T. R. (1982). *Mental arithmetic 4.* Huddersfield, Yorks: Schofield & Sims Ltd.

Hills, M. & Armitage, P. (1979). The two-period, cross-over clinical trial. *Br. J. clin. Pharmac.*, **8**, 7–20.

Jack, D. B., Dean, S. & Kendall, M. J. (1980). Detection of some antihypertensive drugs and their metabolites in urine by thin layer chromatography. Five commonly used β blockers and hydralazine. *J. Chromatography*, **187**, 277–280.

James, I. M., Pearson, R. M., Griffith, D. N. W. & Newbury, P. (1977). Effect of oxprenolol on stage-fright in musicians. *Lancet*, **ii**, 952–954.

James, I. M., Burgoyne, W. & Temple Savage, I. (1983). Effect of pindolol on stress-related disturbances of musical performance: preliminary communication. *J. Roy. Soc. Med.*, **76**, 194–196.

Johnsson, G. & Regardh, C. G. (1976). Clinical pharmacokinetics of β-adrenoceptor blocking drugs. *Clin. Pharmacokin.*, **1**, 233–263.

Richards, H. (1982). *More verbal reasoning tests.* 17th impression. Aylesbury, Bucks: Ginn & Company Ltd.

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