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PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF ±-PROPRANOLOL, +-PROPRANOLOL AND DIAZEPAM IN INDUCED ANXIETY

P.J. TYRER[1] & M.H. LADER
Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF

1 Four equal-sexed groups of eight normal subjects were given single doses of either (±)-propranolol (120 mg), (+)-propranolol (120 mg), diazepam (6 mg) or placebo using double-blind procedure and their effects studied under three types of experimental stress and at rest.

2 Finger tremor, EEG, averaged auditory evoked response, skin conductance, heart rate and respiratory rate were measured at each time of testing, and subjects also completed performance tests (reaction time, tapping speed and symbol copying) and subjective mood scales.

3 Neither (+)- nor (±)-propranolol had any beneficial effects on mood and physiological tests showed that, although adequate β-adrenoceptor blockade was achieved, there was no evidence of sedation.

4 Diazepam reduced subjective anxiety, significantly lessened the main amplitude of the auditory evoked response and also reduced the proportion of slower rhythms in the EEG.

5 The results suggest that (+)- and (±)-propranolol have no psychotropic effects on induced anxiety and that their modes of action are fundamentally different from that of diazepam.

Introduction

Racemic propranolol (Inderal) was shown to reduce the autonomic symptoms of anxiety by Granville-Grossman & Turner (1966). Since then debate has continued concerning its clinical importance as an anxiety-relieving agent and its possible mode of action. On balance, the beneficial effect of propranolol and other β-adrenoceptor blocking agents in anxiety would appear to be due to peripheral blockade rather than to central action. Thus, definite central effects of propranolol do occur in man (Gillam & Prichard, 1965; Stephen, 1966; Hinshelwood, 1969; Orzack, Branconnier & Gardos, 1973; Bryan, Efiong, Stewart-Jones & Turner, 1974) and in animals (Leszkovsky & Tardos, 1965; Bainbridge & Greenwood, 1971), but only in higher dosages than those used in the clinical studies of anxiety (Granville-Grossman & Turner, 1966; Wheatley, 1969). Practolol, a β-adrenoceptor blocking agent which does not enter the brain in appreciable amounts, is similar in effects to propranolol (Bonn, Turner & Hicks, 1972). Finally, propranolol is of greater benefit in somatic than in psychic anxiety (Tyrer & Lader, 1974a), which also favours a mainly peripheral mode of action.

(+)-Propranolol has only about 1/60 of the β-adrenoceptor blocking activity of the racemic mixture (Howe & Shanks, 1966; Barrett & Cullum, 1968), although its other pharmacological properties are similar. In a small-scale trial it gave no appreciable benefit to anxious patients (Bonn & Turner, 1971), and these authors suggested that β-adrenoceptor blockade is the relevant mechanism in treatment with racemic propranolol. Comparison of the effects of (+)-propranolol and racemic propranolol may therefore be an appropriate way of estimating the relative contributions of β-adrenoceptor blockade and central action in a clinical situation.

Anxiety induced in normal subjects is often considered similar in nature to neurotic anxiety, although differing in degree (Hamilton, 1969; Lader, 1972). Others maintain that there are fundamental differences between them, in both their psychological (Kierkegaard, 1844; Freud, 1926) and somatic (Tyrer, 1973) components. Treatment of induced anxiety with propranolol provides a way of studying the relationship between the somatic and psychic aspects of what is essentially a form of normal anxiety.

[1] Present address: South Academic Block, Southampton General Hospital, Tremona Road, Southampton SO9 4XY.

β-adrenoceptor blocking drugs produce clear-cut physiological changes in man. If clinical effects are also related to β-adrenoceptor blockade, parallel physiological changes should occur. It was therefore decided to measure the subjective and physiological effects of propranolol concurrently to study their inter-relationship. A comparison was made between the effects of placebo, (±)-propranolol (Inderal), (+)-propranolol and diazepam (Valium) to evaluate the role of β-adrenoceptor blockade and to detect similarities and differences between peripherally acting and centrally acting drugs in reducing anxiety.

Methods

Subjects

The paid volunteer subjects consisted of 16 male and 16 female students and postgraduate research workers aged between 18 and 38 years. They were allocated randomly to four drug groups with the constraint that each group comprised four males and four females. Subjects were informed in advance of the stress situations and shown the apparatus. Those with a history of cardiac disease or asthma were excluded from the study.

Drugs

Subjects received three identical capsules containing a total of (+)-propranolol (120 mg), (±)-propranolol (120 mg), diazepam (6 mg) or placebo. Each subject was given only drug.

Experimental design

Each subject was tested on two occasions, 4 weeks apart. No alcohol or psychotropic drugs were allowed in the 24 h before testing. On each occasion, a sequence of five test situations was administered. An interval of 1 h elapsed between the first and second tests but subsequently the tests ran almost consecutively with only a 5 min break. On the first occasion no drug was administered; on the second occasion the drug was given after the first test, the subsequent hour's break being necessary to allow for drug absorption. Thus the subsequent four test situations on the second occasion only were conducted with the subject having taken a drug.

Stimulation procedures

Most of the physiological measures, namely the EEG, averaged auditory evoked response (AER), palmar skin conductance, pulse rate and respiratory rate, were recorded during a reaction time task in which the subject was instructed to press a key in response to 32 auditory click stimuli of 70 dB intensity presented through a loudspeaker behind the subject at intervals varying randomly between 8 and 12 seconds. This procedure constituted the basal or 'rest' situations which were the first and fifth on each occasion.

The three intervening stress situations comprised:

(a) Synchronously with the clicks an electric shock was administered to the upper arm. Before the experiment, the voltage was adjusted so that the shock was unpleasant but bearable and this level was maintained throughout the experiment.

(b) An identical situation to (a) except that isoprenaline was administered by inhaler (Medihaler-Isoforte) in a metered dose of 0.5-1.5 mg, the same dose being given on each occasion, before the first click-shock stimulus. It was predicted that the administration of isoprenaline would augment pre-existing anxiety in a manner similar to adrenaline (Schachter & Singer, 1962).

(c) Whereas these two stresses were standardized, the third was not, but was closer to real-life anxiety than the other two and consisted of the exposure of the subject to a phobic object or situation during the click sequence. Subjects were questioned before the experiment about specific fears, and where appropriate, these were reproduced in the test situation. Several subjects were excluded from the study because they had no phobic symptoms but only five of the thirty-two subjects had symptoms of sufficient severity to warrant a formal diagnosis of phobic anxiety. Of the thirty-two subjects tested, sixteen had a fear of snakes and were exposed to a pet boa constrictor, eight had social fears and had to face people staring at them during the experiment, four had rat phobia, two were phobic of spiders, one had a fear of loud noises and one an examination phobia. The animal phobics were tested in the presence of rats and spiders respectively, the loud noises were produced by the bursting of balloons and the subject with an examination phobia was played a tape recording in which the scene of a forthcoming examination was recreated and the likelihood of failure emphasized throughout. Exposure to the phobic stimulus was never longer than 10 min so that there was little likelihood of the phobias habituating over time (Watson, Gaind & Marks, 1971).

Measurements

General procedure. At each time of testing the measurements were made in the same order. Apart

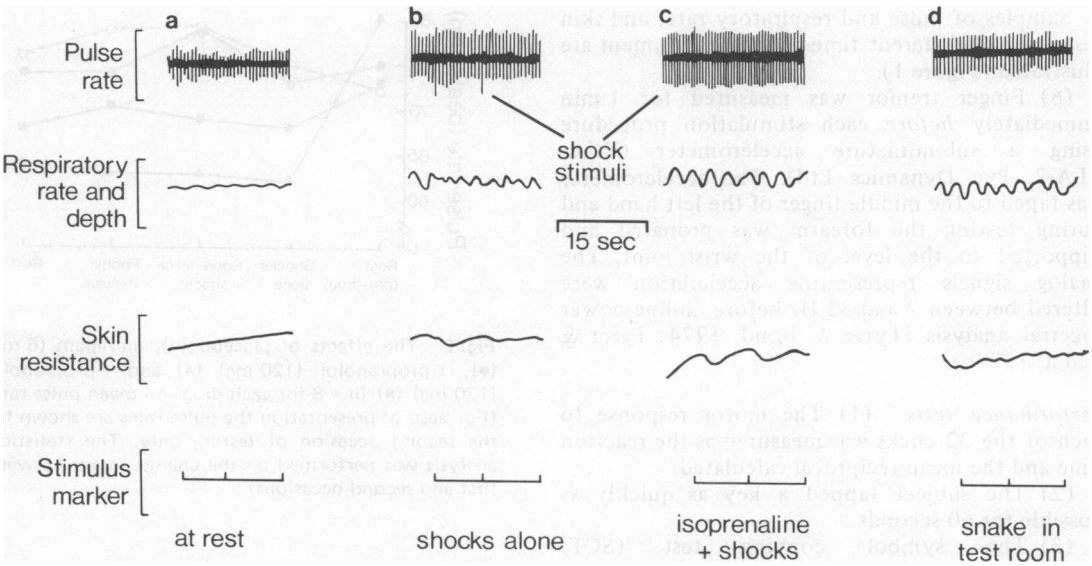

Fig. 1 Samples of polygraph recordings of physiological measurements, (a) at rest; (b) shocks alone; (c) isoprenaline + shocks; and (d) snake in test room.

from the tapping and symbol copying tests, which were given only on the first, third and fifth times of testing to reduce practice effects, each measure was recorded five times on each occasion. The order followed was (i) tremor measurement; (ii) reaction time task, during which the electroencephalogram, average evoked response, skin conductance, fluctuations in skin conductance, pulse and respiratory rates were all recorded simultaneously; (iii) tapping test; (iv) symbol copying test; and (v) rating scales.

Physiological measurements. All the physiological measurements were recorded with the subject sitting in a comfortable chair in a sound-protected room. Five were recorded simultaneously using a PDP-12A laboratory computer on-line (Bond & Lader, 1973):

(1) The electroencephalogram (EEG) was recorded from bipolar saline pad electrodes on the vertex and left temporal region (C_z and T_3 positions in the 10-20 system) during the reaction time task. Five-second epochs of the electroencephalogram, commencing 1 s after each click, were fed into four parallel band-pass filters with frequency ranges:

(a) 2.4-4 Hz; (b) 4-7.5 Hz;
(c) 7.5-13.5 Hz; (d) 13.5-26 Hz.

The samples were rectified and averaged to give the mean voltage in each wave band, and this was also expressed as a percentage of the total voltage between 2.4 and 26 Hz.

(2) The mean auditory evoked response (AER) was measured by averaging the 500 ms epochs of electroencephalogram following each of the 32 click stimuli. Four peaks were identified at different latencies (Bond & Lader, 1972, 1973), including two positive peaks (P_1 and P_2) and two negative ones (N_1 and N_2). The three peak to peak amplitudes (P_1-N_1, N_1-P_2 and P_2-N_2) were also quantified.

(3) Skin conductance (a measure of palmar sweat gland activity) and the number of spontaneous fluctuations in conductance were also measured during the reaction time task using a standard procedure (Lader & Wing, 1966; Bond & Lader, 1972). The mean skin conductance, adaptation in skin conductance and number of fluctuations per minute were all recorded.

(4) Heart rate was measured using ECG electrodes strapped to the upper forearm. From the paper tracing of the ECG the mean heart rate/min was calculated by counting the beats in the 120 s following the first auditory click.

(5) Respiratory rate was measured by using a glass thermistor (Fenwell Electronics Ltd) taped just below the nostril. During the recording the subject was asked to breathe through his nose only so that a polygraph tracing of respiratory rate was obtained during the reaction time task. The mean rate/min was calculated.

Samples of pulse and respiratory rate, and skin resistance at different times in the experiment are illustrated (Figure 1).

(6) Finger tremor was measured for 1 min immediately *before* each stimulation procedure using a sub-miniature accelerometer (Ether BLA-2, Pye Dynamics Ltd). The accelerometer was taped to the middle finger of the left hand and during testing the forearm was pronated and supported to the level of the wrist joint. The analog signals representing acceleration were filtered between 2 and 32 Hz before on-line power spectral analysis (Tyrer & Bond, 1974; Tyrer & Lader, 1974b).

Performance tests. (1) The motor response to each of the 32 clicks was measured as the reaction time and the mean reciprocal calculated.

(2) The subject tapped a key as quickly as possible for 60 seconds.

(3) The symbol copying test (SCT) (Kornetsky, Vates & Kessler, 1959) consists of a series of simple symbols copied as quickly as possible for 90 seconds. The test is one of motor speed and efficiency.

Ratings. (1) Immediately after the physiological and performance tests, the subject completed a mood rating inventory consisting of sixteen linear scales (Bond & Lader, 1974).

(2) Subjects also rated themselves on eight linear scales for bodily symptoms (Tyrer & Lader, 1973).

Results

Statistical analysis was carried out on the change scores between the first and second occasions. These were tested using a split plot analysis of variance to estimate both drug effects and drugs X test situation interactional effects against residual variance. The change scores were chosen for analysis in order to reduce the effects of known differences in inter-individual responses to stress, particularly at a physiological level (Lacey, 1950).

Physiological measurements

Electroencephalogram. There was a relative decrease in the amount of fast EEG activity (13.5-26 Hz) with placebo alone on the second occasion of testing, suggesting that this group of subjects was less anxious because of habituation. The only drug effects found concerned diazepam which induced a relative increase in fast EEG activity and a reduction in slow rhythms. However, the only change to reach significance was the drop in the 4-7.5 Hz waveband ($t = 2.78$; $P < 0.05$).

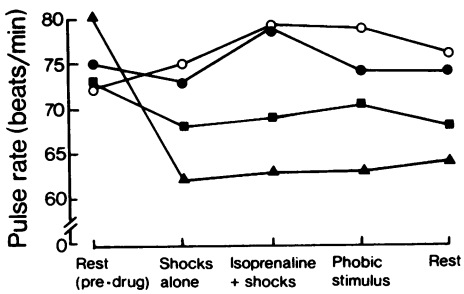

Fig. 2 The effects of placebo (○), diazepam (6 mg) (●), ±-propranolol (120 mg) (▲) and +-propranolol (120 mg) (■) ($n = 8$ for each drug) on mean pulse rate. (For ease of presentation the pulse rates are shown for the second occasion of testing only. The statistical analysis was performed on the change scores between first and second occasions).

Averaged auditory evoked response. Diazepam significantly increased the latency of the second component of the auditory evoked response (N_1) compared with placebo ($t = 2.4$, $P < 0.05$) and (±)-propranolol ($t = 2.9$, $P < 0.02$) and was also associated with a smaller P_1-N_1 amplitude than was placebo ($t = 2.82$, $P < 0.05$) and (±)-propranolol ($t = 4.13$, $P < 0.01$).

Skin conductance. None of the skin conductance variables showed any significant drug effects.

Pulse rate. As expected, there was a highly significant reduction in pulse rate in subjects on racemic propranolol when compared with placebo ($t = 4.77$, $P < 0.01$). (+)-Propranolol also significantly reduced pulse rate at two times of testing (Figure 2).

Respiration rate. Respiration rate showed no significant drug effects.

Finger tremor. Although there was a trend towards a reduction in the amount of tremor with racemic propranolol this did not reach significance.

Performance tests

Neither reaction time, tapping rate or symbol copying tests showed any drug effects, nor was there any consistent trend.

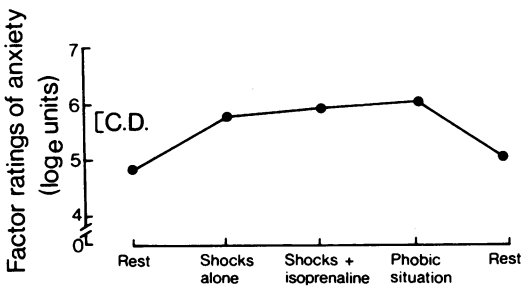

Fig. 3 Effects of stressful procedures on anxiety. The mean scores for the thirty-two subjects on the first (i.e. non-drug) occasion are shown. Differences between means greater than the critical difference (C.D.) are significant at the 0.05 level (Tukey's test) (Winer, 1962).

Rating scales

The rating scale of subjective mood consists of sixteen items. Factor analysis has been carried out on scores for five hundred individuals and revealed three factors, one of general cerebral functioning, another which can be described as a contentedness or pleasure factor, and a third factor of anxiety (Bond & Lader, 1974). The scores in the study described here were converted to these factors by multiplying by the appropriate loading coefficients and drug effects calculated for each one.

To establish whether subjects did in fact feel more anxious during the stressful part of the experiment a one-way analysis of variance was carried out on the scores for the anxiety factor on the first occasion. This confirmed that the phobic situation produced the most anxiety (as measured by these ratings) and that all three of the stress situations led to more anxiety than the rest situations ($F = 19.1$, d.f. 4, 124; $P < 0.001$) (Figure 3).

In the full analysis drug effects were shown only for the anxiety factor and then only during the 'shocks alone' and phobic situations. Diazepam was significantly more effective in reducing anxiety than the other drugs in the first of these situations and all three active drugs were more effective than placebo during the phobic situation ($F = 2.03$, d.f. 9, 84, $P < 0.05$).

Of the bodily symptom scales only one of the scales showed significant drug effects, namely, respiratory difficulty ($F = 3.52$; d.f. 3, 28, $P < 0.05$). Diazepam was again significantly more effective than the other agents in relieving this symptom.

Discussion

Of the four drugs used in this study diazepam had the greatest beneficial effects. In the dose used it was a successful anti-anxiety agent without producing sufficient sedation to impair performance or produce drowsiness. This finding was not unexpected but it serves as a yardstick by which to compare the other drugs. Neither of the stereoisomers of propranolol was significantly different from placebo (except in the phobic situation) and (±)-propranolol was not preferred to the (+)-isomer.

The results therefore differ somewhat from those of studies in anxious patients but are similar to previously reported negative findings in induced anxiety (Eliasch, Lager, Norrbäck, Rosen & Scott, 1967; Holmberg, Levi, Mathé, Rosen & Scott, 1967; Cleghorn, Peterfry, Pinter & Pattee, 1970; Stone, Gleser & Gottschalk, 1973). On the evidence of this study propranolol does not appear to have major anti-anxiety effects but it would be unwise to extrapolate from results in induced (normal) anxiety to pathological anxiety. Gottschalk, Stone & Gleser (1974) suggest that the arousal and maintenance of anxiety are controlled by different mechanisms and that propranolol may only be effective in relieving maintained anxiety. This notion accords with the view that the somatic symptoms of anxiety reinforce pre-existing anxiety (Richter, 1940; Breggin, 1964) and treatment with β-adrenoceptor blocking drugs may reduce anxiety by preventing this feedback. However, as there are marked differences in the responses of anxious patients to beta-blockade (Tyrer & Lader, 1974a) this explanation may need to be qualified.

It is notable that propranolol did not alter bodily symptom ratings to any extent and so subjects seemed unaware of the peripheral effects of β-adrenoceptor blockade. They also concluded, presumably falsely, that diazepam improved their respiratory function. Thus it appears that autonomic symptoms experienced in induced anxiety do not reflect physiological changes accurately. Tyrer (1973) has suggested that subjects with normal anxiety do not regard their bodily symptoms as important because they are usually fully aware of the cause of their anxiety. Their attention is directed towards the source of the anxiety rather than the changes going on in their bodies as a consequence of the anxiety. The results presented here support this view and offers an explanation for the differing findings in psychiatric patients with anxiety. In many such patients there is greater attention paid towards bodily symptomatology because the source of the stimulus producing anxiety is often unknown.

Changes in these symptoms are therefore invested with greater significance than in normal anxiety.

None of the ratings or performance tests suggested that (±)-propranolol or its (+)-isomer produced any central effects in the dosage used. This is in keeping with previous studies using (±)-propranolol (120 mg) (Dunleavy, Maclean & Oswald, 1971; Lader & Tyrer, 1972).

The physiological changes shown in the experiment confirm that diazepam was acting as a central depressant. The relative increase in fast activity in the electroencephalogram is characteristic of sedative agents (Fink, 1969), as in the increase in latency and the reduction in amplitude of the P_1N_1 component of the evoked response (Bergamasco, 1967; Jarvis & Lader, 1971). The peripheral physiological changes produced by diazepam were insignificant by comparison. Racemic propranolol, on the other hand, produced peripheral changes but no central ones. There was certainly no evidence of sedation on any of the physiological measures and there were no similarities between the effects of propranolol and diazepam. (+)-Propranolol was similar in many of its actions to the racemic mixture. The significant reduction in pulse rate may be explained by the small amount of intrinsic β-adrenoceptor blocking activity that (+)-propranolol possesses. This would be equivalent to about (±)-propranolol (2 mg) in the dose used; sufficient to produce significant β-blockade in the circumstances of the experiment.

Taken in conjunction, the physiological and psychological findings of this experiment show that diazepam and propranolol have different effects. Major alteration in autonomic response by beta-blockade produced little in the way of affective change and subjects were essentially unaware of these pharmacological effects. Diazepam, although having no important peripheral physiological effects in this study, led to a significant lessening of anxiety by central pharmacological action. Comparison between the effects of propranolol and diazepam in the dosage used shows that propranolol cannot be regarded as a centrally acting drug. Its effects in this study also make clear that evaluation of its action in normal volunteers is no substitute for clinical testing in morbidly anxious patients, in whom the genesis and reinforcement of anxiety appears to depend on different mechanisms.

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Reprint requests should be addressed to P.J.T.

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