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A COMPARISON OF SOME PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF PROPRANOLOL AND DIAZEPAM IN NORMAL SUBJECTS

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1 Some central and peripheral effects of orally administered propranolol (60 mg), diazepam (5 mg) and placebo were compared in normal subjects.

2 The central effects measured were changes in magnitude of the contingent negative variation (CNV) and subjective anxiety ratings; the peripheral effects were changes in heart rate, blood pressure, galvanic skin response and hand steadiness.

3 After diazepam there was a decrease in CNV magnitude and in the level of subjective anxiety; there was a slight fall in blood pressure but little change in heart rate.

4 After propranolol, on the other hand, there was no significant change in CNV magnitude or anxiety rating, but a significant fall in heart rate and systolic blood pressure.

5 It is concluded that, at the dosage used, propranolol, unlike diazepam, does not affect the central mechanisms determining CNV magnitude or subjective anxiety. The relationship of this finding to the use of β-adrenergic receptor blockers in clinical anxiety states is discussed.

Introduction

The question of whether propranolol and other β-adrenoceptor blocking drugs have effects on the central nervous system in man remains controversial (Granville-Grossman, 1974). Central effects of these drugs are suggested by the findings that they may cause increases in reaction time and impairment of hand-eye co-ordination in normal subjects (Bryan, Efiong, Stewart-Jones & Turner, 1974), that they may improve the mental state as well as relieve the somatic symptoms in anxiety (Nordenfelt, 1965; Frohlich, Dustan & Page, 1966; Frohlich, Tarazi & Dustan, 1969; Suzman, 1971), that patients taking propranolol sometimes develop hallucinations (Zacharias, 1971) and that they are sometimes of value in schizophrenia (Yorkston, Zaki, Malik, Morrison & Havard, 1975). On the other hand, propranolol has no effect on normal sleep EEG patterns and dexamphetamine-induced sleep disturbances (Dunleavy, Maclean & Oswald, 1971), on EEG responses to auditory stimuli, psychomotor function tests and mood ratings in normal subjects (Lader & Tyrer, 1972), nor on subjective anxiety under induced stress in normal individuals (Tyrer & Lader, 1974b) and in chronic anxiety states (Tyrer & Lader, 1974c). Several authors attribute the beneficial effects of β-adrenoceptor blocking drugs in certain types of anxiety to peripheral β-adrenoceptor blockade (Granville-Grossman, 1974; Tyrer & Lader, 1974a, 1974b). By contrast, the anxiolytic effects of diazepam, as well as other benzodiazepines and barbiturates, undoubtedly result from central depressant actions as shown by the reduction in subjective symptoms of anxiety and EEG changes characteristic of drug-induced sedation (Tyrer & Lader, 1974a, b and c).

An objective measure which has been shown to be of value in the investigation of central effects of drugs (Ashton, Millman, Telford & Thompson, 1974, 1975; Tecce, Cole & Savignano-Bowman, 1975) is the electroencephalographic response known as the contingent negative variation (CNV) (Walter, Cooper, Aldridge, McCallum & Winter, 1964). This consists of a slow electronegative potential which develops at the vertex relative to the mastoid between a warning signal and an imperative signal requiring a response from the subject. The CNV probably arises in subcortical regions, including the reticular activating system and possibly the limbic system, which through neural connections, elicit potential changes in the cortex that can be measured from scalp electrodes

(Haider, Ganglberger & Groll-Knapp, 1968; Rebert, 1972; Rebert & Knott, 1970; McCallum, Papakostopoulos, Gombi, Winter, Cooper & Griffith, 1973). The nervous regions involved in the genesis of the CNV are known to be sensitive to many centrally acting drugs, and CNV magnitude is consistently increased by central stimulant drugs such as caffeine, pemoline and amphetamine and decreased by central depressant drugs such as nitrazepam, flurazepam, alcohol, chlorpromazine and barbiturates (Ashton *et al.*, 1974; Ashton *et al.*, 1975; Tinklenberg, 1972; Hablitz & Borda, 1973; Tecce & Cole, 1974; Kopell, Tinklenberg & Hollister, 1972; Kopell, Wittner, Lande, Wolcott & Tinklenberg, 1974; Tecce *et al.*, 1975). Changes in CNV magnitude induced by drugs can be correlated with subjective ratings of central function, such as mood and anxiety scales, and with other physiological variables such as reaction time and autonomic nervous system activity.

Since the CNV is a sensitive indicator of central stimulant and depressant effects of drugs, showing changes in magnitude with doses too small to produce subjective effects (Ashton *et al.*, 1974; 1975), it seemed likely that a central effect of propranolol, whether stimulant or depressant, would be reflected by a change in CNV magnitude. The effects of propranolol on the CNV have not been investigated previously. The present paper reports the results of two experiments designed to compare the central and peripheral effects of orally administered propranolol and diazepam in normal subjects. In the first experiment, the effects of these drugs and a placebo on CNV magnitude, reaction time, heart rate and blood pressure were measured. In the second experiment the effects of these drugs and caffeine on subjective anxiety, hand steadiness, heart rate and galvanic skin response (GSR) under stress were measured, as well as extraversion/introversion and neuroticism scores for each subject.

Methods

The two experiments were carried out as part of a practical course in pharmacology for medical students who acted as subjects and also carried out some of the measurements. Approval was obtained from the appropriate Ethical Committee. The drugs were given orally with 200 ml of hot water to speed absorption in the following doses: propranolol (60 mg); diazepam (5 mg); caffeine citrate (500 mg); placebo: lactose tablets. All tests took place between 09.00 h-11.00 h and all subjects had eaten their normal breakfast; none were taking any other medication. The drugs were randomly allocated and neither the subjects nor the students who acted as observers knew which drug had been given until the end of the experiment.

Experiment 1

Measurements 1 CNV was measured as described by Ashton *et al.* (1974) with slight modifications. Briefly, subjects were presented with series of paired signals. The warning signal was a brief tone (frequency, 4000 Hz; duration, 20 ms) and the imperative signal was a lower tone of longer duration (frequency, 1500 Hz; duration 400 ms) delivered through a loudspeaker. The subject was required to press a button in response to the imperative signal; this stopped the tone and gave a measure of reaction time. The paired warning and imperative signals were separated by an interval of 1.25 s and were presented at random intervals (4-8 s) in a series of ten, each series lasting 1 min 10 s. The subjects were instructed to keep their eyes fixed on a mark throughout each series in order to minimize eye movements. The EEG was derived between the left mastoid and vertex positions from two silver/silver chloride stick-on electrodes and was amplified by a Devices M19 recorder on DC setting with a purpose-built operational amplifier with a time constant of 9 s and a zero offset of 60 μv; on earth electrode was placed on the right mastoid. The output was fed into a PDP8 on-line computer and the average response to each series of ten paired signals was traced out by an X-Y recorder. The magnitude of the CNV thus obtained for each series was measured in terms of area and expressed in μv sec.
2 Reaction time was recorded on a digital counter which was activated by the onset of the imperative tone and stopped by the subject's pressure of a button-switch held in his preferred hand. The mean reaction time for each series of ten signals was recorded in ms.
3 Heart rate was recorded manually from the radial pulse.
4 Blood pressure was measured automatically by a Roche Arteriosonde recorder for the subjects taking propranolol and by a Godart Haemotonograph for the subjects taking diazepam.

Procedure The procedure was similar to that described by Ashton *et al.* (1974). The experiment was repeated at weekly intervals with different students and usually there were three subjects of whom one took propranolol, one diazepam and one placebo. The subjects sat together in a subject room and, after a brief standard explanation of the procedure, the scalp electrodes were applied. The subjects then had a practice run, each subject

responding in turn to a series of ten paired signals. Between turns, the subjects read light literature and did not attend to the other subjects' performance. Beside each subject was seated an observer who counted the radial pulse for 30 s every minute. Observers taking the blood pressure sat at the back of the room and recorded this serially on two of the subjects, taking one reading while the subject was responding to the series of tones ('active' reading) and one reading while the subject was relaxing between series ('resting' reading). The recording apparatus for EEG and reaction time was housed in an adjacent control room, in communication with the subject room through a one-way window and via closed circuit television. From here it was possible for the staff in charge of the experiment to ensure that the subjects and observers were following the instructions correctly and that the subjects maintained eye-fixation during the signal series. Oral communication was possible through an intercom system.

After a resting period of 45 min, which included the practice run for the subjects and observers, the drugs were administered and recordings commenced immediately. The CNV series were repeated every 10 min for each subject and readings were continued until all subjects had responded to eight series, i.e. 70-80 min after taking the drug. At the end of the experiment subjects were interviewed to elicit information concerning any subjective effects associated with the drugs.

Experiment 2

Measurements 1 Personality data were assessed on the Eysenck Personality Inventory (Eysenck & Eysenck, 1964).
2 Anxiety was self-rated on an analogue scale. This consisted of a 100 mm horizontal line in which 0 mm represented 'not at all anxious' and 100 mm represented 'very anxious'. Subjects were instructed to draw a vertical mark across the scale at the point which approximated their level of anxiety. The position of the subjects' rating on the horizontal line was measured in mm.
3 Standing heart rate was counted manually at the radial pulse.
4 GSR was recorded from the palmar skin response (Venables & Sayer, 1963) and measured as the number of spontaneous deflections per minute.
5 Hand steadiness was measured by means of a stylus containing a photosensitive resistor at its tip. The tip of the stylus was held over a target consisting of a pin-point of light. When the tip of the stylus moved fractionally away from the target, as a result of hand movement, a digital counter was activated and a tone started. Return of the stylus to the correct position turned off the counter and the tone. Hand steadiness was recorded as the total time off-target in one minute.
6 Stress was induced by requiring the subjects to answer, in front of their peers, questions on mental arithmetic or on anatomy and physiology. The questions were posed by the teacher while the subject was standing, and continued for 1 minute.

Procedure This experiment was also repeated at weekly intervals with groups of six to eight students who each took one of the following drugs: propranolol, diazepam, caffeine or placebo. After a brief explanation of the procedure, baseline measurements of subjective anxiety, heart rate, GSR and hand steadiness were recorded. After completion of these, the drugs were administered randomly. The subjects then rested for 60 min, during which time they completed the personality inventory.

After the resting period, the subjects were told that they would shortly be subjected to stress in the form of an oral examination. While expecting this stress, they again completed the anxiety rating; during the stress, standing heart rate and GSR were again measured, and immediately afterwards the measurement of hand steadiness was repeated. Thus, while the first and last measurements were not actually carried out during the period of on-going stress, it was felt that anticipatory anxiety in the minute prior to oral examination and carry-over effects in the minute immediately following it were sufficient to ensure that the subject was in fact under some stress during all measurements. Unfortunately the time limitations of the practical class made it impossible to measure, in addition, the effects of the drugs when the subjects were not under stress.

Results

Experiment 1

In this experiment fourteen subjects (nine males and five females) took diazepam (5 mg); fourteen subjects (seven males and six females) took propranolol (60 mg) and eight subjects (five males and three females) took placebo tablets.

CNV The results for the three groups of subjects are shown in Figure 1. A fall in CNV magnitude occurred after diazepam: mean CNV magnitude in the sixth and seventh series (approximately 50 and 60 min after taking the drug) was significantly lower than the mean value in series 1 (0-5 min

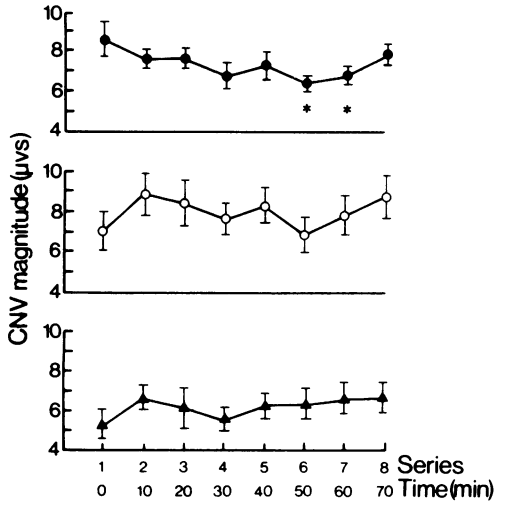

Figure 1 Effect of diazepam (●, 5 mg, $n = 14$), propranolol (○, 60 mg, $n = 13$) and placebo (▲, $n = 8$) on CNV magnitude. Each point is the mean (± s.e. mean) of subjects measured during each CNV series. * Denotes significant difference from mean value in series 1 ($P < 0.05$, Student's t-test, one tailed).

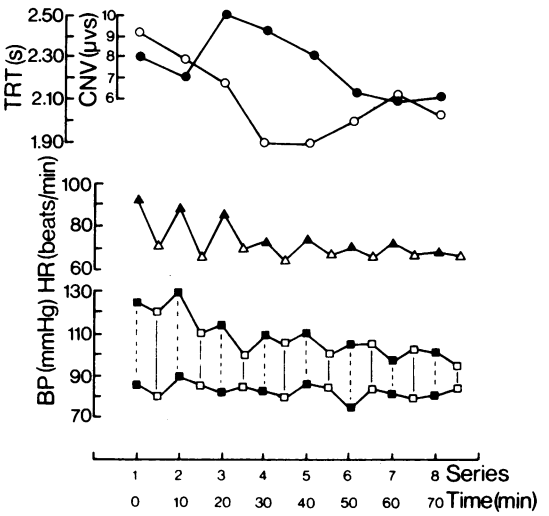

Figure 2 Effect of diazepam (5 mg) on CNV magnitude (●), reaction time (○, TRT), heart rate (▲, △ HR) and blood pressure (■, □ BP) in one subject. ▲, ■ = 'active' readings; △, □ = 'resting' readings. Note reciprocal relationship between CNV and TRT, and decrease in 'active' levels of HR and systolic BP (see text).

after the drug) when little if any of the drug would have been absorbed (Student's t-test). The results with diazepam are very similar to those previously reported with nitrazepam (Ashton *et al.*, 1974). However, although eleven of the fourteen subjects showed a clear fall in CNV magnitude after diazepam, three subjects showed an increase. These three all stated that they felt nervous at the start of the experiment, while after the drug they felt calmer and more able to concentrate. In addition, all three had a low initial CNV magnitude in series 1 (mean 5.83 μv s compared with a mean of 9.36 μv s in the other eleven subjects). A small CNV has previously been noted in anxious and distracted subjects (McCallum & Walter, 1968; Timsit-Barthier, Delaunoy, Koninckx & Rousseau, 1973) and in these subjects the effect of diazepam could well be to increase CNV magnitude by lessening anxiety and allowing better concentration. Four subjects showed an initial slight rise in CNV magnitude over the first 20-30 min followed by a fall at 40-45 min. An example of such a subject is shown in Figure 2. Thus these results suggest that diazepam in this dosage may have a biphasic effect on CNV magnitude: a stimulating effect depending on the level of anxiety and possibly on the amount of drug absorbed, and a depressant effect similar to that of nitrazepam (2.5 mg).

In contrast with diazepam, there was no significant alteration in CNV magnitude after either propranolol or placebo.

Reaction time There was little change in mean reaction time after any of the drugs and no significant differences between either drug and placebo. There was also no significant overall correlation between reaction time and CNV magnitude although many individual subjects appeared to show an inverse relationship between size of CNV and length of reaction time, so that quicker reaction times occurred when the CNV was larger and vice versa. This apparent relationship for one subject is illustrated in Figure 2. These findings are in accordance with those of Papakostopolous & Fenelon (1975).

Heart rate The mean heart rates for the subjects who took diazepam and propranolol are shown in Figure 3. 'Active' heart rate (measured while the subjects were pressing the reaction time button during the CNV series) decreased significantly during the experiment in both groups in series 5-8. Lessening of anxiety with familiarization as the experiment proceeded may have contributed to the fall in heart rate. Unfortunately, it was not possible to make enough measurements on the

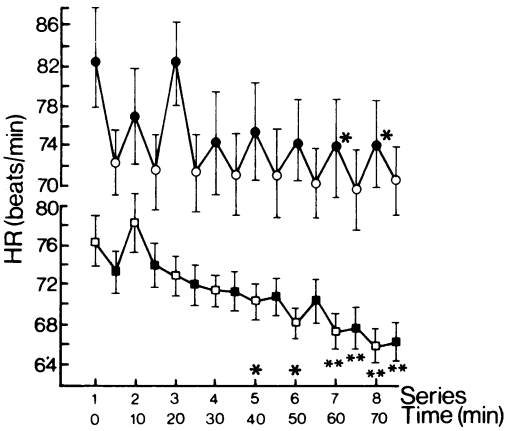

Figure 3 Effects of diazepam (●, ○, 5 mg, $n = 9$) and propranolol (■, □, 60 mg, $n = 14$) on heart rate. ●, ■ = 'active' readings; ○, □ = 'resting' readings. Each point is the mean (± s.e. mean) of subjects measured during and between each CNV series. Asterisks denote significant differences from mean value in series 1 (* $P < 0.05$; ** $P < 0.01$, Student's t-test).

placebo subjects (heart rate recorded on only two subjects) for an adequate comparison to be made, but the subjects on propranolol had a more marked fall than those on diazepam. 'Resting' heart rate (measured while the subjects were resting between CNV series) also decreased significantly in the subjects on propranolol, but altered little in the subjects on diazepam.

The 'active' heart rate was higher than the 'resting' heart rate in the subjects on diazepam and also in the two subjects who took placebo, but this trend appeared to be reversed after propranolol, possibly because β-adrenoceptor blockade was more effective when sympathetic tone was increased during the active periods. The overall changes in mean 'active' and mean 'resting' heart rates are shown in Figure 3. In some subjects on diazepam there was a reduction of the rise in 'active' heart rate during series 5-8 at the same time as the depressant effect on the CNV, as illustrated in Figure 2. A similar phenomenon has been observed before in subjects taking oxypertine who showed a decreased rise in heart rate during mental arithmetic during the period of drug action (Ashton, Savage, Telford & Thompson, 1972). This effect was ascribed to a central 'tranquillizing' action of the drug.

Blood pressure Mean systolic and diastolic blood pressures for the subjects who took diazepam and propranolol are shown in Figure 4. Unfortunately it was not possible to measure blood pressure in the subjects on placebo. Both 'active' and 'resting' systolic blood pressure decreased significantly after both drugs from series 4-8 compared with series 1. 'Active' systolic pressure tended to be higher than 'resting' systolic pressure in the subjects on diazepam although some subjects showed a flattening out of this difference as noted for the heart rate (see Figure 2). 'Resting' systolic pressure tended to be higher than 'active' systolic pressure in the subjects on propranolol, presumably, as in the case of heart rate, because β-blockade was more effective when there was increased sympathetic tone. The fall in systolic pressure resulted in a lower pulse pressure after propranolol, since there was little change in diastolic pressure in these subjects. A slight fall in 'active' distolic blood pressure occurred after diazepam.

Subjective effects Most subjects experienced no subjective effects. Six reported drowsiness, but this was equally distributed between those who took diazepam, propranolol and placebo. Three subjects felt more relaxed and better able to concentrate after diazepam as mentioned above (see Results, Experiment 1, CNV), and two felt stimulated after propranolol.

Experiment 2

In this experiment twenty-seven subjects (seventeen males and ten females) took diazepam (5 mg); twenty-seven subjects (sixteen males and eleven females) took propranolol (60 mg); twenty-nine subjects (seventeen males and twelve females) took caffeine citrate (500 mg), and twenty-seven subjects (fifteen males and twelve females) took placebo.

Personality data The mean scores for extraversion (11.71) and neuroticism (9.93) on the Eysenck Personality Inventory fell within the normal range for medical students (Eysenck & Eysenck, 1964). There was a significant correlation between the scores for neuroticism and for self-rated anxiety (before drug) ($r = 0.413$, d.f. = 100, $P < 0.001$), but no significant correlations between neuroticism or self-rated anxiety and heart rate, GSR, hand-steadiness or response to drugs. It would appear that self-rated subjective anxiety does not necessarily correlate with objectively observed peripheral manifestations of raised sympathetic tone often associated with anxiety. There was also no apparent correlation between extraversion and

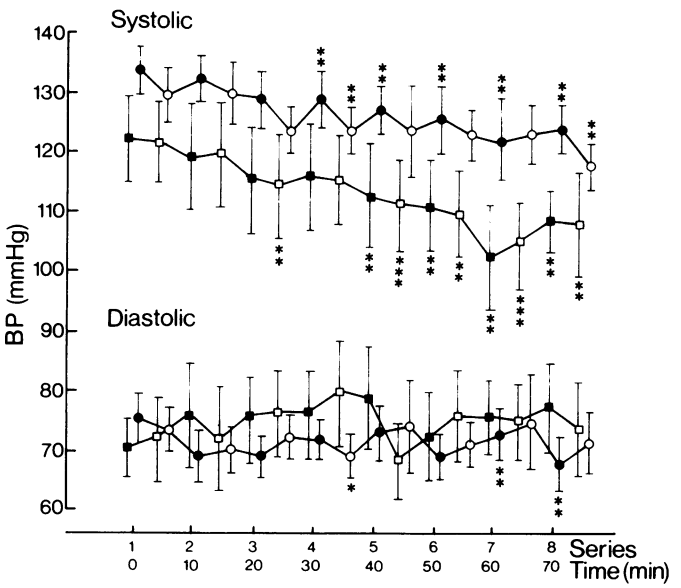

Figure 4 ,Effect of diazepam (●, ○, 5 mg, $n = 14$) and propranolol (■, □ 60 mg, $n = 14$) on blood pressure. ●, ■ = 'active' readings; ○, □ = 'resting' readings. Each point is the mean (± s.e. mean) of subjects measured during and betweeen each CNV series. Asterisks denote significant differences from mean value in series 1 (* $P <$, 0.05; ** $P < 0.01$; *** $P < 0.001$, Student's t-test).

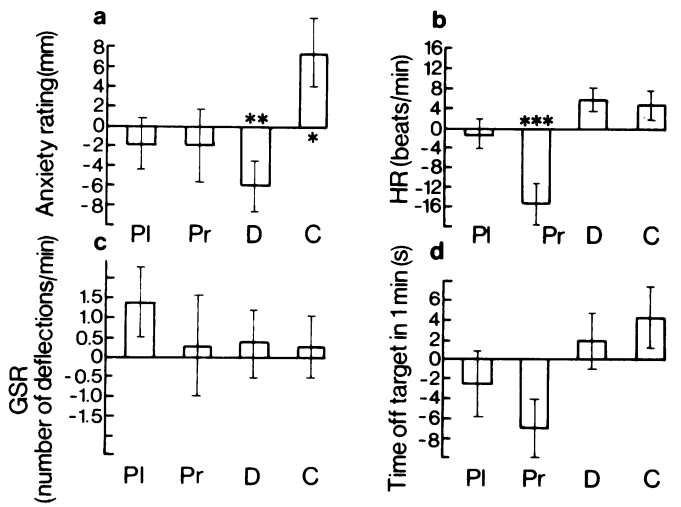

Figure 5 Effects of placebo, (Pl, $n = 27$), propranolol (Pr, 60 mg, $n = 27$), diazepam (D, 5 mg, $n = 27$), and caffeine citrate (C 500 mg, $n = 29$) on (a) anxiety rating, (b) heart rate, (c) GSR and (d) hand steadiness. Each bar represents the mean of the difference between pre- and post-drug measurements (± s.e. mean). Asterisks denote significant differences between pre- and post-drug measurements (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, Student's t-test, one-tailed).

CNV magnitude, although it was thought possible that introverts might have larger CNVs than extraverts because of their postulated greater 'intrinsic cortical arousal' (Eysenck, 1967).

Anxiety ratings The mean differences in the scores for self-rated anxiety measured before and after the drugs are shown in Figure 5a. After placebo, anxiety ratings did not rise in spite of the imposed stress during the post-drug period. This was probably because the initial laboratory situation, during which the 'baseline' (pre-drug) readings were taken, was itself stressful to medical students, as many of them later commented. Mean ratings before and after placebo were 26.18 ± 16.30 and 22.15 ± 15.99 (no significant difference). However, after diazepam there was a significant fall in anxiety ratings (mean pre-drug rating: 23.41 ± 13.36; mean post-drug rating: 16.19 ± 12.55; $t = 2.9811$, d.f. = 28, $P < 0.01$). There was no significant difference between the mean pre- and post-drug ratings after propranolol: 20.96 ± 13.57 and 19.57 ± 16.51 respectively. Anxiety levels after caffeine were higher than before the drug (mean pre-drug rating: 18.0 ± 15.90; mean post-drug rating: 23.27 ± 17.5; $t = 1.9350$, d.f. = 28, $P < 0.05$). Comparisons between the drugs showed significant differences in the pre- and post-drug changes in anxiety ratings between caffeine and placebo ($P < 0.05$), and between diazepam and caffeine ($P < 0.01$), while there was no significant difference in the change pre- and post-drug between propranolol and placebo or caffeine.

These results thus indicate that, in the present circumstances, subjective anxiety rating was decreased by diazepam, increased by caffeine and not affected by propranolol or placebo.

Heart rate Mean differences in heart rate measured before and after the drugs are shown in Figure 5b. There was no significant difference in the pre- and post-drug levels for placebo, but there was a marked fall in heart rate after propranolol from 86.03 ± 11.94 to 71.11 ± 11.64 beats/min ($t = 6.2823$, d.f. = 25, $P < 0.001$), and a slight rise after diazepam and caffeine. Comparisons between drugs showed that the change after propranolol was significantly greater than that after placebo ($t = 3.6786$, d.f. = 52, $P < 0.001$), while the changes after diazepam and caffeine were not significantly different from that after placebo. Thus propranolol caused a drop in heart rate under the conditions of this experiment, while diazepam and caffeine had no appreciable effect.

GSR There was little change in spontaneous GSR deflections during the experiment (Figure 5c) although the post-drug levels were all slightly higher than the pre-drug levels. There were no significant differences between drugs.

Hand steadiness Differences between the pre and post-drug measures of hand steadiness were not significant for any of the drugs. However, mean time off target increased during the post-drug period after caffeine, decreased after propranolol and changed little after placebo or diazepam (Figure 5d).

Discussion

Despite the obvious limitations of a practical class as an experimental situation for investigating drug effects, a clear difference between the actions of diazepam and propranolol emerged from this study. Diazepam had a significant overall effect in decreasing CNV magnitude in Experiment 1 and in decreasing subjective anxiety ratings in Experiment 2. By contrast, propranolol had no effect on the CNV and no effect on self-rated anxiety at a dose which produced peripheral βadrenoceptor blockade as evidenced by a fall in heart rate in Experiments 1 and 2 and a fall in systolic blood pressure in Experiment 1. These results therefore suggest that propranolol, in the dosage used, does not affect the central mechanisms determining CNV magnitude or subjective anxiety, and support the conclusion of Tyrer & Lader (1974a, b and c) that any therapeutic effects in anxiety neurosis are due to peripheral rather than central actions. Diazepam clearly had central actions in depressing CNV magnitude and decreasing subjective anxiety, with a much smaller effect on heart rate and blood pressure than propranolol.

It is possible that different dosages of the drugs may have different effects. Larger doses of propranolol, as used in schizophrenia (Yorkston *et al.*, 1974), or multiple dosage as opposed to a single dose, may have central effects, possibly mediated by other mechanisms than β-adrenoceptor blockade, and these doses might also affect the CNV. Larger doses of diazepam are likely to have a greater depressant effect on the CNV, like that of nitrazepam (Ashton *et al.*, 1974). On the other hand, a smaller dose of diazepam might have produced overall stimulant effects on the CNV. Small doses of benzodiazepines have been reported to cause increased aggressiveness in certain circumstances (British Medical Journal, 1975), and some subjects in the present experiments showed either an increase in CNV magnitude or a biphasic effect. Bidirectional effects on the CNV have been shown

to occur after several other drugs including nicotine (Ashton *et al.*, 1973, 1974, 1975), amphetamine (Teece & Cole, 1974) and cannabis (Low, Klonoff & Marcus, 1973; Braden, Stillman & Wyatt, 1974), and biphasic effects on behaviour are well known to occur with alcohol and barbiturates. In the case of nicotine, the direction of the effect on the CNV was influenced by the dose and the personality of the subject (Ashton *et al.*, 1973, 1974, 1975). In the case of diazepam, it may in addition be influenced by the initial level of anxiety which itself influences CNV magnitude (McCallum & Walter, 1968; Timsit-Berthier *et al.*, 1973). In this context it would be interesting to know how much limbic arousal systems (Routhenberg, 1968) as well as reticular arousal systems (Rebert, 1972) contribute to the magnitude of the CNV.

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