A COMPARISON OF SOME PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF MOTIVAL (FLUPHENAZINE AND NORTRIPTYLINE) AND DIAZEPAM IN NORMAL SUBJECTS

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1 The effects in normal subjects of a single oral dose of Motival (one tablet, containing fluphenazine 0.5 mg and nortriptyline 10 mg) on the contingent negative variation (CNV), reaction time, heart rate, blood pressure and self-rating scales for alertness, anxiety, tension, detachment and depression were compared with those of diazepam (5 mg and 7.5 mg) and placebo or propranolol (60 mg).

2 After diazepam (5 mg: twelve subjects and 7.5 mg: seven subjects) there was a significant decrease in CNV magnitude while after Motival (twelve subjects) there was no significant alteration in CNV magnitude compared to placebo.

3 After diazepam (7.5 mg: seven subjects) there was also a fall in subjective ratings for alertness and tension; this fall was significantly greater than the changes after Motival which did not reduce subjective ratings for alertness or tension below 'average' levels. Anxiety ratings did not differ significantly between the two drugs. Changes after propranolol were intermediate in all scales.

4 It is concluded that under these conditions diazepam caused central nervous system depression while Motival did not.

Introduction

The most frequently prescribed drugs in general practice for the common syndrome of mixed anxiety/depression are the benzodiazepines, but recently there has been increasing use of pharmaceutical products containing neuroleptic/antidepressant mixtures. One such preparation is Motival (Squibb) which contains fluphenazine (0.5 mg) and nortriptyline (10 mg) in each tablet. The benzodiazepines are known to produce sedation in some subjects, but appreciable central nervous system depression with decreased alertness is obviously undesirable in ambulant patients and may possibly be a factor in road accidents. Little information is available about possible central nervous system depressant actions of neuroleptic/antidepressant mixtures although Glegg & Turner (1971) found no effect on critical flicker frequency, disc dotting, serial subtraction and reaction time after single and multiple dose administration of fluphenazine 0.5 mg combined with nortriptyline 10 mg or 20 mg, diazepam 2 mg and placebo in normal subjects. The purpose of the present study was to make a further comparison of some of the central effects of a single dose of Motival and diazepam in normal subjects. The investigation was carried out as a preliminary step before comparing the effects of multiple dosage of these drugs in patients with anxiety/depression.

The measures chosen to assess central effects of the

drugs were the contingent negative variation (CNV), reaction time, and a subjective rating scale for alertness, anxiety, tension, detachment and depression. The CNV was measured because it has been shown to be a sensitive objective indicator of stimulant and depressant effects of drugs on the brain (Ashton, Millman, Telford & Thompson, 1975). CNV magnitude is increased by the central stimulant drugs caffeine, pemoline and amphetamine and decreased by the central depressant drugs barbiturates, alcohol, chlorpromazine, nitrazepam, diazepam and flurazepam (Ashton, Millman, Telford & Thompson, 1974; 1975; Tinklenberg, 1972; Hablitz & Borda, 1973; Tecce & Cole, 1974; Kopell, Tinklenberg & Hollister, 1972; Kopell, Wittner, Lande, Wolcott & Tinklenberg, 1974; Tecce, Cole & Savignano-Bowman, 1975). CNV changes can be correlated with subjective rating scales and measures of autonomic activity (Ashton *et al.*, 1976) which provide further information of clinical relevance in the use of psychotropic drugs.

Subjects and drugs

The investigation was carried out as part of two practical classes in pharmacology for medical students who acted as subjects and also carried out some of the

Figure 1 Mood rating scales for tension, alertness, depression, detachment and anxiety. (*Average so defined refers to the subject's own average).

MOOD RATING SCALES

Instructions

Please rate yourself on *each* of the scales below according to how you feel. Mark an X on the vertical line at a level between 0 and 200 which represents your present state of feeling on each scale. The middle value of 100 represents a normal or average state. For example, on the TENSION scale, a mark at 100 would mean you felt neither tense nor relaxed, but just average on that scale.*

Use the left hand line of each scale on the 1st rating occasion and successive lines for later occasions. If, initially, you felt about 25% 'more tense' than normal (that is, slightly tense) you would place an X near the 125 level on the 1st line of the TENSION scale. On the next occasion you may feel differently and adjust your mark accordingly, using the next line. Ratings of 0 and 200 represent the extremes (most and least) you could feel on any scale. Before starting, please read the scale definitions.

Scales

	Tension	Alertness	Depression	Detachment	Anxiety	()
200						
175						
150						
125						
100						
75						
50						
25						
0						

very much above average
much above average
slightly above average
AVERAGE ---
slightly below average
much below average
very much below average

Occasions: 1 2 3 4 5 1 2 3 4 5 1 2 3 4 5 1 2 3 4 5 1 2 3 4 5 1 2 3 4 5

Scale Definitions

	Above Average		Below Average
TENSION	tense, on-edge, keyed-up, impatient, restless	v	relaxed, calm, patient, at-ease, tolerant
ALERTNESS	alert, bright, active clear-headed, attentive	v	dopey, lethargic, slow, inattentive, muddled, bored.
DEPRESSION	sad, unhappy, pessimistic, quiet, weepy	v	happy, elated, hopeful, optimistic, joyful
DETACHMENT	detached, uninvolved, impersonal, unreal	v	involved, sociable, concerned, aware of detail
ANXIETY	worried, jittery, afraid, wary, lacking confidence	v	assertive, brave, confident, trusting, self-assured

Describe any other mood changes experienced today:

.....

measurements. Approval was obtained from the appropriate Ethical Committee. The drugs were given orally with 200 ml of hot water to speed absorption. In one practical course twelve subjects (ten males; two females) took one tablet of Motival and seven (five males; two females) took diazepam, 7.5 mg. In another course, twelve subjects (seven males; five females) took diazepam 5 mg and twelve (nine males; three females) took placebo: lactose tablets. In both classes twelve subjects also took propranolol (60 mg); the results with this drug have already been reported (Ashton *et al.*, 1976). 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.

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 (6–10 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 μ v; an earth electrode was placed on the right mastoid. The output was fed into a PDP8 on-line computer and the averaged 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 μ v s.
2. Reaction time was recorded on a digital counter which was activated by the onset of the imperative tone and stopped by the pressure of the subject on 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 in most subjects.
4. Blood pressure was measured automatically by a

Roche Arteriosonde recorder for the subjects taking Motival and by a Godart Haemotonograph for the subjects taking diazepam. Unfortunately, it was not possible to measure blood pressure in the subjects taking placebo.

5. Subjective rating scale: subjects were asked to rate themselves for tension, alertness, depression, detachment and anxiety on a scale marked from 0 to 200. The scales used and the instructions given are shown in Figure 1. Only the subjects taking Motival and diazepam (7.5 mg) and one group of those taking propranolol completed these rating scales.

Procedure

The experiments were repeated at weekly intervals with different students. There were usually three subjects in each session who sat together in a subject room. After a brief standard explanation of the procedure, the scalp electrodes were applied. The subjects then had a practice run, each responding in turn to a series of the paired signals. Between series, the subjects read light literature and did not attend to the other subjects' performance. Observers measuring heart rate, and blood pressure sat in the same room. 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, subjects were asked to fill in the first column of the subjective rating scale. The drugs were then 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 8 series, i.e. 70–80 min after taking the drug. Subjective rating scales were filled in at 10, 30, 50 and 70 min.

Results

CNV magnitude

Mean CNV magnitude over time after placebo, diazepam (5 mg) and Motival are shown in Figure 2. Comparison of CNV size at zero time with that at subsequent times in each drug group (Student's *t*-tests) showed that there were no significant changes after placebo; that there was a significant decrease after diazepam sustained from 30 to 60 min, and that there was a transient rise at 30 min after Motival.

Table 1 Analysis of variance of differences in CNV magnitude (μ Vs) from pre-drug level at 30, 40, 50, 60 and 70 min after drug in normal subjects taking placebo (twelve subjects), Motival (1 tablet; twelve subjects) and diazepam (5 mg; twelve subjects)

<i>30 min after drug</i>					
Mean differences from time 0					
Placebo	0.75				
Motival	2.85				
Diazepam	-2.95				
<i>Source of variation</i>	<i>Sum of squares</i>	<i>d.f.</i>	<i>Mean squares</i>	F	P
Between groups	207.62	2	103.81	10.60	<0.001
Within groups	322.89	33	9.78		
Total	530.52	35			
Dunnett's <i>t</i> -test (2-tailed)					
Motival v Placebo		1.6386	NS		
Diazepam v Placebo		2.9091	<i>P</i> <0.05		
<i>40 min after drug</i>					
Mean differences from time 0					
Placebo	1.48				
Motival	1.18				
Diazepam	-1.71				
<i>Source of variation</i>	<i>Sum of squares</i>	<i>d.f.</i>	<i>Mean squares</i>	F	P
Between groups	74.82	2	37.41	3.79	<0.05
Within groups	325.19	33	9.85		
Total	400.01	35			
Dunnett's <i>t</i> -test (2-tailed)					
Motival v Placebo		0.2361	NS		
Diazepam v Placebo		2.4957	<i>P</i> <0.05		
<i>50 min after drug</i>					
Mean differences from time 0					
Placebo	0.77				
Motival	0.78				
Diazepam	-3.12				
<i>Source of variation</i>	<i>Sum of squares</i>	<i>d.f.</i>	<i>Mean squares</i>	F	P
Between groups	122.14	2	61.07	9.23	<0.001
Within groups	218.32	33	6.61		
Total	340.47	35			
Dunnett's <i>t</i> -test (2-tailed)					
Motival v Placebo		0.0095	NS		
Diazepam v Placebo		3.7164	<i>P</i> <0.01		
<i>60 min after drug</i>					
Mean differences from time 0					
Placebo	1.41				
Motival	1.02				
Diazepam	-2.75				
<i>Source of variation</i>	<i>Sum of squares</i>	<i>d.f.</i>	<i>Mean squares</i>	F	P
Between groups	126.84	2	63.42	6.44	<0.01
Within groups	324.81	33	9.84		
Total	451.66	35			
Dunnett's <i>t</i> -test (2-tailed)					
Motival v Placebo		0.3013	NS		
Diazepam v Placebo		3.2486	<i>P</i> <0.05		
<i>70 min after drug</i>					
Mean differences from time 0					
Placebo	1.45				
Motival	1.40				
Diazepam	-1.95				

Source of variation	Sum of squares	d.f.	Mean squares	F	P
Between groups	91.83	2	45.91	4.67	<0.05
Within groups	323.92	33	9.81		
Total	415.76	35			
Dunnett's <i>t</i> -test (2-tailed)					
Motival v Placebo		0.0332	NS		
Diazepam v Placebo		2.6654	<i>P</i> <0.05		

(CNV magnitude at 10 and 20 min after drug was not significantly different from that at zero time after any of the drugs.)

Changes in CNV magnitude were also analysed by means of an analysis of variance of the differences in each series (10–70 min) from the CNV magnitude at zero time for the three drug groups (Table 1). The values of *F* were significant in all series from 30 to 70 min. Comparison of the drugs with placebo by Dunnett's *t*-tests showed that this significance was mainly accounted for by the decrease in CNV magnitude after diazepam. The apparent rise in CNV magnitude at 30 min after Motival was not significantly different from the change after placebo. However

this change was significantly different from that after diazepam ($P<0.001$: Student's *t*-test).

The seven subjects who took diazepam 7.5 mg showed changes in CNV magnitude similar to the 12 who took 5 mg (Figure 3). After propranolol, as previously reported for one group (Ashton *et al.*, 1976), there was no change in CNV magnitude.

Reaction time

There was little change in mean reaction time after any of the drugs and no significant differences between drugs and placebo.

Heart rate

'Active' heart rate (measured while the subjects were pressing the reaction time button during the CNV series) decreased significantly during the course of the experiment after both Motival and diazepam (7.5 mg)

Figure 2 Changes in CNV magnitude after Motival (1 tablet; twelve subjects), diazepam (5 mg; twelve subjects) and placebo (twelve subjects).

*denotes significant change in magnitude from pre-drug level ($*P<0.05$; $**P<0.01$; *t*-tests).

● Motival; ▲ diazepam; ○ placebo.

Figure 3 Changes in CNV magnitude after two doses of diazepam.

*denotes significant change in magnitude from pre-drug level ($*P<0.05$; $**P<0.01$; *t*-tests).

▲ 5 mg diazepam ($n=12$); ● 7.5 mg diazepam ($n=7$).

Figure 4 Mood rating scores after Motival (1 tablet; twelve subjects), diazepam (7.5 mg; twelve subjects) and propranolol (60 mg; twelve subjects).

denotes significant difference between Motival and diazepam ($P < 0.05$; ** $P < 0.01$; t -tests). Results for propranolol were intermediate in all cases, but for clarity are only shown for alertness and tension.

● Motival; ▲ diazepam; ○ propranolol.

(from mean values of 80.6 ± 4.24 beats/min (zero time) to 77.0 ± 3.7 after Motival (at 70 min) and from 94.0 ± 4.6 beats/min to 86.5 ± 3.7 after diazepam; for both drugs $P < 0.05$; t -tests). Lessening of anxiety and familiarisation with experimental conditions over time may have contributed to the fall of heart rate. Unfortunately, it was not possible to take enough measurements on the placebo subjects for an adequate comparison with these to be made. 'Resting' heart rate (measured while the subjects were resting between CNV series) showed little tendency to fall.

Blood pressure

There were no significant changes in either systolic or diastolic blood pressure after Motival. A fall in 'active' systolic blood pressure occurred after diazepam 7.5 mg, from a mean of 134.6 ± 5.0 mmHg at zero time to 121.7 ± 5.3 mmHg at 70 min ($P < 0.05$, t -test). The effects of propranolol and diazepam (5 mg) on heart rate and blood pressure have been described previously (Ashton *et al.*, 1976).

Subjective rating scale

The results of the subjective rating scales for the subjects who took Motival, diazepam and propranolol are shown in Figure 4. There was no true placebo group, but since it has been shown that propranolol does not affect CNV magnitude or subjective anxiety ratings under stress (Ashton *et al.*, 1976; Tyrer & Lader, 1974a and b), it seems reasonable to suggest that

propranolol acted as a placebo for this purpose. All subjects rated themselves as higher than 'average' for alertness, anxiety and tension at the beginning of the experiments before taking any drugs. The ratings of the subjects who took Motival declined to 'average' during the course of the experiment; those of the subjects who took diazepam declined to below 'average', while those after propranolol were intermediate. Between 35 and 75 min after the drugs, the subjects who had taken diazepam rated themselves as significantly less alert and less tense than after Motival ($P < 0.05$ – 0.01 , t -tests). Differences in anxiety ratings, although in the same direction, were not significant. There were no differences between drug groups in ratings for detachment or depression. The differences in the subjective rating scales between Motival and diazepam were consistent with the CNV results: diazepam caused a decrease of CNV magnitude and a decrease in alertness and tension, while Motival did not depress the CNV and the subjects remained at 'average' levels of alertness and tension.

Discussion

A clear difference between the effects of diazepam and Motival emerged from this study. Diazepam decreased CNV magnitude and subjective ratings of alertness and tension while Motival had little effect on CNV magnitude and after this drug subjective ratings of alertness and tension scarcely fell below levels rated as 'average'. Thus this investigation indicates that, under

the single dose conditions used in normal subjects, diazepam produced central nervous system depression while Motival did not.

It is of interest that, in subjective rating scales, feelings of alertness, anxiety and tension are differentiated and rated differently by normal subjects. Decreases in alertness and tension below 'average' levels appeared to be correlated with decreases in CNV for the subjects who took diazepam. Such rating scales, like CNV magnitude, appear to be a more sensitive

measure of subjective feelings than direct questioning since many subjects who showed changes in CNV magnitude and subjective rating scales reported no effects when directly questioned after the experiment.

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