A REPEATED DOSE COMPARISON OF DICHLORALPHENAZONE, FLUNITRAZEPAM AND AMYLOBARBITONE SODIUM ON SOME ASPECTS OF SLEEP AND EARLY MORNING BEHAVIOUR IN NORMAL SUBJECTS

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- 1 Seven normal subjects were given three different hypnotics (flunitrazepam 1 mg, amylobarbitone sodium 100 mg and dichloralphenazone 1300 mg) for four consecutive nights each.
- 2 All three substances improved subjective assessment of the ease of getting to sleep. Flunitrazepam was rated as better than either dichloralphenazone or amylobarbitone sodium in this respect.
- 3 The perceived quality of induced sleep was not altered by any of the preparations.
- 4 There was a disturbance of the subjective ratings of getting to sleep following cessation of treatment with dichloralphenazone, giving tentative support to the existence of a 'rebound' effect.
- 5 Dichloralphenazone produced an impairment in psychomotor performance as measured on a complex reaction time test following four nights medication with the drug.

Introduction

Healthy volunteers who took flunitrazepam under double-blind conditions rated 1 mg and 2 mg doses as both causing a significantly faster onset of sleep and a significantly better quality of sleep than placebo (Bond & Lader, 1975). These volunteers also noticed an anxiolytic effect the following morning. In the same study, EEG changes were observed up to 18 h after medication and behavioural tests showed motor impairment 12 h after drug administration. These changes were similar to those observed after nitrazepam, flurazepam, butobarbitone sodium and amylobarbitone sodium (Bond & Lader, 1972, 1973; Malpas, Rowan, Joyce & Scott, 1970). Such residual effects may be inescapable attributes of all effective hypnotics (Bond & Lader, 1975), but they may be less marked in anxious patients than in healthy volunteers (Malpas, Legg & Scott, 1974; Tansella, Zimmermann-Tansella & Lader, 1974).

Methods

Experimental design

Three drug conditions were compared, amylobarbitone sodium (100 mg), flunitrazepam (1 mg) and dichloralphenazone (1300 mg). Subjects received active compounds for a period of four nights starting on the Monday night of each week, and finishing on the Thursday night. The experiment began on a Friday and on that and the two subsequent Friday, Saturday and Sunday nights, matching placebos were taken. Testing sessions took place on Monday, Wednesday and Friday mornings. Thus each Monday testing session was a pre-test, following three nights on placebo, while each Wednesday testing session followed two nights on active drug and each Friday testing session, except the first, followed four nights on active drug.

The study was double-blind regarding active

medication, and the order of drug presentation was balanced, with each drug being tested equally frequently. The preparations were taken a half hour before retiring to bed, subjects being asked to retain their usual times for retiring. Testing session times ranged from 08 h 30 min to 11.00 h. As far as possible the early risers were tested early, and *vice versa*. At each testing session the subject completed a sleep evaluation questionnaire (SEQ) and was then tested on critical flicker fusion threshold (CFF), as an index of cortical arousal level, and choice reaction time (CRT) to measure the level of psychomotor performance. The SEQ, CFF and CRT testing procedures are described fully elsewhere (Hindmarch, 1975) and summarized below.

Sleep evaluation questionnaire (SEQ)

The SEQ contains a set of 10 cm line analogue questions about the quality and nature of the subject's sleep the previous night and his early morning behaviour. The questions are in four sections rating different subjective aspects of sleep and early morning behaviour; *viz.* getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS) and behaviour following wakefulness (BFW). Provision is also made for persistent and noticeable side-effects to be described, and their extent and severity rated. The questions are answered by putting a mark on the 10 cm answer line, the position of the line depending upon the intensity or extent of the subjective assessment of the parameter to be rated.

Choice reaction time (CRT)

Both CRT and CFF measures were computerized and controlled on line via a NOVA 1B, ensuring standard methods of task presentation. The CRT apparatus allowed the recognition and movement time components of the total response time to be separated. Recognition time is the time between the stimulus light onset, and movement of the index finger from the resting position template. Movement time is the time taken to move the finger from the resting position template to the response template adjacent to the stimulus light. At each testing session twenty-five responses were necessary, but the first five were ignored in the data analysis. There were six stimulus lights, with response templates all equidistant from the resting position template, so that the total response movements required at each response were equivalent. The stimulus lights were fairly widely separated, so that a high level of sustained attention was needed to maintain an optimum performance level.

Critical flicker fusion (CFF)

For the CFF test, the subject looked at a group of four light-emitting diodes, situated at the end of a viewing tube one metre away from the binocular eyepiece. CFF thresholds were determined via a computer programme for the psychophysical method of limits (Woodworth & Scholberg, 1958). The results of this procedure were most equivocal and a fault was found in the programming during the experiment and, therefore, no further mention will be made of these measures.

Data analysis

The experimental design was based upon each subject being his own control. The data for analysis, therefore, consists of each subject's difference scores between the values produced during the testing session conditions which are being compared. The individual subjects' difference scores are grouped and the significance of the difference between conditions is determined by means of the paired *t*-test.

Subjects

The subjects were seven consenting volunteers, four female, three male, with ages in the range 18-27 years. All subjects were in a normal physical and mental condition without a history of psychiatric or physical (hepatic, renal or cardiac) diseases. None was being prescribed concurrent medications other than the contraceptive pill. Subjects received expenses, used public transport and refrained from excessive use of alcohol for the duration of the study.

Results

The mean SEQ and CRT scores for the different drug conditions and testing session periods are shown in Table 1, together with the probability values from the paired *t*-tests carried out for pre-test/post-test comparisons within each drug condition.

Sleep evaluation questionnaire (SEQ)

Getting to sleep was improved in all drug conditions (Figure 1). Following two nights on drug GTS assessments were significantly higher than the pre-drug levels for flunitrazepam ($t = 5.72$, $P < 0.001$), and dichloralphenazone ($t = 4.85$, $P < 0.001$). Following four nights on drug GTS levels were all significantly higher than

Table 1 Choice reaction time (CRT), and sleep evaluation questionnaire (SEQ): Mean group scores under each drug condition, together with significance levels from paired *t*-tests performed on pre-test/late test comparisons within each drug condition

	Flunitrazepam (1 mg)				Amylobarbitone sodium (100 mg)				Dichloralphenazone (1300 mg)			
	Pre-test	Following 2 nights on drug	Following 4 nights on drug	Post-test	Pre-test	Following 2 nights on drug	Following 4 nights on drug	Post-test	Pre-test	Following 2 nights on drug	Following 4 nights on drug	Post-test
RT	0.137	0.382	0.404	0.348	0.357	0.353	0.347	0.337	0.354	0.370	0.359	0.338
MT (s)	0.165	0.173	0.172	0.169	0.163	0.163	0.164	0.157	0.154	0.171	0.178	0.171
CRT (s)	0.536	0.555	0.576	0.517	0.520	0.516	0.511	0.494	0.508	0.541	0.537	0.509
GTS (mm)	39.0	55.0	65.0	44.2	41.4	47.7	53.6	44.8	43.7	54.5	52.6	35.2
QOS (mm)	52.9	53.1	50.5	45.9	50.6	58.5	56.5	51.0	51.4	51.8	57.3	57.1
AFS (mm)	41.6	38.6	35.4	42.4	41.4	21.8	41.8	42.3	46.4	40.3	38.0	41.7
BFW (mm)	43.2	37.7	38.1	44.8	46.7	33.9	46.6	44.1	41.3	36.3	41.2	39.6
SEQ TOT (mm)	44.4	46.2	47.3	44.7	45.0	40.6	49.8	45.6	45.6	45.7	47.3	42.8

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

RT, Recognition time (s); MT, Movement time (s); CRT, Total reaction time (s)

GTS, Getting to sleep (mm); QOS, Quality of sleep (mm); AFS, Awakening following sleep (mm); BFW, Behaviour following wakefulness (mm);

SEQ TOT, Sleep evaluation questionnaire total (mm)

Figure 1 Changes in subjective ratings of getting to sleep (GTS) and quality of sleep (QOS) for all drug conditions (a, flunitrazepam (1 mg); b, amylobarbitone sodium (100 mg); c, dichloralphenazone (1300 mg)).

the pre-drug ratings for each of the drug conditions ($P < 0.001$, flunitrazepam; $P < 0.001$, amylobarbitone sodium; $P < 0.001$, dichloralphenazone). There were no significant differences between GTS levels for the different drug conditions after two nights on drug, but after four nights on active compound the GTS level obtained with flunitrazepam (65.0) was higher than the amylobarbitone sodium (53.6) ($t = 2.26$, $P < 0.05$), and significantly higher than the dichloralphenazone (52.6) ($t = 2.95$, $P < 0.01$) assessments. After 3 days off drug both the flunitrazepam and amylobarbitone sodium GTS scores returned to values around their pre-test levels. However, the GTS assessment following three nights withdrawal from dichloralphenazone was lower than either the corresponding flunitrazepam or the corresponding amylobarbitone sodium level ($P < 0.05$, $P < 0.001$, respectively).

None of the QOS ratings following administration of active compounds were significantly higher, i.e. 'better', than their pre-drug levels (Figure 1). There were no significant changes produced in QOS ratings following withdrawal of the active compounds.

The only significant changes from pre-drug AFS levels was following two nights on amylobarbitone sodium (Table 1) which at 21.8 was significantly lower, i.e. 'worse', than the pre-test level of 41.4 at $P < 0.001$. However, following four nights on amylobarbitone sodium the AFS rating (41.8), showed a return to its pre-drug level. With flunitrazepam, the AFS level after two nights on

active drug (38.6) was slightly lower than the pre-test level (41.6), as was the rating following four nights on active drug (35.4). Neither of these changes approached significance ($t = 0.77$, $P = 0.45$; $t = 1.38$, $P = 0.19$, respectively). With dichloralphenazone, the AFS level after two nights on drug (40.3) was slightly lower than the pre-test level (46.4) but the difference was not significant. Following four nights on drug the AFS level (38.0) was significantly lower than the pre-test level ($t = 2.89$, $P < 0.02$). The AFS level obtained following two nights on amylobarbitone sodium was significantly lower than both the corresponding flunitrazepam level ($P < 0.001$), and the dichloralphenazone level ($P < 0.01$).

The only significant change in BFW ratings was a reduction from 46.7 to 33.9 after two nights on amylobarbitone sodium ($P < 0.02$), but following four nights on the drug the BFW ratings (46.6) had returned to the pre-test level (Table 1). With flunitrazepam, no significant changes occurred, although the ratings following two nights (37.7) and four nights (38.1), on the drug were both slightly lower than the pre-test level (43.2). The BFW rating following dichloralphenazone for two nights (36.3) was lower than the pre-test level (41.3), but not significantly so, while after four nights on the drug the rating (41.2) showed a return to the pre-test value.

Six of the seven subjects reported side effects e.g. nausea, tiredness the day following medication, headaches, lethargy and prolonged dreaming. However, none of these effects were severe or consistently reported and since several of the reported side effects followed placebo it can only be assumed that there are no consistent or persistent side effects noted by subjects in this present investigation.

Choice reaction time (CRT)

Recognition speed. None of the changes in recognition speed (Table 1) reached an acceptable level of statistical significance. The recognition speeds under medication with amylobarbitone sodium and dichloralphenazone are similar to those obtained at the pre-test and post-test assessments. Recognition speed decreases following two nights and four nights on flunitrazepam, but the changes are far from significant (pre-test/two nights on active drug comparison, $P = 0.336$; pre-test/four nights on active drug comparison, $P = 0.352$).

Movement speed. With amylobarbitone sodium and flunitrazepam, the pre-test and active drug movement speed values are all similar. With

dichloralphenazone, the movement speed following four nights on the drug (0.177 s) was slower than the pre-test movement speed (0.170 s, $P < 0.05$).

Total response speed. None of the changes in overall response speed were significant (Table 1); although, with both flunitrazepam and dichloralphenazone, the mean active drug CRT was slower than either the pre-test or post-test CRT.

Discussion

All three drug conditions led to improvements in the subjective assessment of the ease of 'getting to sleep', both after two nights and after four nights on the drugs. Furthermore, after four nights on flunitrazepam the GTS ratings were significantly higher than those produced for either amylobarbitone sodium or dichloralphenazone. With

dichloralphenazone the post-test GTS ratings were depressed suggesting a 'rebound effect'. None of the drug conditions led to significant changes in reported 'quality of sleep' (QOS) ratings. Following two nights on amylobarbitone sodium both 'awakening from sleep' (AFS) and behaviour following wakefulness (BFW) ratings were impaired, but after four nights on amylobarbitone sodium the subjective assessment of early morning behaviour had returned to its pre-test values. With flunitrazepam there were slight reductions in the (AFS) and (BFW) ratings but these reductions were not significant and similarly with dichloralphenazone (AFS) and (BFW) levels were reduced.

Neither flunitrazepam nor amylobarbitone sodium significantly affected psychomotor performance. Dichloralphenazone, however, produced an impairment in movement speed after four nights on the drug, although recognition speed was not affected.

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