A COMPARISON OF THE CLINICAL AND PSYCHOLOGICAL EFFECTS OF DIAZEPAM AND AMYLOBARBITONE IN ANXIOUS PATIENTS

CHRISTA ZIMMERMANN TANSELLA, M. TANSELLA & M. LADER

Cattedra di Psicologia Medica, Istituto di Clinica Psichiatrica di Verona, Università di Padova, 37134 Verona, Italy, and Institute of Psychiatry, University of London, London SE5, England

1 Twenty-four anxious inpatients were treated with diazepam, amylobarbitone sodium and placebo in flexible dosage for 1 week. They each received all three treatments according to a fully-balanced design, using double-blind procedures.

2 The clinical and the psychological effects of the drugs were assessed by the comprehensive battery of psychiatrist's ratings, subjective and psychological tests before treatment and at the end of each week of treatment. The tests included self-rating of anxiolytic and hypnotic effects, reaction-time, card sorting, coding and cancellation tasks, arithmetic and tapping.

3 Diazepam improved significantly subjective anxiety and insomnia, while amylobarbitone improved only the self-rated quality of sleep. Occasion effects were absent on clinical measures, indicating that the patients did not respond to non-specific temporal factors. Performance on motor tasks improved over time because of the expected practice effect, but an impairment relative to placebo was detected on two motor tests after the barbiturate and on four other tests with a cognitive component after the benzodiazepine.

Introduction

Benzodiazepines have been extensively studied both in normal subjects and in anxious patients with respect to their hypno-sedative, anxiolytic, muscle relaxant and anticonvulsant properties (Lader & Marks, 1971). Comparatively few studies have been carried out on anxious patients assessing both therapeutic effects and effects on psychological performance. The few studies available are consistent in reporting only minor impairment in the performance of anxious patients (Lader, Bond & James, 1974; Tansella, Zimmerman Tansella & Lader, 1974; Malpas, Legg & Scott, 1974; Moore, 1977), in contrast to the appreciable drops in performance found in single dose studies in normal subjects, (Malpas, Rowan, Joyce & Scott, 1970; Bond & Lader, 1972; 1973; 1975). The lack of persistent residual effects on performance measures could be due to the development of tissue tolerance since anxiolytic drugs were taken in most patient studies for at least 1 week. But even after the first night of medication with 20 mg nordiazepam, no impairment could be detected the following morning (Tansella *et al.*, 1974), so that other explanations are more likely: patient samples have a high variance for such performance tasks as their performance is more prone to influence by mood changes, motivation and attitude; or they may indeed react differently than normals to both the therapeutic qualities and unwanted effects of anxiolytic drugs as is suggested by the minor electroencephalographic

changes and the very rare occurrence of subjective feelings of hangover in anxious patients (Malpas *et al.*, 1974).

Because of the inverted U-shape relationship between arousal and performance, anxiolytic drugs taken by anxious patients would result in improvement on those tests impaired by anxiety and in impairment on those tests improved by arousal, but even in tests impaired by anxiety and improved by anxiolytic treatment, higher doses would eventually impair the general performance of anxious patients. Since most studies have used a fixed dosage schedule (Malpas *et al.*, 1974; Tansella *et al.*, 1974; Salkind & Silverstone, 1975) or a flexible dosage schedule self-adjusted by anxious outpatients (Lader *et al.*, 1974; Moore, 1977), it is also possible that the dosages were not high enough for anxious patients to result in impaired performance. Diazepam is the most widely prescribed benzodiazepine compound. No studies have been carried out so far on hospitalised anxious patients treated under strictly controlled conditions and consequently there are no data on the possible effects on performance of this benzodiazepine when given in the full dosage necessary for very anxious patients who need admission to hospital for crisis intervention.

The aim of the present study in newly admitted anxious patients was therefore a clinical investigation of the effects of oral diazepam, given in a flexible

dosage schedule on simple and complex motor tasks, attention and concentration tasks as well as on objective manifest symptoms and subjective feelings of anxiety. This was done within the context of a double blind cross-over trial in which the effects of diazepam were compared with those of amylobarbitone sodium and placebo.

Methods

Patients

Twenty-four newly admitted patients with the primary diagnosis of anxiety neurosis took part. Most complained of insomnia. Patients with obsessional, hysterical or depressive features were excluded. Eighteen were female and ages ranged from 29–60 years (mean 41.7, s.d. 8.7). The mean number of years of education was 5.0 (s.d. 1.5) and most of the patients were from the lower social classes. The purpose and the nature of the study were explained to the patients who gave informed consent. Two patients refused consent.

Nine patients who originally entered the trial dropped out because of worsening symptoms; they were switched over to regular anxiolytic therapy and had to be replaced. We were able to collect data only for seven of these nine patients, the remaining two having withdrawn in the early phase of the wash-out period. Five of these seven patients dropped out while on placebo, at the end of the wash-out or in the first week of the trial. The other two patients withdrew later in the trial having had at least 1 week of active treatment.

We compared the total anxiety score on initial assessment of these five patients with that of the eight patients who had placebo in the first week and completed the trial. We also compared the initial total score of all seven interviewed dropped-out patients with the initial total score of all 24 patients who completed the study. Neither comparison was significant although the excluded patients were somewhat less anxious on admission than the patients of the study. The dropped-out patients may be considered therefore as similar in anxiety to the patients participating in the study and the possibility of bias in the choice of patients can be excluded.

Drugs

The drugs were administered as identical looking white-yellow capsules containing 5 mg diazepam, 100 mg amylobarbitone sodium or placebo. The dosage was flexible, ranging from three to nine capsules a day and was determined by the doctor-in-charge. The capsules were given three times a day at 10.00 h, 15.00 h and 20.00 h. Additional capsules of

the same drug were given at night (22.00 h), for complaints of insomnia. The number of capsules ingested was carefully recorded each day and blood samples were taken during and at the end of each treatment for analysis for plasma concentrations. These results have been presented elsewhere (Tansella, Zimmermann Tansella, Ferrario, Preziati, Tognoni & Lader, 1978). During the trial no other psychotropic drugs were allowed, and no formal psychotherapy was given except of a simple supportive nature.

Experimental design

About a third of the patients were not receiving drugs at the time of initial assessment and the rest underwent a placebo 'wash-out' period of 4–7 days under single-blind conditions. Each drug was given for a week and the drug order was assigned according to a fully balanced Williams' Square design in which each treatment was followed by each other treatment an equal number of times. This allows computation of any possible 'carry-over effects'. Each patient was allocated randomly to one of the six treatment sequences allowed for by the cross-over design with the sole constraint that each sequence should be assigned to three females and one male. The conditions were double-blind, neither the doctor adjusting the dosage, the raters nor patients being aware of the identity of the treatment. Each subject was tested on four consecutive weekly occasions. Clinical assessment was always performed the evening before the test session which took place the next morning at 09.00 h, approximately 11 h after the last ingestion. In this session the patients were tested on a comprehensive battery of subjective tests and performance measures.

Personality assessment

Before the first occasion only, Italian versions of the following personality assessments were administered:

1. *Maudsley personality inventory* (Eysenck, 1959). Two scores are obtained, one along the normality-neuroticism dimension, the other along the dimension of extraversion-introversion.
2. *Manifest anxiety scale* (Taylor, 1953). Proneness to manifest anxiety is estimated.
3. *Raven progressive matrices 38* (Raven, 1954). This is a measure of intellectual efficiency and the score was the number of items correct in 20 min.

Clinical assessment

On the last evening of the 'wash-out' period and of every treatment week the following assessments were made, in the order given:

1. *Hamilton anxiety-rating scale* (Hamilton, 1959). The patient was interviewed jointly by a psychiatrist and a clinical psychologist (MT and CZT). After the interview which lasted 20–30 min with a 'time-focus' related to the previous 2 days, the Hamilton Rating Scale for Anxiety States (RSAS), modified by the use of visual analogue 100 mm lines instead of discrete categories, was completed by the two raters independently. The total score and the items score for insomnia were calculated. Hamilton (1959) subjected the scale to factor analysis and extracted two factors of psychic and somatic anxiety. These factor scores were calculated by multiplying the individual series on each symptom by Hamilton's factor loading and totalling them within the two factors. The reliability between the two raters was assessed separately on each occasion according to the method proposed by Maxwell & Pilliner (1968). The obtained coefficients of agreement over all 15 items of the scale ranged from 0.80 to 0.94 and the mean values were therefore used.

2. *Morbid anxiety inventory* (Salkind, 1973). This inventory estimates anxiety level and was completed by the patient with respect to the last 2 days.

3. *Anxiety self-rating*: A visual analogue 100 mm linear scale was used to measure anxiety. The subject rated himself on the scale by placing a mark across the line (today I felt not anxious at all–very anxious), the score being the distance in mm from the left hand extreme.

Subjective evaluations

The following self-assessments were carried out on the test morning:

1. *Insomnia self-ratings*: Two visual analogue 100 mm linear scales were used to measure retrospectively quality of sleep the previous night (very good–very poor) and actual state in terms of sleepiness at the time of rating (very alert – very sleepy).

2. *Performance self-rating*: After each of the following performance tests the patient completed a 100 mm linear scale, indicating how good he thought his performance had been on the task (very good – very bad), the score being the distance in mm, from the left hand extreme.

Performance measures

The following tests were completed in the order given:

1. *Auditory choice reaction time*. Twenty relevant stimuli (800 Hz tones of 25 ms duration and 70 dB

intensity) were interspersed randomly with 30 irrelevant stimuli (1200 Hz tones, 25 ms, 70 dB), the inter-stimulus interval being 10 s. The subject pressed a key with his preferred hand. The reciprocal transformation was used to give a speed score. The mean reaction-time and coefficient of variation of response to the relevant stimuli were computed.

2. *Simple auditory reaction time*. Twenty tones (1000 Hz, 25 ms, 70 dB) were presented at intervals varying randomly between 10 and 20 s. The mean reciprocal response (speed score) and coefficient of variation were calculated.

3. *Card sorting*. The technique was similar to that of Bond & Lader (1973). Cards were sorted using the preferred hand into two categories or four categories, and equivalent 'motor' sorts were carried out in which the subject merely dealt the cards into two or four piles without matching. Each type of sort was carried out twice and the means of the two trials were recorded. By subtraction of the 'motor' time from the sorting time, an estimate was obtained of 'decision' time.

4. *The digit symbol substitution test (DSST)*. This subtest of the Wechsler Adult Intelligence Schedule comprises a coding task in which symbols are substituted for numbers. The score was the number of items completed correctly in 90 s.

5. *The symbol coping test (SCT)* utilises the same symbols as the previous test but the subject had only to copy and not code them. The score was the number of completed items in 90 s.

6. *The Gibson spiral maze* tests motor speed and co-ordination and provides two scores, one of errors and one of speed.

7. *Cancellation tasks* a) the subject has to cross out 4's in lines of numbers, the frequency of fours being 40 in 400. b) The subject crosses out 2's which are preceded by 8's or 9's. The frequency was 30 in 100. c) The subject crosses out any numbers which are immediately preceded or followed by the same number ('pairs'). Again the frequency was 1 in 10. In all three tasks the time of completion was recorded.

8. *Arithmetic*. Each item consisted of a written sum of two 4-digit numbers. The score was the number totalled correctly in 3 min.

9. *Tapping rate*. Using the first two fingers of his preferred hand, the subject tapped as rapidly as possible, the number in 60 s being registered on a mechanical counter.

Analysis of data

To correct the carry-over effects due to the cross-over design used, a full Williams three-way analysis of variance (subjects, drugs, order) (Cochran & Cox, 1957) was carried out on change scores from pre-treatment, drug effects being estimated against between-occasion within-subject error variance. The analysis corrected main treatment effects for drug effects which had persisted from the previous week's treatment. Newman-Keul's tests (a *t*-test for comparing two of a set of means which a *F* test has shown are not all alike) was computed for the difference between corrected treatment means (Winer, 1971). Between-patient product moment correlations were calculated between various clinical and demographic data and some measures of drug effect.

Results

Dosage

The mean dosage attained for diazepam was 25 mg/day, for amylobarbitone sodium 463 mg/day and for placebo six capsules.

Drug effects

Only the eight variables showing significant drug effects will be presented. The relevant statistics are summarized in Table 1.

Self-rating of anxiety (visual analogue)

Neither placebo nor amylobarbitone effected any significant decrease in subjective anxiety from pre-treatment levels. By contrast, diazepam lowered anxiety ratings by almost two-thirds and was very significantly more effective than the barbiturate. No

occasion effects were found suggesting that these patients did not respond to hospital admission or non-specific temporal factors.

Self-rating of sleep

Both amylobarbitone and diazepam substantially and significantly improved quality of sleep as compared with the placebo week. Again, occasion effects were not significant.

Performance measures

Card sorting Card sorting into two categories improved significantly over occasions, in accord with the well known effects of practice on this task. The practice effect also shows as an improvement between the pre-treatment and placebo occasions. After the week's treatment with diazepam, although the performance of pre-treatment occasion is maintained, there is a significant impairment on this task as compared with the placebo and amylobarbitone sodium week.

Gibson spiral maze time Also the performance in this test improves significantly over occasions. After the week's treatment with amylobarbitone sodium, some improvement over pre-treatment remains, but performance is significantly impaired as compared with the placebo week. Diazepam treatment is associated with definite impairment with respect to amylobarbitone sodium.

Cancellation of 4's time The occasion effect for this test just misses the 0.05 level of probability. After 1 week of diazepam there is a significant impairment in this task as compared to placebo and amylobarbitone sodium and to pre-treatment.

Cancellation of consecutive pairs time There is a

Table 1 Drug and occasion effects

Variable	Means corrected for carry-over effects				t-tests†, 36 df			F-ratio; 2,21 df
	Pre	Placebo	Amylobarbitone	Diazepam	PI v A	PI v D	A v D	
Self-rating of anxiety (mm)	64.2	51.2	59.6	24.2	NS	**	**	0.43
poor sleep (mm)	75.5	70.2	26.5	27.4	**	**	NS	0.46
Card-sorting into two categories (s)	21.5	18.5	19.5	21.5	NS	**	**	4.37*
Gibson maze time (s)	44.5	31.7	35.8	39.3	**	**	**	5.03*
Cancellation task 4's time (s)	65.9	54.0	58.6	73.9	NS	**	**	3.16
2's time (s)	101.6	87.9	90.0	115.5	NS	**	**	4.72
Pair's time (s)	112.0	83.3	91.4	124.4	NS	**	**	5.83**
Tapping rate (number/min)	321.0	341.1	316.1	298.4	**	**	*	10.22**

† computed on change scores from pre-treatment, corrected for carry-over effects.

NS $P > 0.05$, * $P < 0.05$, ** $P < 0.01$.

significant improvement over occasions in this task. Amylobarbitone sodium compared with placebo had no significant effect on performance while diazepam impaired this task with respect to placebo, amylobarbitone sodium and pre-treatment.

Cancellation of 2's time Again a significant occasion effect was found, patients improving over occasions. Amylobarbitone sodium did not affect performance, but diazepam resulted in significant impairment with respect to placebo, amylobarbitone sodium and pre-treatment.

Tapping rate Patients improved their performance significantly over occasions. Although improvement over pre-treatment remains, amylobarbitone sodium reduces significantly the tapping rate when compared to placebo, while diazepam results in definite impairment with respect to placebo, amylobarbitone sodium and also to pre-treatment.

Correlation with outcome

Correlations were computed between several clinical and demographic variables and the variables listed in Table 1 which showed significant drug effects, for each drug condition separately.

With amylobarbitone therapy, the only clinical variable to show correlations was rating of poor sleep. This correlated 0.47 ($n=24$; $P<0.05$) with the Maudsley Personality Inventory neuroticism score, -0.57 ($P<0.01$) with MPI extraversion score and 0.70 ($P<0.001$) with the Taylor MAS. This suggests that best sleep response to the barbiturate was associated with initially low neuroticism, high extraversion and low trait manifest anxiety. With diazepam, a similar but less strong correlation was found between rating of poor sleep and MAS ($r=0.46$; $P<0.05$).

Discussion

The general severity of the patients' anxiety states explain the high daily dosages of diazepam and amylobarbitone sodium reached by them, which were higher than those usually reported for anxious outpatients (Lader *et al.*, 1974; Malpas *et al.*, 1974). Despite the high dosages of both active drugs, patients reported no feelings of hangover in terms of sleepiness the following morning at the time of rating, thus confirming previous findings of the extremely rare occurrence of hangover feelings in anxious patients after benzodiazepines (Dement, Zarcone, Hoddes, Smythe & Carskadan, 1973; Malpas *et al.*, 1974; Tansella *et al.*, 1974), feelings of drowsiness being reported only after a week of 30 mg flurazepam by general practitioner insomniac patients (Salkind &

Silverstone, 1975). More hang-over feelings have been reported by anxious patients after barbiturates (Lasagna, 1954; Haider, 1968; Wyss & Mader 1965) although recent studies with daily dosages of amylobarbitone sodium up to 200 mg failed to repeat these findings (Malpas *et al.*, 1974; Perkins & Hinton, 1974; Tansella *et al.*, 1974).

In this study diazepam and amylobarbitone sodium given for 1 week each showed no significant clinical effects as evaluated by the patient's self-assessment on the Morbid Anxiety Inventory or by the Hamilton Anxiety rating scale. Since the agreement between the two raters in assessing the anxious symptomatology was good over all occasions and good reliability and validity has been demonstrated also for the M.A.I. (Salkind, 1973), these negative findings suggest therefore that 1 week of treatment is not sufficient to evidence clear differential drug effects. Even 2 weeks' treatment with diazepam had no anxiolytic effects in terms of the patient-rated Morbid Anxiety Inventory (Bonn, Salkind & Linford Rees, 1971) and most studies could not detect anxiolytic effects in terms of psychiatrists' ratings after 1 week of treatment for example with nitrazepam (Malpas *et al.*, 1974) and nordiazepam (Tansella *et al.*, 1974). Definite clinical effects as evaluated by psychiatrists were found only after 2 weeks of treatment with clorazepate (Robin, Curry & Whelpton, 1974) and diazepam (Saario, Linnoila & Mattila, 1976; Dasberg, 1975). Because of the experimental design chosen for this study, and the high drop-out rate, a prolongation of each treatment for another week, requiring the patients to stay 2 months in hospital was impracticable. On the other hand the advantage of using patients as their own control is that it avoids variability between patients and requires a smaller number of subjects.

However the patients' relatively crude self-evaluation of anxiety and quality of sleep, using visual analogue scales, showed significant drug effects, the diazepam improving both subjective feelings of anxiety and quality of sleep and the amylobarbitone sodium improving sleep only. That patient reports are more sensitive to drug effects than doctors' ratings has been observed before (Hesbacher, Rickels, Hutchinson, Raab, Sablosky, Whalen & Phillips, 1970) suggesting their combined use in drug trials.

While occasion effects were absent on clinical measures, indicating that patients did not respond to non-specific temporal factors, performance on most psychological tests improved over time, showing the expected practice effect observed in previous studies (Bond & Lader, 1973; Tansella *et al.*, 1974). In spite of this changing background of performance improvement over time, significant drug effects emerged on six tasks, including simple motor (tapping) and more complex psychomotor tests with cognitive elements (sorting into two categories, Gibson spiral maze, cancellation tasks). After the week's treatment

with amylobarbitone sodium, some improvement over pre-treatment generally remained, but there was a consistent deficit in performance as compared with the placebo week which reached significance with respect to the Gibson spiral maze time and tapping rate, indicating less efficient accuracy and slowing of motor speed. Performance after diazepam was significantly worse than after amylobarbitone sodium in all six tasks, and definite impairments with respect to pre-treatment were found for the cancellation tasks and tapping rate, suggesting some slowing of motor speed as well as diminished attention and accuracy. Increased time to complete the Gibson spiral after 1 week of amylobarbitone sodium and one week of nordiazepam (Tansella *et al.*, 1974) and diazepam (Bond *et al.*, 1974) has been reported before, and tapping rate was decreased after 1 week of flurazepam (Salkind & Silverstone, 1975). Reaction time tasks, symbol substitution and symbol copying tests and arithmetic seemed to be less sensitive to drug effects in these studies and this was the case also in the present study.

Since the high level of anxiety reported by the patients in the pre-treatment condition is likely to be associated with the initial poor performance, alleviation of anxiety should have increased performance. In fact the lower levels of anxiety reported under amylobarbitone sodium and placebo condition are accompanied by a substantial improvement in performance for all six tasks. Performance deteriorates however under diazepam treatment where least anxiety was reported. This fits with the postulated inverted U-shape relationship which predicts optimal performance when drive (anxiety) is neither too low nor too high, the optimal drive level being relatively high for simple tasks. Since our patients were on a high dosage of diazepam in order to get symptomatic relief, an impairment in performance due to the high dosage was expected. However, it is not clear to what extent the reported low anxiety level after diazepam *per se* was responsible for the deteriorated performance. One explanation is that anxious persons normally never obtain the low anxiety levels of calm persons (Eysenck, 1970) and that the high dosage of diazepam by which patients could reach a 'normal' low level of anxiety pushed them towards behavioural impairment.

The patients' ratings of insomnia and their respective performance confirm previous observations in normals (Bond & Lader, 1972) that sleep deprivation produces less impairment than residual effects after a drug-induced night's sleep: performance tended to be better under placebo condition where patients slept poorly than under amylobarbitone sodium where patients slept well.

Patients' judgement of their performance showed no drug effects, replicating our previous findings in normal subjects (Zimmerman Tansella, Tansella & Lader, 1976). This type of evaluation might reflect more the individual's need for achievement and his style of coping with success and failure than his temporary clinical symptomatology. Another explanation would be that the patient had no objective indicators for evaluating their performance correctly. No feedback was given and small differences in the performance might be very difficult to perceive subjectively from one week to the other.

The significant correlations between sleep response to the two active compounds and questionnaire defined neuroticism and anxiety proneness confirm previous observations that patients with characterological 'trait' anxiety and hence with a more continuously symptomatology often respond poorly to drugs in general, to barbiturates in particular, (Greenblatt & Shader, 1974) in contrast to patients with 'state' anxiety and a characteristic cyclic or intermittent nature of symptomatology.

In conclusion, diazepam after 1 week of treatment produced an anxiolytic effect on only one subjective measure; both diazepam and amylobarbitone sodium induced a significant self-reported sleep improvement. In contrast to these minor clinical effects marked performance deficits were found in six measures after a week of diazepam treatment and in two of these measures after the barbiturate. This impairment after diazepam seems to be an unavoidable consequence of adequate symptomatic relief.

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