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A Comparison of the Psychotropic Profiles of Tofisopam and Diazepam

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Summary. Twelve normal subjects were tested on a number of measures both before and 1, 3 and 5 h after 10 mg diazepam, 100 and 200 mg tofisopam and a placebo. The measures included self-ratings of mood, bodily symptoms, hostility and sleep, the electroencephalogram (EEG), reaction time, tapping, digit symbol substitution, the symbol copying test, and plasma levels. Diazepam showed a clear profile of action, producing EEG changes, pronounced sedation and psychological impairment. The last two effects were maximal at 1 h and had worn off by 5 h. The EEG was recorded at 3 h only. Tofisopam in no way resembled diazepam. It produced no changes on the EEG or psychological tests and a very mild stimulant effect was apparent on the ratings. While diazepam was easily detectable in the blood, tofisopam did not bind to benzodiazepine receptors.

Key words: tofisopam, diazepam; electroencephalogram, sedation, pro-drug

Anxiolytic drugs produce residual sedation when given in effective clinical doses and the benzodiazepine compounds are no exception to this rule. Tofisopam is a new benzodiazepine which has been claimed to exert anxiolytic effects without producing the hitherto inevitable sedation. It has the formula shown in Fig. 1 and was developed in Hungary. Among Western countries, it has been available in France for some years (Trade name, Grandaxine; Laboratories de L'Ozothine). Tolerance is good and high doses have been given with few side-effects (Varady et al. 1975). It differs from other benzodiazepines in that it has no muscle-relaxant or anti-convulsant properties, and not only is it reported to produce little daytime sedation but it is not effective as a hypnotic (Boszormenyi 1975; Kangas et al. 1980). It has also been shown to have some anxiolytic effects at a mean daily dose of 178.7 mg when compared to placebo, especially for patients with somatic complaints (Goldberg and Finnerty 1979) and when compared to nitrazepam as an oral premedicant tofisopam produced less sedation and yet diminished excitement and apprehension more (Kangas et al. 1980).

It was therefore decided to compare tofisopam with an established and well-tried benzodiazepine, diazepam, and a placebo on a variety of measures to ascertain if there were any marked differences in their psychotropic profiles.

Materials and Methods

Subjects

Twelve normal healthy subjects took part in the study. They were six males and six females, aged between 21 and 47 years. They were all employees of the Institute of Psychiatry.

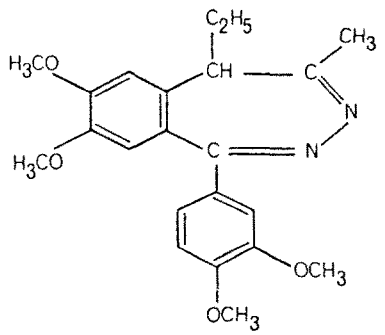

Fig. 1. Formula of tofisopam

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Drugs

Two doses of tofisopam (100 mg and 200 mg) were compared with one dose of diazepam (10 mg) and a placebo. The subjects were given four identical-looking white capsules on each occasion.

Experimental Design

Each subject was tested on four separate occasions at two-weekly intervals. The drugs were assigned according to three 4×4 Latin square designs and the conditions were doubleblind. The subjects were tested before each drug and at 1 h, 3 h and 5 h after each drug. Testing was carried out between 9.30 a.m. and 4 p.m. and the time of each testing and of drug ingestion was kept constant for all subjects on all occasions. Subjects were allowed to continue their normal work activities between testings but were asked not to discuss the treatment effects with each other. They were instructed not to drink alcohol on the evenings preceding the test day nor on the day itself. They were allowed their normal intake (which was recorded) of caffeine-containing beverages and nicotine but were instructed not to increase their intake if they felt sleepy. These substances were not excluded because of possible withdrawal effects. However, the use of therapeutic CNS drugs during the trial was not permitted.

Self-Ratings

Mood Rating Scale. Feeling at the time of each testing was measured on a series of sixteen analogue scales. This mood rating scale has been subjected to a principal component analysis which yielded three factors (Bond and Lader 1974). The first factor is one of *alertness* and consists of nine of the scales: alert-drowsy, strong-feeble, muzzy-clear-headed, well co-ordinated-clumsy, lethargic-energetic, mentally slow-quick witted, attentive-dreamy, incompetent-proficient and interested-bored. The second factor measures *contentedness* and the five scales which load on it are: contented-discontented, troubled-tranquil, happy-sad, antagonistic-amicable and withdrawn-gregarious. The third factor, *calmness,* is composed of two scales: calm-excited and tense-relaxed. On each scale, the subject had to mark the point along a 100 mm line that represented how he felt.

Bodily Symptom Scale. A similar scale was constructed to measure bodily symptoms. Fourteen side-effects which have been reported after tofisopam or diazepam were tested: anxiety, sweating, shaking or trembling, palpitations, nausea or sickness, loss of appetite, restlessness, dryness of mouth, muscular tension, irritability, physical tiredness, headache, dizziness, indigestion or stomach trouble, and the subject rated them between absent and very severe.

Sleep Scale. Three additional analogue scales were used to measure sleep: quality of sleep (very bad – very good), onset of sleep (very abrupt – very slow) and feeling on awakening (very sleepy – very alert), on the morning of the test and the morning after.

Hostility – Guilt Inventory. This is a rating scale developed by Buss and Durkee (1957) consisting of 75 items grouped into 8 subsections; assault, indirect hostility, irritability, negativism, resentment, suspicion, verbal hostility and guilt. A total hostility score is also derived.

Physiological Measures

Electroencephalogram[1]. The EEG was recorded from vertex and left temporal electrodes (Bond and Lader 1972). It was analysed by broad waveband analysis into four parallel band-pass filters with upper and lower frequencies set as follows: (1) 2.4–4 Hz; (2) 4–7.5 Hz; (3) 7.5–13.5 Hz; (4) 13.5–26 Hz. The outputs of these four filters were fed into four analog-to-digital converter inputs of a PDP-12A computer. Thirty-two 5-s epochs of EEG were analysed for two conditions: eyes open and eyes closed. The mean rectified voltage in each waveband was calculated.

A Fourier analysis was also completed. The samples were filtered between 2 and 32 Hz before on-line power spectral analysis using a PDP-12A computer. The spectrum was estimated by calculating the autocorrelation function followed by a Fourier transformation. Each record was analysed in sections of 4.8 s duration and smoothed to give values at 0.5 Hz intervals. The power was averaged for each cycle per second between 2 and 32 Hz. Sixteen samples were averaged for the eyes open and eyes closed conditions.

Psychological Measures

Auditory Reaction Time. Simple auditory reaction time to a click of moderate intensity (70 db) was measured. Thirty-two stimuli were presented through earphones with a random interval of 3–5 s and a rectangular distribution. The mean reciprocal was calculated.

Tapping Rate. The subject tapped a key as quickly as possible for 60 seconds. The inter-tap-interval was calculated.

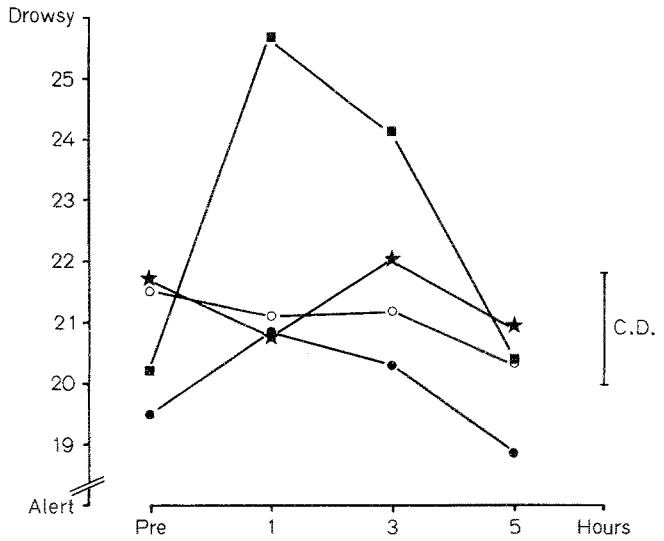

Fig. 2. Mean scores on factor 1 (sedation) of the mood rating scale before, 1, 3 and 5 h after placebo (✶), diazepam 10 mg (■) and tofisopam 100 mg (○), 200 mg (●). Means further apart than the critical difference (C.D.) are significantly different at the 0.05 level of confidence at least

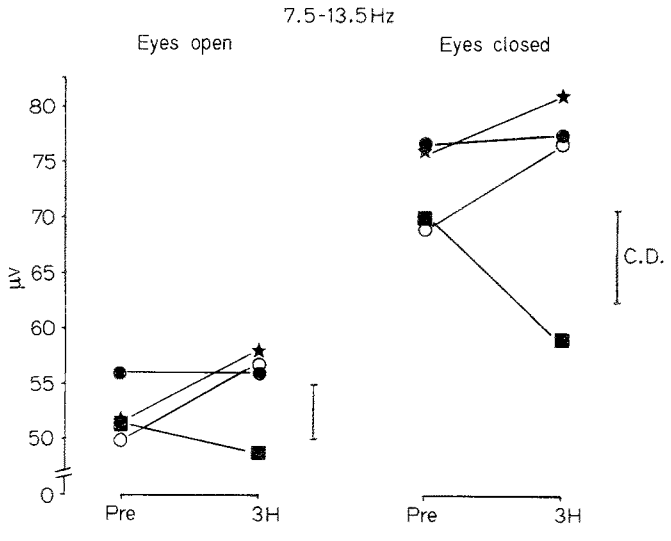

Fig. 3. Mean scores in microvolts on the 7.5–13.5 Hz waveband of the electroencephalogram under eyes open and eyes closed conditions pre and 3 hours after placebo (✶), diazepam (■), tofisopam 100 mg (○) and 200 mg (●) ■

The Digit Symbol Substitution Test. This is a subtest of the Wechsler Adult Intelligence Schedule (W.A.I.S.) involving coding skills. The score was the number of items correct in 90 s.

The Symbol Copying Test. This test measures the motor component of the D.S.S.T. The same symbols are used but the subject has only to copy them. The score was the number correct in 90 s.

Plasma Samples Analysis[1]. A 10 ml blood sample was taken 3½ h after the drug. The blood was placed in a sodium heparin bottle, centrifuged and the plasma stored at −4 °C until analysis. Samples were measured for benzodiazepine-like activity using a radioreceptor assay. Plasma (200 μl) was extracted with 1 ml hexane which was blown off with nitrogen at room temperature (20 °C). 1.65 ml 50 mm Tris/Cl buffer, pH 7.4 at 0 °C was added to each dry tube. The assay was performed at 0 °C. ^{3}H Diazepam (1.5 nM (final concentration) was added to each tube and the final volume made up to 2 ml with 250 μl calf brain-P_2 preparation (≙ 5 mg original tissue wet weight). Each tube was incubated for 15 min then filtered over Gf/B glass fibre filters and washed with 10 ml cold Tris. Each filter was counted in 10 ml Instagel (Packard) in a Packard Tri-Carb Scintillation Counter.

Stereospecific binding i.e., that to the benzodiazepine receptor was measured by the following procedure. Two sets of tubes were used:

[1] Tests which were administered only at the pre-drug and 3 h post-drug testings

Group A – tubes contain Tris buffer, ^{3}H Diazepam and calf brain.
Group B – tubes contain Tris buffer, ^{3}H Diazepam + 30 μM "cold" Diazepam calf brain.
Stereospecific Binding = A–B.
A standard curve was constructed using different amounts of "cold" diazepam and diazepam equivalents calculated from that.

Analysis of Data

A 4 way analysis of variance was calculated, the main sources of variance being subjects, drugs, occasions and times. Differences between drugs were obtained from the drugs × times interaction and were estimated against within-subject within-occasion error variance. Tukey's test (Winer 1962) was computed for the difference between means.

Results

Self-Ratings

1. Mood Rating Scale

Factor 1. Eight of the nine scales loading on this factor showed highly significant changes, so that the factor score was highly significant ($p < 0.001$). The subjects rated themselves as more drowsy after 10 mg diazepam at 1 h and 3 h but no effect remained at 5 h (Fig. 2).

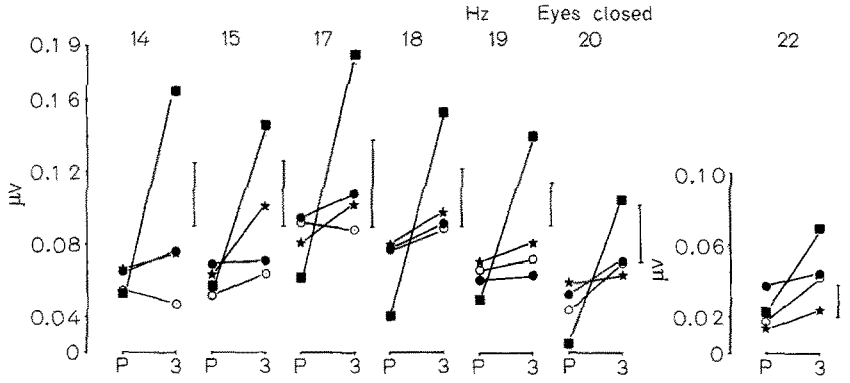

Fig. 4. Mean scores in microvolts on 14, 15, 17, 18, 19, 20 and 22 Hz on fourier analysis of the electroencephalogram under the eyes closed condition. Symbols as in Fig. 3

Tofisopam showed some significant effects in the opposite direction. On the higher dose of tofisopam (200 mg) the subjects rated themselves as slightly more alert than placebo at 5 h ($p < 0.05$).

Factor 2. The factor score showed no significance.

Factor 3. This factor score showed no significance.

2. Bodily Symptom Scale

Two of the fourteen scales showed significant effects. The subjects felt significantly more physical tiredness after diazepam ($F = 5.56$; $p < 0.001$) at 1 and 3 h. They experienced more dizziness after diazepam ($F = 2.90$; $p < 0.01$) at 1 h.

3. Sleep Rating Scale

The subjects felt slightly more sleepy on awakening the morning after taking diazepam 10 mg ($F = 3.03$; $p < 0.05$) compared to placebo and 100 mg tofisopam.

4. Hostility – Guilt Inventory.

The only significant finding on this inventory was that the subjects showed an increase in their ratings on the assault scale after placebo compared to the other drugs ($F = 3.85$; $p < 0.02$).

Physiological Measures

Electroencephalogram

a. Broad Waveband Analysis. Diazepam 10 mg caused a significant decrease in the amount of activity in the 7.5–13.5 Hz waveband under both eyes open ($F = 3.18$; $p < 0.02$) and eyes closed ($F = 3.99$; $p < 0.02$) conditions (Fig. 3). Tofisopam produced no significant effects.

b. Fourier Analysis. Diazepam significantly decreased the voltage at 6 Hz ($F = 2.99$; $p < 0.05$) under the eyes open condition. There was also a significant increase in the voltage at 17 ($p < 0.05$), 18 ($p < 0.05$), and 22 Hz ($p < 0.01$) under this condition and at 14 ($p < 0.001$), 15 ($p < 0.01$), 17 ($p < 0.01$), 18 ($p < 0.001$), 19 ($p < 0.001$), 20 ($p < 0.02$) and 22 Hz ($p < 0.05$) under the eyes closed condition after diazepam (Fig. 4). Tofisopam produced no statistically significant effects.

Psychological Measures

Auditory Reaction Time. There was a significant slowing of reaction time after diazepam at 1 h which persisted to 3 h ($F = 9.96$; $p < 0.001$) (Fig. 5). Diazepam also produced an increase in variability at 3 h ($p < 0.001$).

Tapping Rate. There was a significant increase in the inter-tap interval i.e., a slowing of tapping speed, at 1 h after diazepam ($F = 2.06$; $p < 0.05$) (Fig. 5).

Digit Symbol Substitution Test. Diazepam significantly decreased the number of items completed at 1 h and 3 h ($F = 2.44$; $p < 0.02$). Tofisopam produced no significant effects on any of these tests (Fig. 5).

Symbol Copying Test. The subjects copied significantly fewer symbols 1 h. after diazepam ($F = 2.25$; $p < 0.02$). This effect had worn off by 3 h. At 5 h all drugs showed worse scores than placebo but this was due to an increase in the placebo scores (Fig. 5).

Plasma Samples

The E max values obtained are shown in Table 1. The placebo values represent the limits of sensitivity of the technique. The values after diazepam are in the expected range. Apart from Subject 4, the values after tofisopam do not differ from those after placebo.

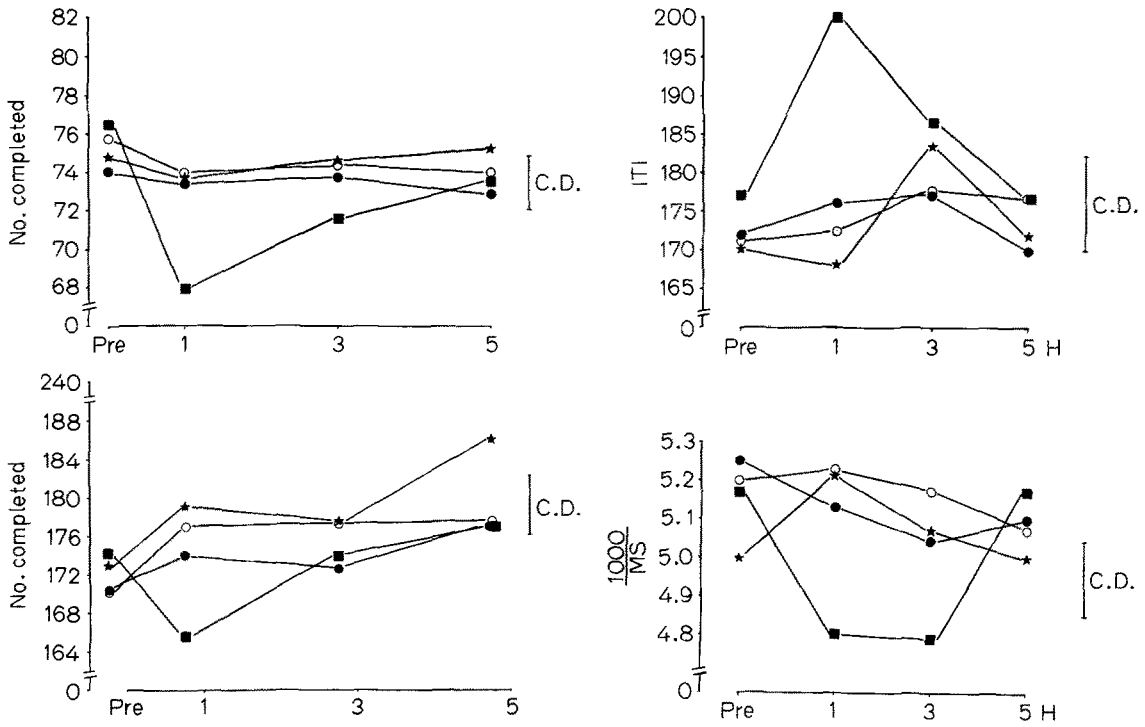

Fig. 5. Effects of the drugs on digit symbol substitution (top left), symbol copying (bottom left), tapping, measured by the inter-tap-interval (I.T.I.), (top right) and reaction time, represented by the mean reciprocal, (bottom right). Means and 0.05 critical differences are shown. Symbols as in Fig. 3

Table 1. Plasma levels of drugs (ng/μl, diazepam equivalent)

S	Placebo	Tofisopam 100	Tofisopam 200	Diazepam
1	5	13	9	100
2	11	5	5	214
3	0	7	14	114
4	5	54	14	71
5	0	/	5	171
6	15	7	14	148
7	20	0	0	100
8	16	5	10	171
9	5	5	6	103
10	5	14	0	111
11	0	6	0	60
12	11	10	5	185

Discussion

In this study, diazepam shows a clear profile of action similar to that obtained previously with other benzodiazepines (Bond and Lader 1972, 1973, 1975). It produced EEG changes, a decrease in the amount of activity in the 7.5–13.5 Hz waveband which is roughly equivalent to alpha and an increase in fast wave or beta activity, which are characteristic of benzodiazepines and have been found previously after diazepam (Karniol et al. 1976), pronounced sedation at 1 h which persisted to 3 h and a corresponding impairment of psychological performance. The last two effects are very similar to those found with lorazepam recently except that lorazepam's action is later, about 4 h (File and Bond 1979).

Tofisopam in no way resembled diazepam in these effects. It produced no changes in the EEG or psychological tests and displayed no sedative action. There was evidence, however, of a very mild stimulant effect associated with tofisopam and it is interesting to note that this did not occur until 3–5 h after drug administration. This is very different from diazepam where the effects are maximal at 1 h postdrug and seems to suggest one of two alternatives; either it is slowly absorbed and distributed to the brain or it is a pro-drug and is transformed to an active metabolite. In vitro studies showed that tofisopam did not bind to our receptor preparation which may support the idea that it is a prodrug requiring metabolic transformation before showing psychotropic effects and binding to receptors. Such a process would appear to be slow but could be investigated after chronic dosage of normals or patients.

Thus, tofisopam is an unusual benzodiazepine in that it is mildly stimulant and shows no sedative actions in single doses given to normal subjects. In fact a

recent study failed to show psychological or sedative effects after single or multiple doses (Seppälä et al. 1980) and in another study, a dose of 75 or 150 mg tofisopam given to healthy volunteers produced no effects on mood or psychomotor tests in contrast to diazepam 10 mg and lorazepam 2.5 mg (Lammintausta et al. 1980). If anxiolytic properties can be confirmed, it has a most useful profile of action. It is by no means unique in the claimed lack of sedative properties while being anxiolytic. Clobazam, a 1, 5 benzodiazepine, also seems to have these desirable properties (Hanks et al. 1979).

Neither benzodiazepine displayed any effect on the aggression ratings which is interesting in view of the recent postulations relating increased hostility to benzodiazepine action (Kochansky et al. 1975, 1977). In fact the only increase in hostility in the present study was caused by placebo on the assault scale of the Hostility - Guilt Inventory. Although this is not seen as a particularly important finding, it does indicate a need for caution in interpreting such findings after benzodiazepines.

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