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Effect on postural sway of various benzodiazepine tranquillizers

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1 The effects of various benzodiazepine tranquillizers (clobazam 20 mg, bromazepam 6 mg and lorazepam 2 mg) were investigated by posturography in 16 subjects in a controlled trial. Twelve received each of the three anxiolytics for 1 week in a cross-over design, four received placebo for 1 week during the three successive treatment periods. A pharmacodynamic study was carried out after the first administration, and another assessment was done after 1 week of treatment.

2 The first administration of lorazepam caused the most marked disturbances of body sway (increase of spectral energies, length and amplitude of the stabilogram).

3 The first administration of bromazepam was also accompanied by an increase of the posturographic parameters, although less marked.

4 Administration of clobazam did not produce any impairment of equilibrium, indicating that it is devoid of any sedative effect measurable by posturography.

5 No changes of the postural sway can be detected on the measurement recorded 10 h after the last dose of 1 week's treatment.

Keywords benzodiazepine clobazam lorazepam bromazepam posturography psychomotor performance

Introduction

It is now possible to measure the orthostatic postural activity objectively and precisely by means of vertical force platforms (posturography). The projection of the centre of gravity of a subject standing upright and stationary is in perpetual movement about a mid-position, and the precision with which the automatic equilibration system maintains this point close to the mid-position depends on the state of arousal of the subject. The recording of orthostatic posture therefore appears to be a useful tool for monitoring the changes in general arousal of a subject under the effect of psychotropic drugs.

Clobazam is a 1.5 benzodiazepine possessing a rapid and long-lasting anxiolytic activity (Barzaghi *et al.*, 1973; Hunt *et al.*, 1974) and causing only a few sedative effects, in contrast to other benzodiazepines (Berry *et al.*, 1974; Borland & Nicholson, 1974; Hindmarch, 1979a, b; Hindmarch *et al.*, 1977; Salkind *et al.*, 1979; Taeuber *et al.*, 1979; Wittenborn *et al.*, 1979; Sittig *et al.*, 1982). Its serum peak occurs 2–3 h after oral absorption. Its elimination half-life is of the order of 18 h and elimination occurs principally in the metabolised form in the urine. Its main metabolite, desmethylclobazam, also possesses anxiolytic activity and its elimination half-life is of the order of 42 h (Rupp *et al.*, 1979).

This anxiolytic was compared with two other compounds of the same therapeutic class, bromazepam and lorazepam.

Bromazepam is a 1.4 benzodiazepine with an elimination half-life of the order of 20 h (Kaplan *et al.*, 1976). It is eliminated principally in the metabolised form in the urine. Its main metabolite, 3-hydroxybromazepam, possesses anxiolytic properties, but is devoid of clinical effects as it is very rapidly eliminated.

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Lorazepam is a 1.4 benzodiazepine with an elimination half-life of the order of 15 h (Greenblatt *et al.*, 1979a, b). It is eliminated principally in the glucuro-conjugated form in the urine. Its metabolites are devoid of pharmacological activity.

Kinetic steady state, for these two drugs, as for clobazam, is reached after less than 8 days' treatment.

The purpose of this study was to attempt to assess objectively the sedative effects of these three drugs used at a current dosage in ambulatory treatment.

The dose regimen was chosen from the manufacturers prescribing information as available in France (Vidal, 1983), but as far as current practice in the United Kingdom is concerned, these doses are not necessarily considered to be equally potent.

Methods

Subjects

Sixteen healthy consenting ambulant subjects (eight females and eight males with a mean age of 25 years, a mean height of 170.75 cm and a mean weight of 62.43 kg) were admitted to the study. All of them were free of any disorders which might disturb either measurements (cerebellar or vestibular syndrome, past history of head injury) or the effects of the drug (hepatic or renal disorder). They refrained from any other medication (with the exception of the contraceptive pill for three women) during all the study. In addition, for the 24 h preceding the test session, they abstained from taking stimulants (coffee, tea, coca-cola, tobacco) as well as alcohol.

Study procedure

This was a controlled trial carried out on a double-blind basis, over a period of 36 days, in two parallel groups. In the first one (12 subjects), each volunteer received the three benzodiazepine tranquillizers (clobazam 20 mg, bromazepam 6 mg and lorazepam 2 mg) for 1 week in a cross over design. In the second one (four subjects), each volunteer received placebo for 1 week at the three successive treatment periods. The three sequences of treatment were separated by 1 week wash out interval.

The four compounds were packaged in identical capsules. The daily dosage was one capsule, administered at 08.00 h on an empty stomach the first day (in order to perform a pharmacodynamic study) and at 22.00 h from the second to the seventh day of each week's treatment.

The order of the drug's administration and the placebo group's allocation were determined by balanced drawing lots of randomised permutations. A pharmacodynamic study was performed after the administration of the first dose of each compound. Three posturographic recordings were done: a reference one (H0) at 07.30 h before the administration of the compound and two others, 2 and 4 h (H2 and H4) after the administration of the compound (i.e. at about 10.00 h and 12.00 h). Another posturographic measurement was done on the eighth day (D8) at 08.00 h (i.e. about 10 h after the last dose of the compound), after 1 week of treatment when steady state had been reached.

Assessment criteria: posturography

When standing at rest, the body is never completely stationary: it sways permanently in accordance with specific, complex rhythms, the amplitude and frequency of which allow for the different sensorimotor systems that locate and maintain the centre of gravity within the polygon of support. These movements, which allow for postural control, are of a very small amplitude and the subject is normally unaware of them. However, it is now possible to record them without difficulty and this is the purpose of posturography.

The apparatus is composed of a square platform (50 × 50 cm) made up of two lightweight alloy plates, which are sensitive to variations in pressure, and on which the subject stands upright. Four test elements are fixed to the four sides of the platform (front, back, left and right) and two pressure transducers (strain gauges) attached to them. The test elements are connected in pairs along the antero-posterior and right-left diagonals, forming two Wheastone bridges. The platform was calibrated using masses of known weight in all four directions. The precision was of the order of 1% (Patat, 1982).

A reference point was fixed to the centre of the platform so that the subject's feet could be exactly positioned on a repetitive basis in order to obtain reliable meaurements (Seidel *et al.*, 1978a, b). Subjects stood erect and motionless staring at a fixed point about 3 m in front of them, without shoes, arms by their sides, feet at an angle of 30°. The posturographic recordings lasted about 2 min (1 min eyes open; followed by 1 min eyes closed). This length of time prevented interference with the tracings from muscle fatigue (Gantchev *et al.*, 1971; Yamamoto & Iido, 1979).

These conditions complied with the recommendations proposed by the International Society of Posturography (Kapteyn *et al.*, 1983). The variations in pressure, while standing erect, detected by the transducers were then transformed into electrical signals, amplified and stored on an analog tape recorder, as two separate tracings. These signals corresponding to the sagittal and lateral body sway are named stabilograms (Figure 1). The data processing was done using a PDP 11/34 computer. The analog signals were converted into 1024 bites at a sampling frequency of 20 Hz (i.e. duration of 51.20 s). The signals were then normalized and filtered on a high pass filter with a cut-off frequency of 0.05 Hz to suppress the continuous residual frequency which might disturb the low frequency analysis (Seidel *et al.*, 1978a). Lastly power spectral density was calculated (Figure 1).

This kind of analysis was chosen because it has the advantage of better highlighting the different mechanisms governing equilibrium. The lower frequencies (less than 0.5 Hz) of the posturographic signal give a good illustration of the permanent movements of the centre of gravity's projection within the polygon of support of balance and mainly reflects the influence of vestibular input (Njiokiktjien, 1971; De Wit, 1972; Kapteyn, 1972, 1973; Kapteyn & de Wit, 1972; Gurfinkel, 1973). In the higher frequency band (ranging from 0.5 to 2 Hz) the signal reflects postural readjustment mainly of muscular origin (Njiokiktjien, 1971; Gurfinkel, 1973; Aggashian *et al.*, 1973; Mauritz & Dietz, 1980). In addition, patients suffering from cerebellar syndrome exhibit an energy peak in the region of 3 Hz (Dichgans *et al.*, 1976; Njiokiktjien *et al.*, 1978; Diener *et al.*, 1984). Parameters were calculated for the four spectra (principal peak amplitude, total energy which accounts for the overall postural activity, slow energies under 0.5 Hz and faster energies from 0.5 to 2 Hz) and for the stabilograms (total length defined as the sway path travelled by the centre of foot pressure on the platform and standard deviation).

It should be noted that the body sway tracings retain the same characteristics over several recordings conducted under identical conditions, in particular, where the amplitude of the sway is concerned, in respect of their frequency (Bessineton *et al.*, 1976) and their energies (Seidel *et al.*, 1978a, b; Spaepen *et al.*, 1979). Intra-individual differences are therefore slight and quantification of posturographic recording enables very precise assessment of each individual's balance characteristics. However, there are some fairly major inter-individual differences which are indicative of the predominance of one or other of the sensori-motor mechanisms involved in maintaining balance and which are characteristic of each subject.

Statistical analysis

The root mean square of the posturographic was calculated in order to ensure a distribution closer to the 'normal' one. Analysis of variance testing the drug and the time effects, was performed on an equilibrium index which provides a more general assessment of the postural activity. It consisted of the sum of the sagittal and lateral posturographic parameters in the two conditions eyes open and eyes closed. The pairwise comparisons of the means were done using the Student Newman Keuls method with the level of significance fixed at 0.05.

Results

No statistical analysis was done on the data calculated from the spectra of the four subjects, who received placebo during the three sessions, because of the small number in this group. The data were only considered for descriptive purposes and this enabled the good reproducibility of the measurement over time to be demonstrated.

The analysis of the results from the treated group showed, mainly after the first dose, a significant increase of the posturographic parameters for the measurements with eyes open

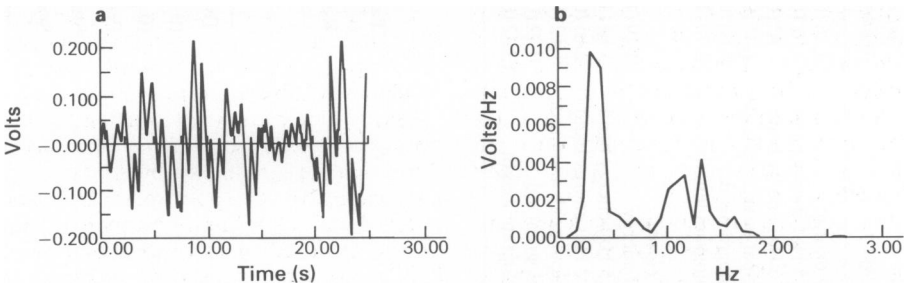

Figure 1 (a) Stabilogram: recording of body sway in the standing posture. (b) Power spectral density of stabilogram.

Table 1 The mean values and s.d. of the root mean square of balance index (sum of sagittal and lateral posturographic parameters)

Eyes open	*Before treatment*	*Clobazam 20 mg*			*Bromazepam 6 mg*			*Lorazepam 2 mg*		
		H2	*H4*	*D8*	*H2*	*H4*	*D8*	*H2*	*H4*	*D8*
Total energy	3.26 (0.87)	3.62 (1.78)	3.30 (0.99)	3.36 (0.97)	5.12 (2.18)	4.33 (2.22)	3.81 (2.83)	8.32 (4.16)	5.68 (2.38)	3.44 (1.12)
(0–0.5 Hz) energy band	2.91 (0.89)	3.35 (1.83)	2.95 (1.02)	3.00 (1.01)	4.85 (2.24)	3.95 (2.22)	3.45 (2.81)	8.01 (4.15)	5.36 (2.39)	3.08 (1.14)
(0.5–2 Hz) energy band	1.42 (0.22)	1.27 (0.27)	1.43 (0.26)	1.49 (0.19)	1.51 (0.40)	1.68 (0.64)	1.54 (0.64)	2.12 (0.83)	1.78 (0.63)	1.47 (0.36)
Principal peak amplitude	1.41 (0.45)	1.64 (0.86)	1.51 (0.56)	1.47 (0.39)	2.40 (1.12)	1.96 (1.19)	1.73 (1.27)	4.21 (2.50)	2.85 (1.53)	1.56 (0.66)
Stabilogram s.d.	0.68 (0.09)	0.71 (0.12)	0.67 (0.06)	0.71 (0.12)	0.79 (0.13)	0.75 (0.12)	0.72 (0.18)	0.91 (0.17)	0.82 (0.17)	0.71 (0.11)
Stabilogram length	12.70 (1.04)	12.59 (1.12)	12.69 (1.16)	12.58 (0.97)	13.07 (1.27)	13.01 (1.36)	12.81 (1.19)	13.73 (1.19)	13.39 (1.15)	12.64 (1.10)
Eyes closed										
Total energy	4.19 (1.22)	5.35 (2.45)	4.41 (1.78)	4.73 (1.31)	6.27 (3.60)	5.25 (2.83)	4.44 (2.08)	9.10 (5.10)	7.29 (4.04)	5.27 (2.30)
(0–0.5 Hz) energy band	3.62 (1.14)	4.75 (2.30)	3.92 (1.54)	4.27 (1.29)	5.75 (3.54)	4.71 (2.85)	3.96 (2.05)	8.38 (4.85)	6.55 (3.83)	4.69 (2.24)
(0.5–2 Hz) energy band	2.05 (0.53)	2.30 (1.24)	1.94 (1.03)	2.02 (0.45)	2.34 (1.13)	2.17 (0.81)	1.94 (0.64)	3.36 (1.95)	3.10 (1.52)	2.31 (0.87)
Principal peak amplitude	1.52 (0.50)	2.07 (1.05)	1.83 (0.82)	1.87 (0.50)	2.50 (1.51)	2.19 (1.36)	1.74 (0.89)	3.84 (1.99)	3.14 (1.94)	2.04 (1.04)
Stabilogram s.d.	0.72 (0.13)	0.79 (0.17)	0.75 (0.15)	0.77 (0.11)	0.80 (0.21)	0.69 (0.22)	0.72 (0.13)	0.95 (0.23)	0.90 (0.24)	0.77 (0.16)
Stabilogram length	13.42 (0.78)	13.59 (1.31)	13.26 (1.35)	13.29 (0.62)	14.06 (1.54)	13.58 (1.17)	13.58 (1.33)	15.02 (1.54)	14.41 (1.75)	13.79 (0.86)

Table 2 Results of ANOVA for each time session (treatment effect). Pairwise comparisons of the treatments (C = clozabam 20 mg, B = bromazepam 6 mg and L = lorazepam 2 mg) are calculated using the Student Newman Keuls method. Two treatments underlined by the same line are not significantly different

	Eyes open				*Eyes closed*			
	HO	*H2*	*H4*	*D8*	*HO*	*H2*	*H4*	*D8*
Total energy	NS	L B C*	L B C*	NS	NS	L B C*	L B C*	NS
(0–0.5 Hz) energy band	NS	L B C*	L B C*	NS	NS	L B C*	L B C*	NS
(0.5–2 Hz) energy band	NS	L B C*	NS	NS	NS	L B C**	L B C*	NS
Principal peak amplitude	NS	L B C*	L B C**	NS	NS	L B C*	L B C*	NS
Stabilogram s.d.	NS	L B C*	L B C*	NS	NS	L B C*	L B C**	NS
Stabilogram length	NS	L B C*	L B C**	NS	NS	L B C*	L B C**	NS

*$P < 0.05$, **$P < 0.01$

Table 3 Results of ANOVA for each treatment (time effect). Pairwise comparisons of the times (H0, H2, H4 and D8) are calculated using the Student Newman Keuls method. Two times, underlined with the same line, are not significantly different

Eyes open	*Clobazam*	*Bromazepam*	*Lorazepam*
Total energy	NS	NS	H2 > H4 > D8 H0*
(0–0.5 Hz) energy band	NS	H2 H4 D8 H0**	H2 > H4 > D8 H0*
(0.5–2 Hz) energy band	D8 H4 H0 H2**	NS	H2 H4 D8 H0*
Principal peak amplitude	NS	NS	H2 > H4 > D8 H0*
Stabilogram s.d.	NS	NS	H2 > H4 > D8 H0*
Stabilogram length	NS	NS	H2 H4 > D8 H0*
Eyes closed			
Total energy	H2 D8 H4 H0**	H2 H4 D8 H0**	H2 H4 D8 H0*
(0–0.5 Hz) energy band	H2 D8 H4 H0**	H2 H4 D8 H0**	H2 H4 D8 H0*
(0.5–2 Hz) energy band	NS	NS	H2 H4 D8 H0*
Principal peak amplitude	H2 D8 H4 H0**	H2 D8 H4 H0**	H2 H4 > D8 H0*
Stabilogram s.d.	NS	NS	H2 H4 > D8 H0*
Stabilogram length	NS	NS	H2 H4 D8 H0*

$^{*}P < 0.05$, $^{**}P < 0.01$

and, particularly, with eyes closed (Tables 1, 2 and 3, Figure 2). The drug which caused the most pronounced disturbances was lorazepam. Body sway recordings differed significantly after the first dose of lorazepam from the pretreatment measurement. These changes induced by lorazepam at H2 and H4 were so marked that this drug can also be significantly distinguished from clobazam and bromazepam. The modifications produced by bromazepam was intermediate between those induced by lorazepam and clobazam. Only the measurement taken 2 h after administration was significantly different from the pretreatment one, particularly for the total energy and the slow energies. The administration of clobazam produced the least changes in body sway.

Lastly, no significant modification of equilibrium was observed after a week of treatment by each of the three anxiolytics studied.

This trial allowed the three anxiolytics studied to be classified in decreasing order of sedative effect, as evidenced by the changes in orthostatic postural activity: lorazepam 2 mg, was accompanied by the most pronounced effects; bromazepam 6 mg, intermediate and clobazam 20 mg, induced the least marked alterations.

Discussion

This study confirmed the results of previous trials carried out mainly by means of tests exploring psychomotor performance and cognitive functions, which had shown the lack of any side effects of clobazam on arousal (Berry *et al.*, 1974; Borland & Nicholson, 1974; Hindmarch, 1979a, b; Hindmarch *et al.*, 1977; Salkind *et al.*, 1979; Taeuber *et al.*, 1979; Wittenborn *et al.*, 1979; Sittig *et al.*, 1982). Acute or chronic administration of 20 mg clobazam, in this study, was not accompanied by any identifiable effect on balance. In contrast, the first dose of bromazepam and, in particular, of lorazepam produced a marked enhancement of the index of equilibrium, eyes open and eyes closed. This might reflect rapid absorption and distribution of the drug, causing rapid onset of clinical effects with a reduction in anxiety, but equally well might be evidence of unwanted effects with, in particular, reduced arousal, drowsiness and muscle fatigue (Greenblatt *et al.*, 1981).

However, these unwanted effects do not necessarily increase in parallel with the elevation in plasma levels obtained after repeated administrations. In fact, rapid habituation, principally in as far as the sedative effects are concerned, may be observed in the case of long-term administration and be accompanied by attenuation or even disappearance of the unwanted effects (Wittenborn *et al.*, 1979; Aranko *et al.*, 1983).

This study clearly differentiated lorazepam from clobazam by its pronounced sedative effects, especially after a single dose, and corroborated the results observed by Hindmarch & Gudgeon (1980) and Siegfried *et al.* (1981) in psychomotor performance. A number of other studies have also reported major sedative effects accompanied

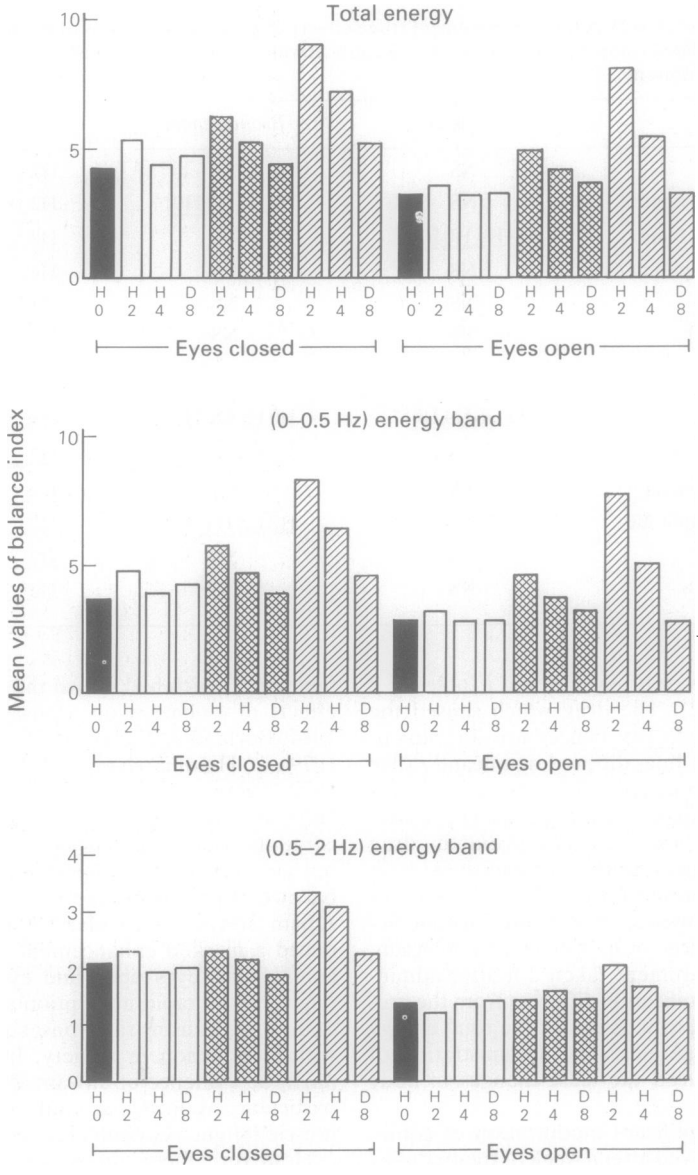

Figure 2 Evolution of the mean values of balance index (sum of the sagittal and lateral spectral energies of body sway) after an acute administration of each tranquillizer (H2: 2 h; and H4: 4h) and after repeated administration for a week (D8: Day 8). ■ before treatment, □ clobazam 20 mg, ■ bromazepam 6 mg and, ▨ lorazepam 2 mg.

by disturbances of psychomotor performance after the administration of lorazepam (Bell *et al.*, 1973; Seppala *et al.*, 1976; File & Bond, 1979; Seppala *et al.*, 1982). Bromazepam is in an intermediate position. It differed significantly neither from lorazepam nor from clobazam, but, 2 h after the initial dose, it caused a significant enhancement of postural sway compared with the pre-treatment measurement. This confirmed the disturbances of psychomotor performance already noted during previous studies (Saario, 1976; Saario & Seppala, 1976; Hobi *et al.*, 1982).

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