EFFICACY AND TOLERANCE: COMPARATIVE STUDIES WITH BROtizOLAM AND FLUNITRAZEPAM

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- 1 Efficacy of and tolerance to 0.25 mg brotizolam and 2.0 mg flunitrazepam were compared over a period of 6 days in ambulatory patients complaining of sleep disturbance. The study was double-blind and randomised with a parallel group design.
- 2 Both drugs improved sleep. More patients assessed sleep latency as shorter during the first night of ingestion with flunitrazepam than with brotizolam, but assessments were comparable over the next 5 days. The number of patients who considered that the frequency of nocturnal awakenings was less did not differ significantly between drugs.
- 3 Tolerance to brotizolam (0.25 mg) was assessed more favourably than with flunitrazepam (2.0 mg).
- 4 The study suggests that brotizolam (0.25 mg) is indicated for patients who have difficulty in falling asleep and staying asleep, and who must preserve their alertness during the early part of the next day. Flunitrazepam (2.0 mg) is equally effective, but at this dose there is a higher incidence of adverse effects.

Keywords brotizolam flunitrazepam efficacy tolerance hypnotic sleep

Introduction

There are many factors which influence the usefulness of an hypnotic and these may be related to the nature of the sleep disturbance. One such factor is the efficacy of a drug in reducing awakenings during the night and such an effect is particularly useful when it is free of residual sequelae the next day. However, the pharmacokinetic profile of an hypnotic which reduces awakenings during the latter two-thirds of the night without effects on awakening is critical: the rate of fall in plasma level after attaining the peak plasma concentration must be optimum.

It is in this context that we have carried out a comparative study between brotizolam (Lendormin®) and flunitrazepam as they have very different pharmacokinetic profiles. With brotizolam the fall in plasma level is related mainly to elimination and so with a mean elimination half-life of around 4.4 h (Jochemsen *et al.*, 1983; Bechtel *et al.*, 1983) the fall is not too fast over the period when nocturnal awakenings can be expected. On the other hand with flunitrazepam there is a particularly rapid fall in plasma level during the distribution phase (Amrein *et al.*, 1979). In the study we have compared 0.25 mg brotizolam and 2.0 mg flunitrazepam: 2.0 mg flunitrazepam is currently recommended in several

European countries, though there would appear to be some doubts that this is the most appropriate dose (Bond & Lader, 1975; Lader *et al.*, 1982; Nicholson *et al.*, 1980).

Methods

The study was carried out with 193 ambulatory patients (80 males, 113 females) from 21 centres with acute sleep disturbances requiring medication. Exclusion criteria were pregnancy and lactation, myasthenia gravis, dependency on psychotropics or alcohol, hypersensitivity to diazepines, and hepatic failure. A randomised, parallel group design was used. In each group the patients ingested a placebo on the first day and the appropriate medication (0.25 mg brotizolam or 2.0 mg flunitrazepam) for the next 6 days. The study was double-blind.

The physician recorded gender, age, height and weight of each patient as well as the diagnosis, treatment of primary disease and current medication. The nature of the sleep disturbance was recorded as difficulty in getting to sleep, difficulty in sleeping through the night or difficulty with getting to sleep and sleeping through the night. Previous hypnotic medication

was noted and whether it was taken occasionally or regularly.

Efficacy of and tolerance to the drug were assessed by the physician at the end of treatment using a three-point scale (good, satisfactory and unsatisfactory). Side-effects were assessed as mild, moderate or severe with no, dubious, probable or certain connection with the medication.

Each morning the patients assessed their sleep and alertness. They estimated how long it took them to fall asleep (about 5 min, about 15 min, about 30 min, or more than 1 h), how often they woke up (not at all, once or twice, three or four times, more than four times), how well they slept (extremely well, well, moderately, badly), how deeply they slept (very deeply, moderately deeply, superficially), how many hours they slept (more than 8 h, less than 8 h, less than 6 h, less than 4 h), and what time they woke up in the morning and their condition (fresh/wide awake, still rather tired/unpleasantly tired).

Each evening the patients assessed their condition during the day (well, moderate, unwell) and whether any events during the day could affect their sleep during the coming night.

The chi-square homogeneity test was used for direct comparison of the drugs. It was applied to the evaluation of efficacy and safety and to the sleep questionnaire data for days 2–7. Sleep changes during ingestion according to each of the subjective criteria of sleep latency, frequency of awakening, sleep quality, subjective condition in the morning, were assessed using the values for day 1 (placebo) and day 7 in each of the two treatment groups by means of the McNemar test. The chi-square values were calculated from contingency tables by reduction of the original scales to two levels, i.e. sleep latency was considered as less or equal to 15 min or as greater than 15 min, frequency of awakening was considered as nil or once/several times, sleep quality was considered as excellent/good or fair/poor and the subjective condition in the morning was considered as refreshed or slightly tired/unpleasantly tired.

Results

Ninety-eight patients (20–91 years) were assigned to

the brotizolam group (BG) and 95 patients (21–84 years) were assigned to the flunitrazepam group (FG). Data for gender and age, height and weight for each group are given in Table 1. In both groups the patients' ages varied widely, but approximately equal numbers of patients were found in the age groups 40–50, 50–60 and 60–70 years. In the initial assessment of their sleep problems, 61 patients (32 BG and 29 FG) complained of difficulty in getting to sleep, 26 patients (17 BG, 9 FG) of difficulty in staying asleep and 107 patients (49 BG, 58 FG) of both types of disturbance.

The illnesses of the patients frequently involved multiple diagnoses including hypertension (11 BG, 11 FG), cardiac and peripheral vascular disease (27 BG, 26 FG), pulmonary disease (9 BG, 4 FG), degenerative bone disease including fractures (13 BG, 13 FG), diabetes and obesity (9 BG, 7 FG), disease of the central nervous system (10 BG, 7 FG), psychiatric (13 BG, 7 FG), and diseases of the liver, biliary and gastrointestinal tracts (6 BG, 8 FG).

The physicians assessed the efficacy of brotizolam as good in 55.1%, satisfactory in 27.6% and unsatisfactory in 12.2% of patients, and of flunitrazepam as good in 56.2%, satisfactory in 30.2% and unsatisfactory in 10.4% of patients. Tolerance to each drug was found to be good in 84.7% of cases with brotizolam and 69.8% with flunitrazepam. It was satisfactory in 7.14 and 16.7% respectively and unsatisfactory in 6.1 and 9.4% respectively (Figure 1). Because of missing data from some patients, 93 patients from each group for the efficacy studies and 96 and 92 patients from brotizolam and flunitrazepam groups for the safety studies were used in the statistical analysis. The chi-square homogeneity test showed that there were no significant differences in efficacy between the two drugs, but that more patients tolerated brotizolam better than flunitrazepam ($P = 0.057$).

Brotizolam and flunitrazepam induced an average sleep latency, as assessed by the patients, of between 15 and 30 min, and this did not change over the course of the 6 days with either treatment. Frequency of wakening, sleep quality, subjective condition after wakening each reflected a trend towards an improvement during the course of treatment. Brotizolam and flunitrazepam were both superior to placebo ($P < 0.001$) in all four sleep parameters using the comparison between the first day with placebo and the last day of drug treatment.

Table 1 Age and anthropometric data

	Brotizolam group Men (44); Women (54)				Flunitrazepam group Men (36); Women (59)			
Age (years)	56.2	12.3	59.4	14.9	55.1	13.3	56.7	14.8
Height (cm)	171.6	6.5	164.6	5.7	173.7	5.3	164.8	5.6
Weight (kg)	75.7	11.5	64.6	8.05	76.5	8.1	65.8	12.5
Over 60 years of age (<i>n</i>)	17		27		13		27

Figure 1 Physicians' assessment of efficacy and tolerance. Comparison of brotizolam (0.25 mg) and flunitrazepam (2.0 mg) ■ good, □ satisfactory, ▨ unsatisfactory.

There was a tendency for patients weighing 65 kg or more to assess the efficacy of brotizolam as greater than those weighing 65 kg or less ($P < 0.06$). This relationship was not observed with flunitrazepam. Sleep latency on day 2 was assessed by more patients as shorter with flunitrazepam than with brotizolam ($P < 0.058$). Initial inspection of the data suggested that over the period of medication the number of patients who fell asleep within 15–30 was always greater with flunitrazepam than with brotizolam, while the number of patients who reported two or less awakenings at night was always greater with brotizolam than with flunitrazepam, but it was not possible to establish these differences statistically.

Thirteen patients after brotizolam and 27 patients after flunitrazepam complained of side-effects—the most frequent being tiredness, drowsiness and hangover. Headache, gastric symptoms and dizziness were also reported both during brotizolam and during flunitrazepam treatment, but were unlikely to have been related to the drugs. Three patients after brotizolam and eight patients after flunitrazepam prematurely discontinued the study. The reasons for the withdrawals from brotizolam were tiredness, insufficient effect and an unconnected side-effect, and from flunitrazepam were tiredness and hangover.

Discussion

The present study has shown that the clinical effectiveness of 2.0 mg flunitrazepam and 0.25 mg brotizolam over a period of several days is broadly comparable. The pharmacokinetic profile of brotizolam

would have been consistent with a greater reduction in the frequency of nocturnal awakenings than would have been expected with flunitrazepam, but this difference which was suggested by a cursory inspection of the data, was not significant.

Though it was not possible to establish differences in the hypnotic profile between 2.0 mg flunitrazepam and 0.25 mg brotizolam an important finding was that flunitrazepam led to a greater incidence of adverse effects—interpreted by the physicians as reduced tolerance and by the patients as side-effects—than 0.25 mg brotizolam. This would suggest that 2.0 mg flunitrazepam is too high a dose in clinical practice, and this would be consistent with experience elsewhere, where the drug has been introduced in the dose range 0.5–1.0 mg.

Flunitrazepam, in the dose range 0.5–1.0 mg, may well prove to be a useful drug in the management of sleep onset insomnia when freedom from residual effects is a consideration, but the question arises that in view of the rapid fall in plasma levels associated with its distribution phase whether 1.0 mg would be as effective as 0.25 mg brotizolam in maintaining sleep during the night when frequent nocturnal awakenings is the problem. Indeed, the present studies suggest that the clinical profile of brotizolam is likely to prove superior to that of flunitrazepam. Brotizolam (0.25 mg) is appropriate for patients who have difficulty in getting to sleep and in maintaining their sleep, and is useful for those who must preserve their alertness during the early part of the next day. On the other hand, though flunitrazepam may be useful in patients with sleep onset insomnia, it is possible that only doses which may lead to residual effects will be effective when the patients have particular difficulty in staying asleep.

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Wirksamkeit und Verträglichkeit: Vergleichsstudien mit Brotizolam und Flunitrazepam

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1 Wirksamkeit und Verträglichkeit von 0,25 mg Brotizolam und 2,0 mg Flunitrazepam wurden während 6 Tagen an ambulanten Patienten, die über Schlafstörungen klagten, verglichen. Es handelte sich um eine randomisierte Doppelblindstudie mit paralleler Gruppenanordnung.

2 Beide Substanzen verbesserten den Schlaf. Die Einschlafzeit in der ersten Behandlungsnacht wurde von mehr Patienten unter Flunitrazepam als unter Brotizolam als kürzer empfunden, doch waren die Beurteilungen der folgenden 5 Tage vergleichbar. In der Zahl der Patienten, die die Aufwachhäufigkeit pro Nacht als geringer beurteilten, zeigte sich für beide Substanzen kein signifikanter Unterschied.

3 Die Verträglichkeit von Brotizolam (0,25 mg) wurde günstiger beurteilt als die von Flunitrazepam (2,0 mg).

4 Die Studie deutet darauf hin, dass Brotizolam (0,25 mg) indiziert ist für Patienten mit Einschlaf- und Durchschlafstörungen, die in den frühen Stunden des folgenden Tages ihre uneingeschränkte Leistungsfähigkeit benötigen. Flunitrazepam (2,0 mg) ist gleichermassen wirksam, doch treten bei dieser Dosierung häufiger Nebenwirkungen auf.

Efficacité et tolérance: études comparatives du brotizolam et du flunitrazépam

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1 L'efficacité et la tolérance de 0,25 mg de brotizolam et de 2,0 mg de flunitrazépam ont été comparés pendant une période de 6 jours chez des patients en traitement ambulatoire se plaignant de troubles du sommeil. Cette étude a été réalisée en double aveugle et la succession laissée au hasard par un plan de groupes parallèles.

2 Les deux médicaments ont amélioré le sommeil. Un plus grand nombre de patients a constaté que le temps de latence avant l'arrivée du sommeil avait été plus bref, la première nuit, après la prise du flunitrazépam, mais les appréciations ont été comparables pour les deux préparations durant les 5 jours suivants.

Le nombre de patients ayant estimé que la fréquence des éveils nocturnes avait été moindre n'a pas présenté de différence significative entre les deux préparations.

3 La tolérance au brotizolam (0,25 mg) a été considérée meilleure que celle au flunitrazépam (2,0 mg).

4 Les résultats de cette étude semblent indiquer que le brotizolam (0,25 mg) convient aux patients ayant des difficultés à s'endormir et à rester endormis, mais devant disposer de toutes leurs facultés durant les premières heures du jour suivant. Le flunitrazépam (2,0 mg) est également efficace, mais, à cette dose, la fréquence des effets secondaires est supérieure.

Eficacia y tolerancia: estudios comparativos con brotizolam y flunitrazepam

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1 La eficacia y tolerancia de 0,25 mg brotizolam y 2,0 mg flunitrazepam han sido objeto de comparación durante un período de 6 días en pacientes ambulatorios que presentaban trastornos del sueño. El estudio fue doble-ciego y randomizado, con un diseño de grupos paralelos.

2 Ambos fármacos mejoraron el sueño. Durante la primera noche de ingestión un mayor número de pacientes valoró el período de latencia del sueño como más breve con flunitrazepam que con brotizolam, pero las valoraciones resultaron comparables durante los 5 días subsiguientes. Por lo que respecta al número de pacientes que consideraron que la

frecuencia de despertares nocturnos era menor no se dan diferencias significativas entre los fármacos.

3 En cuanto a la tolerancia, brotizolam (0,25 mg) mereció una valoración más favorable que flunitrazepam (2,0 mg).

4 El estudio sugiere que brotizolam (0,25 mg) está indicado en pacientes que presentan dificultades tanto para conciliar como para mantener el sueño, y que deben preservar su estado de alerta durante la primera parte de la jornada siguiente. Flunitrazepam (2,0 mg) resulta igualmente eficaz, pero a esta dosis conlleva una mayor incidencia de efectos secundarios.