COMPARATIVE STUDY ON THE EFFICACY OF AND THE TOLERANCE TO THE TRIAZOLODIAZEPINES, TRIAZOLAM AND BROtizOLAM

EDDA GOETZKE¹, P. FINDEISEN² & INÉS B. WELBERS³

¹ Department of Medicine, ² Department of Data Processing, Boehringer Ingelheim KG, ³ Central Department of Medical Services, Boehringer Ingelheim Zentrale GmbH, 6507 Ingelheim am Rhein, Federal Republic of Germany

1 Efficacy of and tolerance to 0.25 mg brotizolam and 0.25 mg triazolam were compared in hospitalised patients (aged 20 to 69 years) with sleep difficulties.

2 Over 6 days there were no differences in efficacy and tolerance. The physicians reported the effectiveness of the drugs as good-to-satisfactory in 88.6% with brotizolam and 92.0% with triazolam. The patients reported with both drugs reduced time to fall asleep, less awakenings, increased duration of sleep and improved condition on awakening.

Keywords brotizolam triazolam tolerance efficacy hypnotic insomnia

Introduction

Demethylation of the 1,4-benzodiazepines usually leads to metabolites which are slowly eliminated. This is seen with diazepam which is metabolised predominantly to desmethyldiazepam and leads with daily ingestion to accumulation of the metabolite as well as to the parent compound (Greenblatt *et al.*, 1980). To avoid this pathway the 1-position of the diazepine ring has been substituted with complex radicals, but often, in man at least, it is broken off and the long-acting metabolite is formed. However, the development of the triazolodiazepines in which complex heterocyclic ring structures are placed across the 1,2-position has led to compounds which are resistant to breakdown. The major metabolites are hydroxy derivatives, and these are rapidly conjugated with glucuronic acid and excreted in the urine. Two important examples of this group of drugs are the triazolo-benzodiazepine, triazolam (Eberts *et al.*, 1981) and more recently the triazolo-thienodiazepine, brotizolam (Lendormin®) (Bechtel, 1983; Koch, 1979; Krueger, 1983; Kuhn *et al.*, 1983; Saletu *et al.*, 1981; Velasco *et al.*, 1981). In this study we have compared their effectiveness and tolerance using the 0.25 mg dose in each case.

Methods

The study was carried out as a multicentre study in hospitalised patients who required an hypnotic

because of sleep difficulties. Exclusion criteria were pregnancy and lactation, acute or chronic hepatic and renal insufficiency, psychosis, patients known to be dependent on hypnotics, tranquillisers or alcohol, hypersensitivity to diazepam and myasthenia gravis.

The physician recorded the gender, age, height and weight of each patient as well as the diagnosis, treatment of primary disease, operation (if any) 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, and the previous use of hypnotics was noted.

Efficacy of and tolerance to the drugs were assessed by the physician at the end of each treatment period together with the night nurses' reports and the patients' assessments. The assessments of efficacy were on a three-point scale (good, satisfactory and unsatisfactory). Side effects were also assessed (mild, moderate or severe) and their connection (none, dubious, probable or certain) with the drug under study noted. These assessments were made each morning after ingestion of a placebo or drug overnight when the physician also noted whether the patient was found asleep and whether the patient seemed well rested and fresh. Pulse rate, systolic and diastolic pressure, rectal temperature and bowel movements were recorded at that time.

The night nurse recorded the time of ingestion of

the tablets and whether it was considered that the patient fell asleep in less or more than 30 min. If the patient was found awake during the night it was recorded whether this was one–three times or more than three times.

Each morning the patients assessed their sleep and their early morning 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).

It was a double-blind, crossover trial and the ingestion of drugs was randomised. The duration of the study was 14 days, and each assessment period lasted 7 days. On the first day of each 7-day period the patients ingested placebo and over the next 6 days they ingested either 0.25 mg brotizolam or 0.25 mg triazolam.

The data provided by 79 patients were adequate for statistical analysis, and for each drug a mean value was calculated from the verum nights of each treatment period. A two-way analysis of variance was applied to the 79×2 matrix of the mean values. To show change in the various parameters for each treatment the values for day 1 (placebo) and for day 7 (final treatment day) were compared in a two dimensional frequency table using the McNemar test. The efficacy of the two preparations was compared in a similar way.

Results

There were 86 in-patients (54 women and 36 men) aged between 20 and 69 years. Gender, age, height and weight data are given in Tables 1 and 2. Diagnoses were multiple and included diseases of the cardiovascular system (34), asthma, bronchitis and emphysema (7), diseases of the liver, biliary and intestinal tracts (15), diabetes and obesity (9),

Table 2 Distribution of age by gender

	Age (years)			
	20–44	45–54	55–64	65–69
Male	5	10	14	5
Female	28	13	5	6

disease of the central nervous system (7) and gynaecological disorders (12).

Thirty-eight patients complained of difficulties in getting to sleep, 15 of difficulties in sleeping without waking and 35 with difficulties in both getting and staying asleep. Of those who complained of difficulties in getting to sleep, 21 had taken other hypnotics and of those who complained of difficulties in sleeping without waking, eight had taken other hypnotics. Twenty-eight of the 35 who had both difficulties had taken hypnotics previously. The physicians assessed the efficacy of brotizolam and triazolam as good or satisfactory in 88.6% and 92.0% respectively, and tolerance as good or satisfactory in 97.7% with both drugs. There were no differences in the assessments of efficacy and tolerance, and there were no changes of clinical relevance in blood pressure, pulse rate and temperature during the two 7-day periods of ingestion.

Night nurses reported that with brotizolam and triazolam 34 and 39 patients respectively fell asleep within 30 min preceding the treatment period (day 1 with placebo) and that the average number of patients who fell asleep within 30 min over the next 6 days was 55.5 for each treatment. Before treatment (day 1 with placebo) 54 and 57 patients for brotizolam and triazolam respectively were found asleep throughout the night, and the average number of patients found asleep over the next 6 days were 70.5 and 73.8 respectively.

The patients were unable to differentiate between the two drugs ($P > 0.1$). For each drug they assessed that the time required to fall asleep was less, the frequency of awakening was reduced, quality of sleep was improved, duration of sleep increased and condition after awakening improved when day 7 was compared with day 1 (all comparisons $P < 0.01$) (Table 3, Figures 1 and 2).

Patients weighing 65 kg or less assessed the efficacy of brotizolam as less than those weighing

Table 1 Age and anthropometric data

	Men (n = 34)			Women (n = 54)		
	Age (years)	Height (cm)	Weight (kg)	Age (years)	Height (cm)	Weight (kg)
Mean	53.7	173.2	77.0	45.8	165.8	65.7
s.d.	11.0	6.1	14.4	13.8	5.4	14.3
Range	22–69	152–184	54–128	20–75	151–179	42–130
Median	55.0	174.0	75.7	43.0	165.5	64.5

Table 3 Assessments by patients on day 7 after 6 days of medication compared with day 1 (placebo)

Drug (mg)	Time to fall asleep (min)			
	less than 5	5-14	5-29	Greater than 30
Brotizolam 0.25	5 (3)	36 (20)	22 (21)	13 (32)
Triazolam 0.25	6 (Nil)	45 (27)	21 (22)	7 (30)
Drug (mg)	Frequency of awakenings			
	0	1-2	3-4	More than 4
Brotizolam 0.25	34 (19)	30 (28)	9 (16)	3 (13)
Triazolam 0.25	32 (14)	37 (26)	4 (22)	4 (15)
Drug (mg)	Duration of sleep (h)			
	More than 8	6-8	4-6	Less than 4
Brotizolam 0.25	40 (17)	21 (24)	9 (19)	6 (16)
Triazolam 0.25	38 (22)	28 (22)	10 (21)	3 (14)

Figure 1 Patients' assessments. B = brotizolam 0.25 mg, T = triazolam 0.25 mg and P = placebo

Figure 2 Patients' assessments. B = brotizolam 0.25 mg, T = triazolam 0.25 mg and P = placebo

more than 65 kg and though it was not possible to establish the same effect with triazolam, it is suggested by the data. No relation could be established between the efficacy of the drugs and age or gender.

Side effects were reported by five patients (two after brotizolam and three after triazolam). In two patients the effect was probably connected with the drug (hangover and mild skin allergy after triazolam). Four patients withdrew from the trial (one after brotizolam, three after triazolam) either because of side effects or lack of efficacy.

Discussion

It is clear from these studies that the efficacy of and tolerance to triazolam and brotizolam are similar. Both drugs in the 0.25 mg dose led to an improvement in sleep onset and in nocturnal awakenings as assessed by the patients, and these

improvements were without residual effects the next day. These findings would be consistent with pharmacokinetic (Bechtel, 1983; Jochemsen *et al.*, 1983) and pharmacodynamic (Goetzke *et al.*, 1983; Rittmeyer *et al.*, 1983) studies which would suggest that the absence of a fast and prolonged distribution phase, as with flunitrazepam, may be more likely to be associated with a sustained effect over the night, while a fast elimination phase may be consistent with both well maintained sleep and absence of residual sequelae the next day. It was also of interest that the heavier subjects reported better efficacy with brotizolam. This observation may be related to the high lipophilicity of brotizolam as the possibility arises that elimination rates may be related to body weights (Bechtel, unpublished data).

It is concluded from these studies that the dose of brotizolam which should be used in hospitalised patients with sleep difficulties is the same as that for triazolam. The efficacy of both drugs in this dose

(0.25 mg) was reported as good-to-satisfactory in around 90% of patients, and is adequate for the majority of patients.

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Vergleichsuntersuchungen über Wirksamkeit und Verträglichkeit der Triazolodiazepine, Triazolam und Brotizolam

E. GOETZKE, P. FINDEISEN & I.B. WELBERS

1 Die Wirksamkeit und Verträglichkeit von 0,25 mg Brotizolam und 0,25 mg Triazolam wurden bei stationären Patienten (20-69 Jahre) mit Schlafstörungen verglichen.

2 Über einen Zeitraum von 6 Tagen fanden sich weder Unterschiede in der Wirksamkeit noch in der Verträglichkeit. Die Ärzte beurteilten die

Wirksamkeit der Arzneimittel als gut bis zufriedenstellend bei 88,6% der mit Brotizolam und bei 92,0% der mit Triazolam behandelten Patienten. Bei beiden Arzneimitteln wurde eine verkürzte Einschlafzeit, selteneres Aufwachen, eine Schlafverlängerung sowie ein besseres Befinden beim Aufwachen beobachtet.

Etude comparative de l'efficacité et de la tolérance des triazolo-diazépines triazolam et brotizolam

E. GOETZKE, P. FINDEISEN & I.B. WELBERS

1 L'efficacité et la tolérance de 0,25 mg de brotizolam et de 0,25 mg de triazolam ont été comparées chez des patients hospitalisés (de 20 à 69 ans) présentant des troubles du sommeil.

2 Aucune différence d'efficacité et de la tolérance n'a été constatée pendant les 6 jours de l'essai. Les médecins ont rapporté une efficacité

bonne à satisfaisante dans 88,6% des cas traités par le brotizolam contre 92,0% pour ceux traités par le triazolam. Les patients ont indiqué que les deux préparations ont réduit le temps de latence jusqu'au début du sommeil et le nombre de réveils, augmenté la durée du sommeil et amélioré leur état au réveil.

Estudio comparativo sobre la eficacia y tolerancia de las triazolo-diazepinas triazolam y brotizolam

E. GOETZKE, P. FINDEISEN & I.B. WELBERS

1 En pacientes hospitalizados (edades comprendidas entre 20 y 69 años) con trastornos del sueño se estudiaron la eficacia de 0,25 mg brotizolam y 0,25 mg triazolam y su tolerancia.

2 Durante un período de 6 días no se produjeron diferencias en cuanto a la eficacia y tolerancia. Los médicos comunicaron que la eficacia de los

fármacos fue entre buena y satisfactoria en el 88,6% de los casos tratados con brotizolam y en el 92,0% de los tratados con triazolam. Con ambos fármacos los pacientes comunicaron una reducción del tiempo necesario para conciliar el sueño, menor número de despertares, aumento de la duración del sueño y un mejor estado general al despertar.