COMPARATIVE PHARMACOKINETICS OF BROtizOLAM AND TRIAZOLAM IN HEALTHY SUBJECTS

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1 Pharmacokinetics of oral brotizolam (0.50 mg) and triazolam (0.50 mg) were studied in healthy young volunteers.

2 The plasma concentration profile of brotizolam can be described as a one compartmental open model with first-order absorption. The absorption of triazolam was less regular and in half of the subjects was not consistent with first-order kinetics. Inter-individual variability in absorption rate (peak times) was larger for brotizolam.

3 Mean peak times were 1.1 ± 1.0 h for brotizolam and 1.2 ± 0.5 h for triazolam. Mean peak concentrations were 7.3 ± 3.1 ng/ml and 5.0 ± 3.9 ng/ml respectively.

4 The elimination half-life of brotizolam was twice that of triazolam with mean values of 5.0 ± 1.1 h and 2.6 ± 0.7 h respectively. There was no correlation between the half-lives of the two drugs.

5 Protein unbound fraction was similar for triazolam and brotizolam with mean values of $9.9 \pm 1.5\%$ and $8.4 \pm 0.7\%$ respectively.

Keywords brotizolam triazolam oral administration comparative pharmacokinetics healthy volunteers

Introduction

Brotizolam and triazolam are two triazolodiazepines, which are relatively short-acting hypnotics, free from residual effects on performance in the dose range of about 0.20–0.40 mg (Nicholson & Stone, 1980; Nicholson *et al.*, 1980). Triazolam (Halcion®), a 1,4-benzodiazepine, is marketed in most European countries. It has elimination half-lives in the range of 1.5–3.5 h (Eberts *et al.*, 1981; Jochemsen & Breimer, 1981). Brotizolam (Lendormin®), a 1,4-thienodiazepine, has half-lives in the range of 3–6 h (Jochemsen *et al.*, 1983). They are metabolized by the same pathways: the major metabolites are the 1-methylhydroxy- and the 4-hydroxy-derivatives. The hydroxy-compounds are presumably rapidly glucuronidated and excreted in the urine.

We have compared the pharmacokinetics of oral brotizolam and triazolam in the same group of healthy volunteers using a specific assay method for the determination of unchanged brotizolam and triazolam in plasma.

Methods

Experimental design

The subjects were eight healthy young volunteers, aged between 21 and 26 years; five males and three females (Table 1). All subjects had normal renal and hepatic function and none used medication apart from those females who took the combined oral contraceptive. The protocol was reviewed by an ethical committee and the volunteers gave their written informed consent.

The subjects received triazolam (Halcion®, 0.50 mg) and brotizolam (Lendormin®, 0.50 mg) orally with an interval of at least 3 weeks between the two. The tablets were swallowed with 150 ml of water.

The subjects fasted from 24.00 h on the night preceding the study and no food, fluid or tobacco was allowed for 3 h after drug administration. During this period the subjects remained in the

Table 1 Subject characteristics

Subject	Gender	Age (years)	Weight (kg)	Height (m)	Cigarettes (number/day)
1	F	21	52	1.61	>15
2	F	23	58	1.61	5-10
3	F	26	72	1.68	5-10
4	M	24	82	1.86	>15
5	M	24	63	1.80	-
6	M	22	73	1.82	5-10
7	M	23	76	1.80	5-10
8	M	24	76	1.76	>15

supine position. Venous blood samples were drawn via a flexible cannula at the following times after drug administration: 20, 40, 60, 80, 100 and 120 min and 3, 4, 6, 9 and 12 h. A 24 h sample was taken by separate venepuncture. Following brotizolam administration, additional samples were taken at 32 and 48 h. All blood specimens were collected in heparinized tubes and, after separation, the plasma samples were stored at -20°C until analysis.

Triazolam and brotizolam plasma concentrations were determined by capillary gas chromatography with a solid injection system and electron capture detection (Jochimsen & Breimer, 1981; Jochimsen *et al.*, 1983)

The binding of triazolam and brotizolam to plasma proteins was determined by equilibrium dialysis in the Dianorm equilibrium dialysis system (Diachema, Abcoude, The Netherlands), with a control sample drawn immediately before administration of the drug. Duplicate 1.0 ml samples spiked with [^{14}C]-brotizolam (gift from Boehringer Ingelheim; spec. act. $98 \mu\text{Ci}/\text{mg}$) or with [^{14}C]-triazolam (gift from Upjohn, Kalamazoo; spec. act. $108 \mu\text{Ci}/\text{mg}$) to contain a total concentration of 12.0 ng brotizolam/ml or 9.0 ng triazolam/ml, were dialyzed at 37°C against an equal volume of isotonic 0.067 M phosphate buffer (pH 7.4), using a semi-permeable membrane with a molecular cut-off of 10,000 μ .

Preliminary experiments had indicated that 2 h was the appropriate equilibrium time. Binding was independent of total plasma concentration between 1 and 25 ng/ml for both compounds.

Pharmacokinetic analysis

Pharmacokinetic calculations were performed by compartmental analysis. The following function was fitted to the plasma concentrations:

$$C = C_1(e^{-\lambda_1(t-t_{\text{lag}})} - e^{-k_a(t-t_{\text{lag}})}) \quad (1)$$

in which t_{lag} is the absorption lag-time. C_1 is a hybrid intercept term, λ_1 is the apparent first-order elimination rate constant and k_a is the apparent first-order absorption rate constant. The exponents of the equation were used to calculate absorption ($t_{1/2,\text{abs}}$) and elimination half-life ($t_{1/2,z}$).

Elimination half-life was also determined by linear regression of the terminal part of the log plasma concentration vs time curves. For the calculation of the area under the curves (AUC), the trapezoidal rule with extrapolation to infinity was applied.

Results

In Figures 1 and 2 plasma concentration-time profiles for brotizolam and triazolam are given for two different volunteers. For brotizolam, the plasma concentration time course could be described satisfactorily by a one-compartment open model. For triazolam, the fit of the one-compartment model to the data points was very good in the elimination phase but a large scatter of the data points around the fitted function was observed in the absorption phase in half of the subjects. Considering the data points, it is likely that absorption in these volunteers occurred at an irregular rate and was not consistent with a continuous first-order process. Absorption of both triazolam and brotizolam occurred relatively rapidly and there was no significant difference between the absorption parameters of the two drugs. The mean peak time was 1.1 ± 1.0 h for brotizolam and 1.2 ± 0.5 h for triazolam; considerable interindividual variability, particularly for brotizolam, was observed (Figure 3a). Absorption lag time and absorption half-life averaged 8 ± 12 min and 10 ± 11 min respectively for brotizolam and 14 ± 14 min and 10 ± 9 min for triazolam. The mean peak concentration (C_{max}) of brotizolam was 46% higher than that of triazolam: 7.3 ± 3.1 ng/ml vs 5.0 ± 3.9 ng/ml respectively (Figure 3b).

In Table 2 the individual values of the elimination half-lives as calculated by linear regression are given for the two hypnotics. The mean value was 5.0 ± 1.1 h for brotizolam and 2.6 ± 0.7 h for triazolam. When determined by compartmental analysis, these values were 5.1 ± 1.2 h and 2.5 ± 0.7 h respectively.

In Table 3, area under the curve (AUC) values are given for each individual. Mean values were 3397 ± 1279 ng ml $^{-1}$ min for brotizolam and 923 ± 538 ng ml $^{-1}$ min for triazolam.

Protein binding data for brotizolam and triazolam are presented in Table 4. The mean value of the free fraction (%) was 8.4 ± 0.7 for brotizolam and 9.9 ± 1.5 for triazolam.

Discussion

This study shows that absorption of brotizolam and triazolam proceeded generally quite rapidly.

Figure 1 Brotizolam (○) and triazolam (●) plasma concentration curves for subject 6, following oral administration of triazolam (Halcion®, 0.50 mg) and brotizolam (Lendormin®, 0.50 mg).

Figure 2 Brotizolam (○) and triazolam (●) plasma concentration curves for subject 3, following oral administration of triazolam (Halcion®, 0.50 mg) and brotizolam (Lendormin®, 0.50 mg).

Figure 3a) Comparison of peak times of brotizolam (B, median 0.7 h) and triazolam (T, median 1.3 h) after oral administration of 0.50 mg of each drug (tablet).

b) Comparison of the peak concentration of brotizolam (B, median 6.8 ng/ml) and triazolam (T, median 3.6 ng/ml) after oral administration of 0.50 mg of each drug (tablet).

However, absorption of triazolam often occurred at an irregular rate and for brotizolam considerable inter-individual variability in absorption rate was observed, resulting in a large difference between median and mean values of absorption parameters.

Clinically, a rapid rate of absorption is important for a hypnotic as such drugs are frequently prescribed for patients who experience difficulties

in getting to sleep. If the active compound is not rapidly absorbed, early sleep may not be obtained and the patient will be tempted to take a second dose, leading to overdosing and prolonged effect. Biopharmaceutical factors governing the rate and extent of absorption are very important in this

Table 2 Elimination half-lives (h) of brotizolam and triazolam.

Subject	Brotizolam	Triazolam
1	4.9	3.0
2	6.1	3.9
3	5.8	1.8
4	5.8	2.8
5	6.0	2.1
6	3.1	2.4
7	4.4	2.3
8	4.0	2.1

Mean $\pm$ s.d. 5.0 $\pm$ 1.1 2.6 $\pm$ 0.7

Table 3 Areas under the curves (ng ml⁻¹ min) for brotizolam and triazolam following oral administration of Lendormin® (0.50 mg) or Halcion® (0.50 mg).

Subject	Brotizolam	Triazolam
1	4616	378
2	5912	1002
3	2765	302
4	2693	1926
5	2871	1236
6	2134	780
7	2506	558
8	3680	1203

Mean $\pm$ s.d. 3397 $\pm$ 1279 923 $\pm$ 538

Table 4 Protein binding (% free drug) of brotizolam and triazolam

Subject	Brotizolam	Triazolam
1	9.4	11.1
2	7.8	10.9
3	8.7	8.9
4	8.1	8.9
5	7.5	7.8
6	9.1	11.8
7	9.0	11.0
8	7.7	8.6
Mean $\pm$ s.d.	8.4 $\pm$ 0.7	9.9 $\pm$ 1.5

respect (Breimer, 1979; Breimer & Jochemsen, 1981). In another study it was also shown that brotizolam absorption may not be complete (Jochemsen *et al.*, 1983). No data on absolute bioavailability are available for triazolam.

It has not yet been determined whether the irregularities and variability in triazolam and brotizolam absorption observed are due to the physico-chemical characteristics of the drugs or to their pharmaceutical formulation.

The elimination half-life of brotizolam is twice that of triazolam, but is still quite short. There will be no accumulation with either of the two drugs when they are taken every night. The elimination half-life is dependent upon two parameters: the volume of distribution and the metabolic clearance of the drug. For brotizolam, the absolute values of those parameters have been determined following i.v. injection: volume of distribution 0.63 l/kg and total clearance 109 ml/min (Jochemsen *et al.*, 1983). For triazolam, an estimate of these parameters can be made using the data shown in Table 3, assuming that liver blood flow is approximately 21 ml/min/kg, that the haematocrit is approximately 0.5 and that the partition coefficient of triazolam between blood and plasma is about zero (Jochemsen, unpublished results; Rowland, 1972. Mean values of volume of distribution and total clearance as calculated on the basis of these data and assumptions are 1.1 l/kg and 334 ml/min respectively. Furthermore, it can be calculated that the extraction coefficient of triazolam is approximately 0.45. It is clear that triazolam, in contrast to brotizolam, is an intermediate extraction drug, i.e. elimination is not only dependent on drug metabolizing enzyme activity, but also on liver blood flow. The same is true for the imidazole-benzodiazepine derivative midazolam (Amrein *et al.*, 1981).

Brotizolam and triazolam have the same two major metabolites: the 1-methyl-hydroxy- and the 4-hydroxy-derivatives (Eberts *et al.*, 1981; Boehringer Ingelheim, product information). The 4-hydroxymetabolites have a pharmacological activity which is far less than that of the parent drugs, but the 1-methyl-hydroxymetabolites probably have comparable activity (Gall *et al.*, 1978; Jochemsen *et al.*, 1982; Sethy & Harris, 1982; Jochemsen *et al.*, unpublished results). These active compounds are, however, not present in plasma in measurable amounts following a single dose of brotizolam or triazolam to young healthy subjects (Jochemsen *et al.*, 1982; Jochemsen *et al.*, unpublished results).

Although brotizolam and triazolam are metabolized via the same pathways there was no correlation between the half-lives of the two drugs ($r < 0.29$). This can also clearly be deduced from the extreme examples given in Figures 1 and 2. In principle, of course, it is not elimination half-life but rather (intrinsic) clearance which is the appropriate parameter for correlation. However, it has been shown that for benzodiazepines metabolized by a similar enzyme system and administered to the same subject, a significant correlation between elimination half-lives existed (Greenblatt *et al.*, 1982). A major problem with triazolam and brotizolam is the *intraindividual* variability in elimination half-life. For brotizolam it is likely that this is almost entirely due to variability in clearance (Jochemsen *et al.*, 1983).

Triazolam and brotizolam are both highly protein bound, indicating that factors influencing protein binding will also influence clearance and volume of distribution of these drugs. The degree of binding is the same for the two drugs, while the unbound fraction found for triazolam agrees well with the value reported by Eberts *et al.* (1981) (11% at 37°C).

In conclusion, the present study has shown that brotizolam and triazolam both have a short elimination half-life, which is favourable with regard to the requirement for a limited duration of action and the avoidance of accumulation during chronic use of the drugs (Breimer, 1979; Breimer & Jochemsen, 1981). Correlating well with these results, is the observation that there are no residual effects on performance the next day (Nicholson & Stone, 1980; Nicholson *et al.*, 1980). In fact, these performance studies have shown that the ratio of hypnotic activity to residual sequelae is almost the same for brotizolam and triazolam.

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Vergleichende Pharmakokinetik von Brotizolam und Triazolam bei gesunden Versuchspersonen

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1 Die Pharmakokinetik von oralem Brotizolam (0,5 mg) und Triazolam (0,5 mg) wurde bei gesunden, jungen Freiwilligen untersucht.

2 Das Plasmakonzentrationsprofil von Brotizolam kann als offenes Ein-Kompartiment-Modell mit Resorption erster Ordnung beschrieben werden. Die Resorption von Triazolam war weniger gleichmäßig und bei der Hälfte der Probanden nicht mit einer Kinetik erster Ordnung in Einklang zu bringen. Brotizolam zeigte eine stärkere interindividuelle Variabilität der Resorptionsrate (Zeitpunkte der Maxima, t_{max}).

3 T_{max} betrug im Mittel $1,1 \pm 1,0$ Stunden für Brotizolam und $1,2 \pm 0,5$ Stunden für Triazolam. Die mittleren Höchstkonzentrationen lagen bei $7,3 \pm 3,1$ ng/ml bzw. $5,0 \pm 3,9$ ng/ml.

4 Die Eliminationshalbwertszeit von Brotizolam war doppelt so lang wie die von Triazolam mit Mittelwerten von $5,1 \pm 1,1$ Stunden bzw. $2,6 \pm 0,7$ Stunden. Es bestand keine Korrelation zwischen den Halbwertszeiten der beiden Substanzen.

5 Die nicht an Eiweiss gebundene Fraktion war bei Triazolam und Brotizolam fast gleich mit Mittelwerten von $9,9 \pm 1,5\%$ bzw. $8,4 \pm 0,7\%$.

Pharmacocinétique comparative du brotizolam et du triazolam chez des sujets en bonne santé

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1 La pharmacocinétique du brotizolam (0,5 mg) et du triazolam (0,5 mg) appliqués par voie orale a été étudiée chez de jeunes volontaires en bonne santé.

2 Le profil de concentration plasmatique du brotizolam peut être décrit comme un modèle ouvert à un compartiment avec absorption du premier ordre. L'absorption du triazolam a été

moins régulière, et ne pouvait être qualifiée de cinétique du premier ordre, pour la moitié des sujets. La variabilité interindividuelle du taux d'absorption (temps des pics, $t_{\max}$) a été plus large dans le cas du brotizolam.

3 Les temps des pics ont été en moyenne de $1,1 \pm 1,0$ h pour le brotizolam, et de $1,2 \pm 0,5$ h pour le triazolam. Les pics de concentration moyens ont été, respectivement, de $7,3 \pm 3,1$ ng/ml et $5,0 \pm 3,9$ ng/ml.

4 La demi-vie d'élimination du brotizolam a été deux fois celle du triazolam, les valeurs moyennes ayant été, respectivement, de $5,0 \pm 1,1$ h et $2,6 \pm 0,7$ h. Il n'a pas été constaté de relation entre les demi-vies de ces deux substances.

5 La fraction non liée aux protéines a été similaire pour le triazolam et le brotizolam, les valeurs moyennes ayant été, respectivement, de $9,9 \pm 1,5\%$ et $8,4 \pm 0,7\%$.

Farmacocinética comparativa de brotizolam y triazolam en personas sanas

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1 En voluntarios jóvenes sanos se estudió la farmacocinética de brotizolam (0,5 mg) y triazolam (0,5 mg) después de su administración oral.

3 El perfil de concentración plasmática de brotizolam puede describirse como modelo abierto de un compartimento con absorción de primer orden. La absorción de triazolam fue menos regular y en la mitad de los casos incompatible con una cinética de primer orden. La variabilidad interindividual en el índice de absorción (tiempos máximos) fue mayor para brotizolam.

3 Los tiempos máximos medios fueron $1,1 \pm 1,0$ h

para brotizolam y $1,2 \pm 0,5$ h para triazolam. Las concentraciones máximas medias fueron $7,3 \pm 3,1$ ng/ml y $5,0 \pm 3,9$ ng/ml respectivamente.

4 La vida media de eliminación de brotizolam fue doble de la correspondiente a triazolam con promedios de $5,0 \pm 1,1$ h y $2,6 \pm 0,7$ h respectivamente. No se dió correlación entre las vidas medias de ambos fármacos.

5 La fracción no fijada a proteínas fue similar para triazolam y brotizolam, con promedios de $9,9 \pm 1,5\%$ y $8,4 \pm 0,7\%$ respectivamente.