PHARMACOKINETICS OF ORAL BROtizOLAM IN PATIENTS WITH LIVER CIRRHOSIS

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1 Disposition of oral brotizolam (0.5 mg) was studied in male patients with liver cirrhosis (patients) and in other patients (control) matched for age, weight, smoking and drinking habits.

2 Absorption of brotizolam was relatively rapid in both groups with a median peak time (range) of 1.0 (0.5–2.0) h. Peak concentrations were also similar with median values of 7.1 (3.2–10.7) ng/ml in patients and 9.4 (2.9–19.0 ng/ml) in controls.

3 Elimination half-life was longer in patients than in controls. The median values were 12.8 (9.4–25) h and 6.9 (4.4–8.4) h respectively ($P < 0.01$). In two patients hardly any drug elimination was observed, indicating severe impairment of drug metabolizing activity. The prolongation of the elimination half-life was likely to be due to a decrease in clearance (45 ml/min in patients compared with 64 ml/min in controls), and an increase in volume of distribution (0.62 l/kg and 0.39 l/kg respectively).

4 Median values of protein unbound fraction of brotizolam were 9.2 (7.8–10.4) % in controls and 12.4 (10.4–18.9) % in patients. Clearance of unbound drug was 612 ml/min and 380 ml/min respectively.

Keywords brotizolam pharmacokinetics cirrhosis

Introduction

Brotizolam is a 1,4-thienodiazepine that before long will be introduced as a short-acting hypnotic. It is inactivated in the human body through biotransformation, the primary steps being hydroxylation in the 1-methyl- and the 4-position (Boehringer Ingelheim, product information). The elimination half-life of brotizolam is relatively short (3–6 h) in young healthy subjects (Jochensen *et al.*, 1983a). It was demonstrated recently that the kinetics of brotizolam are considerably influenced by age: the mean elimination half-life in the elderly subjects was twice as long as in young subjects. This could be explained by a decrease in metabolic clearance (Jochensen *et al.*, 1983b). Another well-known major factor influencing the disposition of drugs that are primarily eliminated in the liver, is liver disease (Closson, 1977; Wilkinson & Schenker, 1976). In the last few years, the influence of liver disease has been studied for several benzodiazepines and differential effects have been observed. The disposition of benzodiazepines

which are primarily oxidized is quite strongly affected, resulting in a significantly prolonged elimination half-life (Klotz *et al.*, 1975; Roberts *et al.*, 1978; Sellers *et al.*, 1979); on the other hand, liver disease has little effect on the disposition of benzodiazepines that are primarily conjugated (Krauss *et al.*, 1978; Sellers *et al.*, 1979; Shull *et al.*, 1976).

The present study was undertaken to compare the pharmacokinetics of brotizolam in patients with liver cirrhosis with that in a group of age-matched control subjects.

Methods

Experimental design

Eight-male patients with liver cirrhosis, diagnosed on the basis of clinical and biochemical data (Table 1) participated in the study. In seven patients the

Table 1 Characteristics of patients with liver cirrhosis.

Patient	Age/weight (years/kg)	Bilirubin ($\mu\text{mol/l}$) (3.4–17.4)	SGOT (u/l) (–18)	Plasma albumin (g/l) (3.5–5.0)	Quick (%) (75–125)	Cholinesterase (u/l) (3000–9300)	Co-medication	Diagnosis
K	50/61	51.0	23	1.6	20	600	Lactulose, acetyl- digoxin, diltiazem, pirenzepine, Mg-Al- hydroxide	Liver cirrhosis,* tuberculosis
E	45/79	32.3	28	3.8	68	2615	Insulin, propranolol glibenclamide	Liver cirrhosis,* diabetes mellitus
P	34/55	102.0	71	2.2	56	1582	Lactulose, Mg-Al- hydroxide	Liver cirrhosis*
I	57/77	13.5	22	3.7	80	3950	Lactulose, Mg-Al- hydroxide	Liver cirrhosis,* ulcus ventriculi
H	34/69	221.0	34	3.0	90	2662	Lactulose, Mg-Al- hydroxide, halopyr- imine HCl	Liver cirrhosis*
W	43/83	42.0	19	3.8	44	4396	Lactulose, propranolol	Liver cirrhosis*
S	48/88	20.4	15	4.2	49	5205	Lactulose, atenolol	Liver cirrhosis*
O	64/78	37.4	11	2.4	33	1281	Lactulose, Mg-Al- hydroxide, digitoxin	Liver cirrhosis*

* Diagnosis made by liver biopsy.

diagnosis was confirmed by liver biopsy. Two of them (E, P) were heavy smokers (>10 cigarettes/day), the others did not smoke at all. The details of associated medical condition and medication are also given in Table 1. Furthermore, eight male, age- and weight-matched control patients were studied, who had a normal liver function. Two of these patients (G, B) were heavy smokers, the others did not smoke at all. The particulars of the control patients are presented in Table 2.

The experiments started between 08.00 and 09.00 h with the intake of 0.5 mg brotizolam (Lendormin®) with 100 ml of water on an empty stomach. Heparinized blood samples were then obtained from a forearm vein at 0, 15, 30, 45, 60 and 90 min and at 2, 3, 4, 8, 12, 24, 32, 48 h after drug administration, the first day of the experiment by means of a flexible cannula and subsequently by venepuncture. One hour after drug administration, the patients were supplied with a breakfast. After separation, the plasma samples were stored at -20°C until taken for analysis. Brotizolam plasma concentrations and protein binding were determined as described elsewhere (Jochimsen *et al.*, 1983a,d).

Data analysis

Brotizolam elimination half-lives ($t_{1/2,z}$) were calculated by least square regression analysis of the terminal log linear part of the plasma concentration

vs time curves. Areas under the curves (AUC) were determined by trapezoidal rule and extrapolation to infinity.

For statistical analysis, the two-tailed rank-order test of Wilcoxon was used with $P < 0.05$ being taken as the minimal level of significance.

Results

A representative example of a plasma concentration vs time profile of brotizolam as observed in six patients with liver cirrhosis (patients) is shown in Figure 1. This profile is quite comparable with that found in the control patient group (controls). In two of the patients (K, S) plasma concentrations showed a profile that differed substantially (Figure 2): hardly any decline of the plasma concentration was noted during the experimental period. This indicates that drug metabolizing capacity is at a very low level. Except for protein binding, these patients were excluded in the comparisons with the control group.

Generally absorption was relatively rapid, median values (range) being 1.0 (0.5–2.0) h in both groups (Figure 3a). Median peak concentration was 7.1 (3.2–10.7) ng/ml in the patients and 9.4 (2.9–19.0) ng/ml in the controls (Figure 3b).

Elimination half-lives were significantly longer in the patients than in the controls, with median values of 12.8 (9.4–25) h and 6.9 (4.4–8.4) h

Table 2 Characteristics of control patients.

Patient	Age/weight (years) (kg)	Bilirubin ($\mu\text{mol/l}$) (3.4–17.4)	SGOT (u/l) (–18)	Plasma albumin (g/l) (3.5–5.0)	Quick (%) (75–125)	Cholinesterase (u/l) (3000–9300)	Co-medication	Diagnosis
J	34/67	3.5	14	3.6	80	4735	Pirenzepine, Mg-Al-hydroxide	Pneumonia
E	38/70	15.3	13	3.7	90	5225	Theophylline, prednisone	Asthma bronchiale
S	30/78	14.0	9	3.6	75	5110	Lactulose	Enteritis
W	54/114	14.0	11	4.0	95	4550	Acetyldigoxin, mexiletine, prazosin, nifedipine, dipyridamol, acetylsalicylic acid	Cardiomyopathy
B	55/71	5.1	11	4.2	100	5427	Lactulose, Mg-Al-hydroxide theophylline, amiloride, hydrochlorothiazide	Chronic bronchitis
M	61/81	27.0*	8	4.5	114	4885	Prednisone, azathioprine, Mg-Al-hydroxide, dipyridamol, acetylsalicylic acid, isosorbide dinitrate	Idiopathic thrombocyto- penia
H	43/68	7.0	18	3.4	75	3830	Pirenzepine, lactulose, Mg-Al- hydroxide, heparin, chlor- methiazole, bromhexin, piracetam	Mallory–Weiss syndrome
G	62/88	14.0	16	3.8	84	4575	Acetyldigoxin, frusemide, clonidine, insulin, heparin	Diabetes mellitus

* Hyperbilirubinaemia due to haemolysis, not caused by liver damage.

Figure 1 Plasma concentration-time profile of brotizolam in a patient with liver cirrhosis following oral administration of 0.5 mg brotizolam.

respectively ($P < 0.01$; Table 3). Assuming that, on an average, bioavailability of brotizolam in this study was the same as determined for healthy young and elderly subjects ($F = 0.7$; Jochemsen *et al.*, 1983a,b), clearance and volume of distribution could be estimated from the AUC values as given in Table 3. Median values were 45 (18–78) ml/min and 0.62 (0.44–2.2) l/kg respectively for the patients and 64 (18–134) ml/min and 0.39 (0.20–0.70) l/kg for the controls. The difference between the clearance values did not reach statistical significance, but the volume of distribution was significantly larger in the patients ($P < 0.05$).

Protein binding was significantly lower in the patients than in the controls: free fraction was 12.4

(10.4–18.9) % and 9.2 (7.8–10.4) % respectively ($P < 0.01$). Clearance of unbound brotizolam was 380 (150–404) ml/min in the patients and 612 (321–1301) ml/min in the controls (NS).

The sensitivity of the patients with liver cirrhosis towards brotizolam appeared to be larger than that of the control patients; the former all slept, but the latter did not sleep at all.

Discussion

The results of this study clearly indicate that liver cirrhosis may affect the pharmacokinetics of brotizolam considerably. In patients with a

Figure 2 Plasma concentration-time profile of brotizolam in a patient with liver cirrhosis whose drug metabolizing activity towards brotizolam must have been completely absent.

Figure 3 Individual and median values of peak time ($t_{\max}$) (a) and peak concentration ($C_{\max}$) (b) following oral administration of brotizolam to patients with liver cirrhosis and a matched control group.

relatively 'normal' plasma concentration profile the median elimination half-life was almost twice as long as in control patients. A further important observation was that two patients showed hardly any decline of brotizolam plasma concentration after absorption had ceased. This indicates that drug metabolizing activity towards brotizolam must

Table 3 Elimination half-life ($t_{1/2,z}$), areas under the curves (AUC) and protein binding of brotizolam following oral administration of 0.5 mg brotizolam to patients with liver cirrhosis and to control patients.

Subject	$t_{1/2,z}$ (h)	AUC (ng ml ⁻¹ min)	Protein binding (% free)
<i>Patients with liver cirrhosis</i>			
K	—	—	15.9
E	13.4	5192	12.6
P	17.9	3142	11.6
I	9.4	5784	10.4
H	25	13697	12.0
W	10.1	5805	12.8
S	—	—	11.7
O	12.1	3295	18.9
Median	12.8	5488	12.4
<i>Controls</i>			
J	8.0	9711	7.8
E	8.3	8457	7.9
S	4.4	3395	8.0
W	6.8	1815	10.3
B	7.0	2976	10.4
M	4.6	4106	9.0
H	8.4	13365	9.5
G	6.6	3598	12.2
Median	6.9	3852	9.2

have been almost completely absent in these patients.

In a previous study in young and elderly subjects, it was demonstrated that brotizolam elimination half-life was about twice as long in the elderly (Jochimsen *et al.*, 1983b). The mean age of the liver patients and the control patients in the present study (47 years) was between the mean age of the young and elderly subjects (23 and 81 years respectively), and there appeared to be a very good positive correlation between mean age and mean elimination half-lives for the three groups ($r = 0.999$, Figure 4).

Plasma protein binding of brotizolam was significantly lower in the patient than in the control group: free fraction was about 40% higher ($P < 0.01$). A decrease in protein with liver cirrhosis was also reported for diazepam, chlor-diazepoxide and nitrazepam (Klotz *et al.*, 1975; Roberts *et al.*, 1978; Sellers *et al.*, 1978; Jochimsen *et al.*, 1983c). Free fraction values as found for the control group were in good agreement with those observed in previous studies (Figure 5; Jochimsen *et al.*, 1983b,d).

Brotizolam could only be administered orally in this study and hence bioavailability should be known in order to calculate clearance and volume of distribution. In previous studies in young and elderly subjects, it was estimated that the mean bioavailability of brotizolam from tablets is 70%, but large variability was observed (Jochimsen *et al.*, 1983a,b). Assuming that, on an average, bioavailability of brotizolam in this study was the same as that found in the previous studies, clearance and volume of distribution values were estimated. Large variability was observed in both groups (Table 3)—probably partly due to inter-individual differences in bioavailability—and therefore median and not mean values were compared. Clearance was about 30% lower in the patients than in the controls and volume of distribution was 60% larger. Brotizolam is a low clearance drug that is highly protein bound (Jochimsen *et al.*, 1983a,d) and hence the activity of the metabolizing enzyme systems involved in its biotransformation is reflected by the clearance of unbound drug. This parameter was about 40% lower in the patients.

It has also been shown in this study that the absorption of brotizolam from 0.5 mg tablets proceeded relatively rapidly in both patients with liver cirrhosis and in the matched control group. Peak times were similar to those observed in a previous study with healthy young subjects (about 1 h; Jochimsen *et al.*, 1983d).

The two groups studied were fairly well matched with regard to gender, age, weight, smoking and drinking habits. A major difference was their medical condition: all control patients had a normal

Figure 4 Relationship between age and brotizolam elimination half-life in healthy subjects (●) and in patients with liver cirrhosis (○), including data obtained in previous studies.

liver function (as judged biochemically) and they had been hospitalized for various diseases. The investigations with brotizolam were performed during the recovery phase of their illness; it is not known what the influence of these various diseases may be on drug metabolizing enzyme activity. In

addition, the control patients used a slightly greater variety of drugs, none of which, however, including prednisone (Breimer *et al.*, 1978), is known to influence drug metabolizing enzyme activity in normal doses significantly.

The effect of liver cirrhosis on drug disposition

Figure 5 Relationship between age and brotizolam protein binding in healthy subjects (●) and in patients with liver cirrhosis (○), including data obtained in previous studies.

has been studied for several benzodiazepines and differential effects have been observed. Chlordiazepoxide and diazepam, benzodiazepines that are primarily oxidized, exhibit much longer elimination half-lives in patients with liver cirrhosis than in age-matched controls, due to a lower metabolic clearance and a large volume of distribution (Klotz *et al.*, 1975; Roberts *et al.*, 1978; Sellers *et al.*, 1979). On the other hand, liver cirrhosis has no influence on the metabolic clearance of oxazepam and lorazepam, benzodiazepines of which the primary biotransformation step is a conjugation reaction (Krauss *et al.*, 1978; Sellers *et al.*, 1979; Shull *et al.*, 1976). The elimination half-life of lorazepam, however, was significantly prolonged in patients with liver

cirrhosis, which was found to be due to a larger volume of distribution (Krauss *et al.*, 1978). The present study demonstrates that the influence of liver cirrhosis on the elimination of brotizolam is attributable to both an impairment of clearance and an enlargement of its volume of distribution. Clearance may be very much reduced as was revealed in the two patients who showed no plasma concentration decline during the experimental period. However, for an exact evaluation of the influence of liver cirrhosis on clearance and volume of distribution of brotizolam, i.v. studies will be necessary.

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Pharmakokinetik von oralem Brotizolam bei Patienten mit Leberzirrhose

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1 Die Kinetik von oralem Brotizolam (0,5 mg) wurde bei männlichen Patienten mit Leberzirrhose (Patienten) sowie anderen Patienten (Kontrolle) gleichen Alters, Gewichtssowie mit gleichen Rauch- und Trinkgewohnheiten untersucht.

2 Die Resorption von Brotizolam erfolgte in beiden Gruppen relativ rasch, der Zeitpunkt der Maxima hatte einen Medianwert (Bereich) von 1,0

(0,5–2,0) Stunden. Die Höchstkonzentrationen waren mit Medianwerten von 7,1 (3,2–10,7) ng/ml in der Patientengruppe und 9,4 (2,9–19,0) ng/ml in der Kontrollgruppe auch annähernd gleich.

3 In der Patientengruppe war die Eliminationshalbwertszeit länger als in der Kontrollgruppe. Die Medianwerte betrugen 12,8 (9,4–25) Stunden bzw. 6,9 (4,4–8,4) Stunden ($P < 0,01$). Bei zwei

Patienten wurde fast keine Substanzausscheidung beobachtet, was eine ernsthafte Beeinträchtigung der Metabolisierungsaktivität anzeigt. Die Verlängerung der Eliminationshalbwertszeit war vermutlich auf eine Abnahme der Clearance (45 ml/min bei der Patientengruppe im Vergleich zu 64 ml/min bei der Kontrollgruppe) sowie auf ein erhöhtes Verteilungsvolumen (0,62 l/kg bzw. 0,39 l/kg) zurückzuführen.

Pharmacocinétique du brotizolam par voie orale chez des patients atteints de cirrhose du foie

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1 La pharmacocinétique du brotizolam (0,50 mg) administré par voie orale a été étudiée chez des patients de sexe masculin atteints de cirrhose du foie (patients) et d'autres patients (témoins) comparables par l'âge, le poids ainsi que la propension à fumer et à boire.

2 L'absorption du brotizolam a été relativement rapide dans les deux groupes, la médiane des temps des pics (marge) a été de 1,0 (0,5–2,0) h. Les pics de concentration ont été également similaires: les valeurs médianes ont été de 7,1 (3,2–10,7) ng/ml pour les patients et de 9,4 (2,9–19,0 ng/ml) pour les témoins.

3 La demi-vie d'élimination a été plus longue chez les patients que chez les témoins. Les valeurs médianes ont été, respectivement, de 12,8 (9,4–25)

4 Die Medianwerte der nicht an Eiweiß gebundenen Brotizolam-Fraktion lagen bei 9,2 (7,8–10,4) % bei der Kontrollgruppe und 12,4 (10,4–18,9) % bei der Patientengruppe. Die Clearance der ungebundenen Substanz betrug 612 ml/min bzw. 380 ml/min.

h et 6,9 (4,4–8,4) h ($P < 0,01$). Il n'a pas été pratiquement constaté d'élimination du médicament chez deux patients, ce qui indique une grave atteinte de l'activité de la métabolisation de cette substance. Le prolongement de la demi-vie d'élimination est vraisemblablement due à une diminution de la clairance (45 ml/min chez les patients, 64 ml/min chez les témoins) et à une augmentation du volume de distribution (0,62 l/kg et 0,30 l/kg, respectivement).

4 Les valeurs médianes de la fraction de brotizolam non fixée aux protéines ont été de 9,2 (7,8–10,4%) pour les témoins et de 12,4 (10,4–18,9%) pour les patients. La clairance de la substance libre a été, respectivement, de 612 ml/min et 380 ml/min.

Farmacocinética de brotizolam oral en pacientes con cirrosis hepática

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1 La farmacocinética de brotizolam oral (0,5 mg) se estudió en pacientes de sexo masculino con cirrosis hepática (pacientes) y en otros enfermos (control) similares en cuanto a edad, peso, costumbres fumadoras y bebedoras.

2 La absorción de brotizolam fue relativamente rápida en ambos grupos con tiempo máximo mediano (margen) de 1,0 (0,5–2,0) h. Las concentraciones máximas fueron similares también con valores medianos de 7,1 (3,2–10,7) ng/ml en los pacientes y 9,4 (2,9–19,0) ng/ml en los controles.

3 La vida media de eliminación fue más prolongada en los pacientes que en los controles. Las medianas fueron 12,8 (9,4–25) h y 6,9 (4,4–8,4) h respectivamente ($P < 0,01$). En dos

pacientes apenas se observó eliminación del fármaco, indicando un grave deterioro de la capacidad de metabolización. La prolongación de la vida media de eliminación se debió probablemente a una disminución de la depuración (45 ml/min en los pacientes en comparación con 64 ml/min en los controles) y a un aumento del volumen de distribución (0,62 l/kg y 0,39 l/kg respectivamente).

4 Las medianas de la fracción de brotizolam no fijada en proteínas fueron 9,2 (7,8–10,4) % en los controles y 12,4 (10,4–18,9) % en los pacientes. La depuración del fármaco no fijado fue de 612 ml/min y 380 ml/min respectivamente.