PHARMACOKINETICS OF BROtizOLAM IN THE ELDERLY

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1 Disposition of brotizolam in patients aged 71–93 years was compared with that of healthy young subjects aged 21–26 years.

2 The mean elimination half-life of brotizolam was about twice as long in the elderly as in the young subjects: 9.3 (4.0–19.5) h and 4.8 (3.1–6.3) h respectively. Increase in elimination half-life was attributable to a decrease in hepatic clearance, i.e. 40 (20–58) ml/min in the elderly and 109 (77–156) ml/min in the young. Volume of distribution and protein binding were the same with mean values of 0.56 (0.45–0.72) l/kg and 9.0 (6.8–11.9) % in the elderly and 0.63 (0.40–0.77) l/kg and 8.4 (7.5–9.4)% in the young.

3 Absorption rate of brotizolam was relatively slow in the elderly with a mean peak time of 1.7 h compared with 1.1 h in the young. Mean bioavailability was almost 70% for both groups. Normalized for body weight and dose (0.25 mg) mean peak concentrations were 247 (137–395) ng ml⁻¹ kg in the young and 343 (251–446) ng ml⁻¹ kg in the elderly.

4 It is unlikely that substantial drug accumulation will occur if elderly patients ingest 0.25 mg brotizolam nightly.

Keywords brotizolam pharmacokinetics young subjects elderly patients

Introduction

Brotizolam is a triazolo-1,4-thienodiazepine that has been shown to have effective sleep inducing properties. There are no residual effects the next morning with doses of up to 0.25 mg at night (Nicholson *et al.*, 1980; Saletu *et al.*, 1979; Sanchez-Martinez, 1982; Velasco *et al.*, 1981). The drug is relatively rapidly inactivated in the human body through biotransformation and its elimination half-life is relatively short: 3–6 h in healthy young subjects (Jochemsen *et al.*, 1983a). The major metabolites are the 1-methylhydroxy- and the 4-hydroxy-derivatives (Boehringer Ingelheim, product information). The pharmacological activity of the latter compound is far less than that of the parent drug, but the 1-methylhydroxy-metabolite probably has comparable pharmacological activity when judged by receptor binding studies (Jochemsen *et al.*, unpublished results).

The ageing process has been shown to influence the kinetics of many drugs, in particular those which undergo oxidative biotransformation (Greenblatt & Shader, 1981; Vestal, 1978; Vestal

& Wood, 1980). Impairment of the rate of drug elimination in the elderly has been demonstrated for those benzodiazepines which are primarily oxidized (e.g. diazepam, chlordiazepoxide, desalkylflurazepam and desmethyldiazepam) (Divoll Allen *et al.*, 1980; Greenblatt *et al.*, 1980a, 1981; Klotz *et al.*, 1975; Klotz & Müller-Seydlitz, 1979; Roberts *et al.*, 1978) and for nitrazepam (Jochemsen *et al.*, 1983b; Kangas *et al.*, 1979). Age, on the other hand, has little, if any, effect on the disposition of benzodiazepines, for which drug conjugation is the primary metabolic step (Divoll *et al.*, 1981; Greenblatt *et al.*, 1979, 1980b; Krauss *et al.*, 1978; Shull *et al.*, 1976). Benzodiazepines are frequently prescribed for elderly patients and age related changes in clinical effects may be due to alterations in protein binding, distribution or clearance.

This study was undertaken to assess the disposition of brotizolam in elderly subjects and to compare this with results obtained in younger subjects.

Methods

Experimental design

Twenty elderly hospitalized patients (10 males and 10 females) with a mean age of 82 years participated, with eight healthy young volunteers (five males and three females) with a mean age of 23 (21–26 years). Table 1 shows their particulars, associated medical conditions and medications.

None of the patients suffered from respiratory disease or hepatic or renal impairment as assessed clinically, radiologically and biochemically. None had psychiatric disorders requiring psychoactive drugs, nor had they taken diazepam or barbiturates within the period 4 weeks before the study. None of the patients smoked or used alcohol to excess. The protocol was approved by the Ethical Committee of Guy's Hospital Medical School.

The patients were divided into three groups

Table 1 Characteristics of the elderly subjects.

Subject	Sex	Age/weight/height (years/kg/cm)	Associated medical condition	Associated medication
Group 1 (i.v. 0.25 mg; 09.00 h)				
MM	F	79/53/135	Chondrocalcinosis	Paracetamol
MR	F	79/58/150	Old CVA; osteoarthritis	Piroxicam
DR	F	79/42/140	Megaloblastic anaemia	Folic acid, hydroxocobalamin
GK	M	71/69/185	Congestive cardiac failure, cervical myelopathy	Furosemide, potassium, fenbrufen
JR	M	87/47/140	Carcinoma prostate with bony metastasis	Diethylstilboestrol, bumetamide, potassium, naproxen
WS	M	86/44/137	Left ventricular failure	Bumetamide, salbutamol
	Mean	80/52/148		
Group 2 (oral 0.25 mg; 09.00 h)				
WM	M	80/55/168	Osteoarthritis	Dextropropoxyphene, paracetamol
FR	M	78/62/152	Congestive cardiac failure, pleural calcification; asbestosis?	Cyclopenthiazide
FB	M	75/67/152	Old CVA; osteoarthritis; UTI	Mephennamic acid, cephalixin
AC	F	89/52/145	Congestive cardiac failure, lumbar spondylosis	Digoxin; fenbrufen
JE	M	86/60/160	Parkinsonism; congestive heart failure; UTI	Levodopa + carbidopa (Sinemet ^R), bromocriptine, trimethoprim; paracetamol
EA	F	86/68/163	Menière's disease; osteoarthritis	Cinnarizine; paracetamol
AJ	F	89/70/168	Myxoedema; leg cramps; senile vaginitis	Thyroxine; quinine
	Mean	83/62/158		
Group 3 (oral 0.25 mg; 21.00 h)				
PMcI	M	80/61/165	Recent CVA	Paracetamol; methylcellulose laxative
AB	F	81/48/153	Dermoid cyst (abdominal)	None
EL	F	82/75/152	Congestive cardiac failure	Digoxin; potassium; bumetamide
FF	F	83/57/152	Osteoarthritis	Paracetamol; ferrous sulphate
EH	F	93/44/142	Myxoedema; congestive cardiac failure; osteoarthritis	Thyroxine; bumetamide potassium; ferrous sulphate
SK	M	85/54/157	Depression	None
JC	M	79/46/168	Pituitary hypothyroidism	Thyroxine; dichloralphenazone
	Mean	83/55/156		

(Table 1). Those in groups 1 and 2 fasted for 9 h before and 2 h after receiving brotizolam 0.25 mg intravenously or orally at 09.00 h. Venous blood samples were taken at 30, 60 and 120 min and at 4, 6, 8, 12 and 24 h after the doses. Following i.v. administration, additional samples were taken at 2, 5, 10 and 15 min, and following oral administration at 90, 150, 180 and 210 min and 10 and 36 h. The patients from group 3 fasted for 4 h before and 2 h after receiving 0.25 mg brotizolam orally at 21.00 h. Venous blood samples were taken at 0, 12, 14, 16, 18, 20, 22, 24, 36 and 48 h after drug administration.

The mean weight of the young subjects was 69 kg (range: 52–82 kg). They had normal renal and hepatic function and took no medication, apart from oral contraceptives. Three of the subjects were heavy smokers (>15 cigarettes per day). The subjects fasted for 9 h before and 3 h after receiving 0.25 mg brotizolam i.v. or 0.50 mg brotizolam orally (Lendormin®) with an intervening period of at least 3 weeks. Venous blood samples were taken at 20, 40, 60, 80, 100 and 120 min and 3, 4, 6, 9, 12, 24, 32 and 48 h. Following i.v. administration additional samples were taken at 15, 30 and 50 min. Blood samples were drawn from a pre-positioned cannula during the first day of the experiment and by separate vein puncture during the rest of the experiment. Samples were collected in heparinized tubes and stored after separation at -20°C until analysis. Plasma concentrations and protein binding of brotizolam were determined as previously described using capillary gas chromatography and equilibrium dialysis respectively (Jochimsen *et al.*, 1983a,c).

Analysis of data

The pharmacokinetic evaluation of the plasma concentration data was performed in agreement with the procedure as published in a previous paper on the pharmacokinetics of brotizolam (Jochimsen *et al.*, 1983a).

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. Clearance (CL) and apparent volume of distribution (V) were calculated from the areas under the curves (AUC) determined by the trapezoidal rule and extrapolation to infinity:

$$\text{CL} = \frac{D}{\text{AUC}} \quad (1)$$

and

$$V = \frac{\text{CL} \times t_{1/2,z}}{0.693} \quad (2)$$

The clearance of unbound drug (CL_u) was calculated according to:

$$\text{CL}_u = \frac{\text{CL}}{f_u} \quad (3)$$

in which f_u is the fraction of unbound drug. Bioavailability (F) was calculated according to:

$$F = \frac{\text{AUC}_{\text{p.o.}} \times D_{\text{i.v.}} \times t_{1/2,z,\text{i.v.}}}{\text{AUC}_{\text{i.v.}} \times D_{\text{p.o.}} \times t_{1/2,z,\text{p.o.}}} \quad (4)$$

For statistical analysis, the unpaired Student's t -test was used, $P < 0.05$ being taken as the minimal level of significance.

Results

Clinical observations

Following intravenous administration all patients fell asleep in less than 2 min; five patients woke up between 90 and 120 min but remained sedated for about 6 h. One patient slept for more than 8 h. After oral administration the onset of sedation was generally between 15 and 20 min and sleep occurred shortly afterwards. Four patients woke up at 180 min and one at 120 min but experienced sedation for about 6 h in total. One patient (A.C.) was found to be more sedated than others and she slept almost all day and through the night. One patient slept for 7.5 h. None of the patients who received the drug at 21.00 h still felt sedated the following morning. The duration of sedation was longer after oral administration but its onset was much quicker after intravenous administration. No untoward side effects were noted.

Most of the young subjects fell asleep within 0.5 h after either oral or i.v. drug administration. One subject fell asleep after about 1 h and one subject was merely sedated and did not fall asleep at all on oral administration. The subjects were woken up after 4 h and none of them reported further feelings of drowsiness during the afternoon.

Pharmacokinetics

Representative examples of plasma concentration curves of brotizolam in an elderly patient following i.v. and oral administration of 0.25 mg brotizolam are shown in Figures 1 and 2 respectively.

I.v. administration

The plasma concentration profile of brotizolam following i.v. administration was qualitatively very similar in young or elderly subjects: concentrations declined rapidly until about 1 h and then the log plasma

Figure 1 Plasma concentration-time profile of brotizolam in an elderly subject (M.M., 79 years) following i.v. administration of brotizolam (0.25 mg).

plasma concentration decay could be fitted to a straight line, indicating a first-order process of elimination. Elimination half-lives were significantly longer in the elderly than in the young subjects with mean values of 9.8 h and 4.7 h respectively ($P < 0.05$) (Table 2; Figure 3). This difference in rate of elimination was associated with changes in plasma clearance and volume of distribution of the drug. Plasma clearance decreased with age; mean values were 109 ml/min in the young volunteers but 40 ml/min in the elderly ($P < 0.001$; Figure 4a). The volume of distribution of brotizolam was also smaller in the elderly patients (291 vs 421), but after correction for body weight, these values were essentially the same for both groups: 0.63 l/kg and 0.56 l/kg in the young and the elderly respectively (Table 2; Figure 4b). The protein unbound fraction of brotizolam ranged from 6.8 to 11.9% and did not change with age (Table 2). Unbound clearance of brotizolam was significantly lower in the elderly patients with 453 ml/min as compared to 1298 ml/min in the young (Figure 4c).

Oral administration

Absorption of brotizolam after oral administration was more rapid in the young than in the elderly; the

Figure 3 Individual and mean values of brotizolam elimination half-life in young and elderly subjects; ● i.v. administration at 09.00 h; ▲ oral administration at 09.00 h and △ at 21.00 h.

mean times to peak plasma concentration were 1.1 h and 1.7 h respectively, although this difference was not statistically significant (Figure 5). The mean peak concentration was 5.6 ng/ml in the elderly and, normalized for dose, 3.7 ng/ml in the young. After normalization for body weight, peak concentrations were 343 ng ml⁻¹ kg and 247 ng ml⁻¹ kg respectively (not significant).

Elimination half-lives in the elderly were similar following oral drug administration at 09.00 h or 21.00 h (8.4 h and 9.6 h respectively), and there was not much change with i.v. administration. But oral elimination half-lives were significantly longer than those found in the young (5.0 h; $P < 0.02$; Table 2,

Figure 2 Plasma concentration-time profile of brotizolam in an elderly subject (P. McI, 80 years) following oral administration of brotizolam (Lendormin®, 0.25 mg).

Table 2 Pharmacokinetic data of brotizolam in elderly and in young subjects.

	Mean values (range)			
	Young subjects		Elderly subjects	
	i.v. (n = 7)	oral (n = 8)	i.v. (n = 6)	oral (n = 6)
Dose (mg)	0.50	0.25	0.25	0.25
Peak plasma concentration (ng/ml)		7.3 (3.8–13.6)		5.6 (5.0–6.6)
Dose and weight normalized peak concentration (ng ml ⁻¹ kg)		247		343
Time of peak concentration (h)		1.1 (0.3–3.0)		1.7 (0.5–3.0)
Elimination half-life (h)	4.7 (3.1–6.3)	5.0 (3.1–6.0)	9.8 (5.6–18.4)	9.1* (4.0–19.5)
Volume of distribution (l/kg)	0.63 (0.40–0.77)		0.56 (0.45–0.72)	
Clearance (ml/min)	109 (77–156)		40 (20–58)	
Free fraction (%)		8.4 (7.5–9.4)		9.0 (6.8–11.9)
Unbound V (l/kg)	7.5 (5.1–9.4)		6.4 (5.0–7.1)	
Unbound clearance (ml/min)	1298 (965–2026)		453 (313–725)	
Bioavailability (%)		70 (48–118)		66

*n = 13.

Figure 3). Combination of the three groups of elderly patients revealed a small gender difference in the elimination half-life of brotizolam in elderly subjects (9.6 h; and 8.9 h in females and males respectively).

Bioavailability of brotizolam in the elderly was estimated by comparing the mean data of the i.v. and oral groups. This was 66%, which is within the range observed in the young subjects (48–118%; mean value 70%).

Discussion

Brotizolam is eliminated in the human body primarily by conversion into two hydroxy-derivatives: 1-methylhydroxy-brotizolam and 4-hydroxy-brotizolam. It is highly protein bound and in a previous study its total clearance was found to be of the order of magnitude of 100 ml/min (Jochemsen *et al.*, 1983a). Therefore its rate of removal from plasma depends on the activity of the

Figure 4 Individual and mean values of total brotizolam clearance (a), volume of distribution (b) and clearance of unbound brotizolam (intrinsic clearance) (c) in young and elderly subjects.

Figure 5 Individual and mean values of peak time ($t_{\max}$) (a) and peak concentrations normalized for weight and dose ($C_{\max}$) (b) following oral administration of brotizolam to young (0.50 mg) and elderly (0.25 mg) subjects.

metabolizing enzymes involved in its biotransformation as well as on plasma binding.

Previous studies with benzodiazepines that undergo oxidative biotransformation (such as chlordiazepoxide, diazepam and desmethyldiazepam) have demonstrated that these drugs generally exhibit longer elimination half-lives in the elderly. This is due to a lower metabolic clearance or to a larger volume of distribution (Divoll Allen *et al.*, 1980; Greenblatt *et al.*, 1980a, 1981; Klotz *et al.*, 1975; Klotz & Müller-Seydlitz, 1979; Roberts *et al.*, 1978).

The results of the present study suggest that activity of the mixed function oxidases involved in hydroxylation of brotizolam is significantly impaired by age: the (intrinsic) clearance of brotizolam was two-three times less in the elderly compared with the young and the elimination half-life was about twice as long (9.3 h vs 4.8 h). On the other hand, volume of distribution and protein binding of brotizolam were not significantly influenced by age.

Greenblatt *et al.* (1982) have suggested that the age-related decline in drug oxidizing enzyme activity is far greater in men than in women. In our study the numbers were too small for a quantitative evaluation of the influence of gender. However, when for the elderly the elimination half-life was compared in women ($n = 9$) and in men ($n = 10$), no significant difference was observed, suggesting that there is no major sex difference with brotizolam in the elderly.

Absorption of oral brotizolam tended to be slower in the elderly than in the young ($t_{\max} = 1.7$ h and 1.1 h respectively). The relatively slow attainment of the maximum plasma concentration was however not reflected in the clinical observations, as most patients fell asleep within 0.5 h. It seems that elderly people will usually fall asleep when plasma concentrations exceed 3 ng/ml. Because brotizolam was not given both i.v. and orally to the same elderly subject, oral bioavailability could only be estimated by comparing the mean data (i.v. and oral) of the two experimental groups. Bioavailability in the elderly was only 66% but this is comparable to the 70% in young subjects.

There is increasing evidence that there may be circadian variations in the kinetics of drug disposition (Lemmer, 1981). However, in our study, there was no significant difference in elimination half-life between administration at 09.00 h or at 21.00 h. Similar results were reported for the elimination half-lives of diazepam and clobazam, but the time of administration had a significant influence on the rate of absorption of these drugs (Chamberlain *et al.*, 1980; Watanabe *et al.*, 1980). The rate of absorption of brotizolam at night could not, for practical reasons, be determined in this study.

The two age groups studied were not entirely comparable with regard to health, smoking habits and concomitant drug intake. The elderly subjects were all non-smokers, whereas three of the young subjects were heavy smokers and three were light smokers. Tobacco may significantly affect drug metabolism in man by (selective) induction of the microsomal oxidizing enzyme system in the liver and other tissues (Vestal & Wood, 1980). It is striking that in the present study heavy smoking was indeed associated with the highest clearance values. Furthermore, the elderly subjects in this study took a variety of other drugs, but most of these are not known to affect drug metabolizing enzyme activity, although stilboestrol may inhibit the metabolism of other drugs as do oestrogens used in oral contraceptives (Abernethy & Greenblatt, 1981) and thyroxine may enhance drug metabolism through the improvement of thyroid function (Eichelbaum, 1976).

In conclusion, the results of this study suggest that brotizolam in a dose of 0.25 mg is an effective hypnotic in the elderly. Onset of drug action is quite rapid despite the relatively slow rate of absorption. The metabolic clearance of brotizolam is significantly impaired in the elderly, which is also the case with some other benzodiazepines that undergo oxidative metabolism. Thus, the elimination half-life of brotizolam in the elderly is about twice as long as in the young. Nevertheless, it is still sufficiently short to avoid significant drug accu-

mulation if 0.25 mg brotizolam is taken every evening. It remains to be established by objective measurements in the elderly whether or not the impaired drug elimination is associated with impaired performance the next morning.

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Pharmakokinetik von Brotizolam bei älteren Menschen

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1 Die Kinetik von Brotizolam bei 71–93 Jahre alten Patienten wurde mit der bei gesunden, jungen Probanden zwischen 21–26 Jahren verglichen.

2 Die mittlere Eliminationshalbwertszeit von Brotizolam war bei älteren Versuchspersonen ca. zweimal so lang wie bei jungen Probanden: 9,3 (4,0–19,5) Stunden bzw. 4,8 (3,1–6,3) Stunden. Die verlängerte Eliminationshalbwertszeit war einer Abnahme der hepatischen Clearance zuzuschreiben, bzw. 40 (20–58) ml/min bei älteren und 109 (77–156) ml/min bei jungen Versuchspersonen. Verteilungsvolumen und Proteinbindung waren gleich mit Mittelwerten von 0,56 (0,45–0,72) l/kg und 9,0 (6,8–11,9)% bei älteren und 0,63 (0,40–0,77) l/kg und 8,4 (7,5–9,4) % bei jungen Personen.

3 Die Resorptionsrate von Brotizolam war bei den älteren Patienten relativ langsam; der Zeitpunkt der Maxima lag im Durchschnitt bei 1,7 Stunden im Vergleich zu 1,1 St. bei den jungen Probanden. Die mittlere Bioverfügbarkeit betrug ca. 70% in beiden Gruppen. Nach Angleichung an Körpergewicht und Dosis (0,25 mg) betrugen die mittleren Höchstkonzentrationen 247 (137–395) ng ml⁻¹ kg⁻¹ bei den jungen und 343 (251–446) ng ml⁻¹ kg⁻¹ bei den älteren Probanden.

4 Es ist unwahrscheinlich, dass eine nennenswerte Substanzkumulation auftritt, wenn ältere Patienten abendlich 0,25 mg Brotizolam einnehmen.

Pharmacocinétique du brotizolam chez les personnes âgées

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1 La pharmacocinétique du brotizolam chez des patients âgés de 71 à 93 ans a été comparée à celle de jeunes sujets de 21–26 ans en bonne santé.

2 La demi-vie moyenne d'élimination du brotizolam a été, chez les patients âgés, environ le double de celle des jeunes sujets: 9,3 (4,0–19,5) h et 4,8 (3,1–6,3) h. L'augmentation de la demi-vie d'élimination a été attribuée à la diminution de la clairance hépatique, qui a été de 40 (20–58) ml/min pour les personnes âgées, et de 109 (77–156) ml/min pour les jeunes gens. Le volume de distribution et la fixation aux protéines ont été semblables, les valeurs moyennes ayant été de 0,56 (0,45–0,72) l/kg et 9,0 (6,8–11,9) % pour les patients âgés, et de 0,63 (0,40–0,77) l/kg et 8,4 (7,5–9,4) % pour les jeunes sujets.

3 Le taux d'absorption du brotizolam a été relativement lent chez les patients âgés: le temps moyen des pics a été de 1,7 h, tandis que celui des jeunes gens a été de 1,1 h. La biodisponibilité moyenne a presque atteint 70% pour les deux groupes. Les pics de concentration, normalisés en fonction du poids corporel et de la dose (0,25 mg) ont été en moyenne de 247 (137–395) ng ml⁻¹ kg⁻¹ pour les jeunes sujets, et de 343 (251–446) ng ml⁻¹ kg⁻¹ pour les patients âgés.

4 Il est peu probable que d'importantes accumulations de ce médicament puissent survenir lorsque les patients âgés prennent une dose de 0,25 mg de brotizolam tous les soirs.

Farmacocinética de brotizolam en la senectud

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1 La farmacocinética de brotizolam en pacientes con edades comprendidas entre 71 y 93 años fue comparada con la correspondiente a individuos jóvenes sanos con edades de 21–26 años.

2 La vida media de eliminación de brotizolam fue

alrededor de 2 veces más prolongada en los ancianos que en los jóvenes con valores promedio de 9,3 (4,0–19,5) h y 4,8 (3,1–6,3) h respectivamente. El aumento de la vida media de eliminación fue atribuible a una disminución de la

depuración hepática, a saber 40 (20–58) ml/min en los ancianos y 109 (77–156) ml/min en los jóvenes. El volumen de distribución y la fijación proteica fueron semejantes con promedios de 0,56 (0,45–0,72) l/kg y 9,0 (6,8–11,9)% en los ancianos y 0,63 (0,40–0,77) l/kg y 8,4 (7,5–9,4)% en los jóvenes.

3 El índice de absorción de brotizolam fue relativamente lento en los ancianos, con un tiempo máximo medio de 1,7 h en comparación con 1,1 h en los jóvenes. La biodisponibilidad, media

fue de casi 70% para ambos grupos. Tras normalización para el peso corporal y dosis (0,25 mg) las concentraciones máximas medias fueron 247 (137–395) ng ml⁻¹ kg⁻¹ en los jóvenes y 343 (251–446) ng ml⁻¹ kg⁻¹ en los ancianos.

4 Es improbable que se produzca una acumulación sustancial del fármaco si pacientes de edad avanzada ingieren 0,25 mg de brotizolam por noche.