PHARMACOKINETICS OF BROtizOLAM IN RENAL FAILURE

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- 1 Kinetics of brotizolam (0.25 mg) were studied in patients with different degrees of renal failure after single and repeated oral ingestion. Serum levels were analysed by radio-immunoassay.
- 2 Patients were divided into three groups according to their renal function, i.e. creatinine clearance values of 45–80, 15–45, or less than 15 ml/min.
- 3 The mean elimination half-life was 6.9–8.15 h, with a considerable variation of the peak concentration and elimination half-life in slight to moderate renal failure. There was no delay in elimination in severe renal failure and there was no drug accumulation.
- 4 No dose adjustment is necessary for brotizolam in renal failure.

Keywords brotizolam pharmacokinetics renal failure

Introduction

Drug action is often modified in patients with renal failure by alterations of absorption, protein-binding, distribution and metabolism, diminished excretion and retention of active metabolites (Anon, 1977).

Benzodiazepines are metabolized mainly in the liver and metabolites are excreted by the kidney, but there is considerable variability between individual compounds in rates of metabolism and excretion (Bennett, 1980). Whereas diazepam can be used without dose adjustment in renal failure, flurazepam should be used with caution.

Up to 65% brotizolam (1% of it unchanged) is excreted by the kidney (Bechtel, 1983) and information on elimination in renal failure is therefore of importance. The purpose of this study was to determine the handling of brotizolam after single and repeated oral dosage in patients with different degrees of renal insufficiency.

severe renal insufficiency (creatinine clearance less than 15 ml/min). The patients were aged between 21 and 63 years, the average being 51 years. Patients with impaired hepatic function were excluded. The patients' personal data are listed in Table 1 and their underlying diseases and concomitant therapy in Table 2.

All patients were informed about the nature of the investigation and each received one 0.25 mg brotizolam tablet with 100 ml water on the first and seventh days at 08.00 h and from the first to the sixth days at 21.00 h. The patients fasted overnight on the first and last trial days and received breakfast 1 h after taking the morning tablet. Blood (5 ml) was collected from each patient shortly before and at 2, 4, 6, 8 and 10 h after taking the tablet. These samples were centrifuged and stored at –20°C until they could be analysed.

The quantitative assay of brotizolam in the serum was performed using a radioimmunoassay specific for brotizolam (Bechtel, 1983).

Methods

Eighteen patients were selected from amongst a group of in-patients and divided into three categories: those with mild renal insufficiency (creatinine clearance 45–100 ml/min), those with moderate renal insufficiency (creatinine clearance 15–45 ml/min) and

Results

Figure 1 shows graphically the mean values of the serum levels of the three groups for the first and seventh days of the study. The serum levels reached their maximum relatively rapidly (after approxi-

Table 1 Patient data

<i>Patient</i>	<i>Sex</i>	<i>Age (years)</i>	<i>Height (cm)</i>	<i>Weight (kg)</i>	<i>Serum creatinine (mg %)</i>	<i>Creatinine clearance (ml/min)</i>
1	F	40	150	59	2.0	60
2	M	58	164	75	1.6	70
3	M	59	172	76	1.8	60
4	F	54	152	73	1.7	60
5	M	56	178	75	1.5	80
6	M	49	176	76	1.3	80
7	M	55	172	81	6.0	15
8	M	37	178	88	2.6	40
9	F	60	162	83	2.7	31
10	M	59	178	70	3.0	25
11	F	63	154	70	2.5	25
12	F	21	160	54	2.7	30
13	F	60	166	61	10.0	< 10
14	M	45	176	67	10.0	< 10
15	M	54	178	76	7.0	< 15
16	F	44	161	69	10.0	< 10
17	M	52	168	73	9.0	< 10
18	M	51	164	61	10.0	< 10

Table 2 Patient data

<i>Patient</i>	<i>Diagnosis</i>	<i>Therapy</i>
1	Chronic pyelonephritis	—
2	Nephrosclerosis	Isosorbide, phenprocoumon
3	Toxic nephropathy	Mezlocillin, digoxin, pirenzepine
4	Glomerulonephritis	Amiloride, hydrochlorothiazide
5	Nephrosclerosis	Allopurinol, atenolol, acetylsalicylic acid, molsidomine, frusemide, penicillamine
6	Renal artery stenosis	Propranolol, hydralazine, clonidine, triamterene, thiazide
7	Chronic interstitial nephritis	Ampicillin
8	Glomerulonephritis	Dihydroergocristine, clopamide, reserpine, allopurinol
9	Plasmacytoma kidney	Cyclophosphamide, digoxin, doxycycline, L-thyroxine
10	Glomerulonephritis	Captopril, propranolol, acetylsalicylic acid, dipyridamole, hydralazine, frusemide, allopurinol, digoxin
11	Renal cysts, pyelonephritis	Heparin, digoxin
12	Kidney transplantation	Azathioprine, fluocortolone, frusemide, gelusil, nystatin
13	Polycystic disease	Frusemide, clemastine
14	Pyelonephritis, paraplegia	—
15	Polycystic disease	Hydralazine, atenolol, metoclopramide
16	Chronic renal failure (unknown aetiology)	Hydralazine, atenolol, frusemide, aluminium hydroxide
17	Glomerulonephritis	Prazosin, metoprolol, clonidine, frusemide, nitroglycerin, allopurinol, hydralazine, captopril
18	Glomerulonephritis	Digoxin, pindolol, calcium, dipyridamole

Figure 1 Serum levels of brotizolam on days 1 and 7 of the trial in patients 1–6 (●, with renal insufficiency), patients 7–12 (■, moderate renal insufficiency) and patients 13–18 (▲, severe renal insufficiency).

mately 2 h). The elimination half-life ($t_{1/2,z}$) was calculated from the serum levels of each patient and ascertained for each group separately. These results are shown in Table 3.

There was a wide range of maximum serum levels and elimination half-lives in patients with mild and moderate renal insufficiency. Isolated extreme values (half-lives of 17.08 and 60.32 h) affected greatly the overall picture. In the patients with severe renal insufficiency, on the other hand, consistent results were found, with an elimination half-life of 6.9 h on the first and 7.61 h on the last trial day.

There was no clinical evidence of cumulation of brotizolam. No increased tiredness was observed

throughout the trial and laboratory parameters and vital functions (blood pressure, pulse rate, temperature, diuresis, bowel movement and appetite) remained unchanged.

Discussion

A wide range of maximum serum concentrations and elimination half-lives for diazepam has been demonstrated (Breimer & Jochemsen 1983). Nevertheless, it was necessary to exclude the more extreme values obtained for some patients in this study—those for patient number 8 because they appear to be caused by

Table 3 Elimination of brotizolam from the serum of patients suffering from renal insufficiency after administration of one 0.25 mg tablet

Patient	$t_{1/2,z}$ (h)	Day 1	$t_{1/2,z}$ (h)	Day 7
		Mean $\pm$ s.d. (h)		Mean $\pm$ s.d. (h)
1	4.05		6.81	
2	11.08		10.57	
3	5.46		8.90	
4	6.70		25.25	
5	8.88		6.33	
6	17.08	8.88 $\pm$ 4.73	—	11.57 $\pm$ 7.83
7	6.70		6.65	
8	60.63		20.66	
9	7.11		8.87	
10	26.28		7.66	
11	—		3.04	
12	9.02	21.95 $\pm$ 23.10	9.03	8.99 $\pm$ 6.06
13	6.49		6.81	
14	3.77		8.18	
15	11.45		8.14	
16	6.78		7.73	
17	8.95		6.61	
18	3.96	6.90 $\pm$ 2.95	8.18	7.61 $\pm$ 0.72

Figure 2 Serum levels of brotizolam on day 1 (●) and day 7 (▲) of the trial in patients with severe renal insufficiency. Δ serum levels corrected by the residual value, which was taken from the extrapolated serum levels (○).

artefact, and those for patients numbers 4, 6 and 10 because there was no correlation between figures obtained on the first and seventh days. There was no apparent relationship between the values obtained and age, weight, underlying disease, concomitant medication or previous administration of diazepam. Even in those patients who were excluded from the overall analysis, no evidence of accumulation of brotizolam was obtained on the seventh day.

The widest range of results occurred in those patients with mild and moderate renal insufficiency, while the values for patients with severe renal insufficiency were clustered together within this range. The consistent pattern of serum concentrations obtained for the patients with severe renal insufficiency indicate clearly, in contrast to the results for the other groups, that there was no delay in elimination or accumulation of brotizolam after repeated administration.

The serum levels recorded on the seventh day were higher than those on the first day; this was caused by the evening administration of brotizolam 11 h previously. If the values obtained for the seventh day are corrected by the residual value, which can be cal-

Table 4 Mean elimination half-lives (excluding the patients with extreme values)

Patient	Degree of insufficiency	Day 1 $t_{1/2,z}$ (h)	Day 7 $t_{1/2,z}$ (h)
1-3, 5	Mild	7.37	8.15
7, 9, 11, 12	Moderate	7.61	6.90
13-18	Severe	6.90	7.61

culated from the half-life, for the previous dose, the curves for the first and seventh days are the same (Figure 2).

If the extreme values obtained for patients 4, 6, 8 and 10 are excluded, the serum half-life is between 6.90 and 8.15 h (Table 4), which falls within the range which was found in a recent study on 24 volunteers with normal renal function, i.e. an average of 7.1 to 7.9 h (Bechtel, 1983).

In summary, there is no prolongation of serum half-life and no accumulation of brotizolam in renal insufficiency, and there is therefore no need to adjust the dose, at least during short-term therapy.

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Pharmakokinetik von Brotizolam bei Niereninsuffizienz

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1 Die Kinetik von Brotizolam (0,25 mg) wurde bei Patienten mit verschiedenen Schweregraden einer Niereninsuffizienz nach einmaliger und wiederholter oraler Einnahme untersucht. Die Serumspiegel wurden mittels Radioimmunoassay bestimmt.

2 Die Patienten wurden in drei Gruppen je nach ihrer Nierenfunktion aufgeteilt, d.h. Kreatinin-Clearancewerte von 45–80, 15–45 oder geringer als 15 ml/min.

3 Die mittlere Eliminationshalbwertszeit betrug 6,9–8,15 Stunden bei erheblicher Schwankung der Spitzenwerte und Eliminationshalbwertszeiten bei leichter bis mittelschwerer Niereninsuffizienz. Es fand sich keine Ausscheidungsverzögerung bei schwerer Niereninsuffizienz und auch keine Kumulation des Arzneimittels.

4 Eine Dosisanpassung bei Niereninsuffizienz ist für Brotizolam nicht erforderlich.

Pharmacocinétiques du brotizolam dans l'insuffisance rénale

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1 La cinétique du brotizolam (0.25 mg), administré par voie orale en dose unique ou répétée, a été étudiée chez des patients présentant divers degrés d'insuffisance rénale. Les taux sériques ont été analysés par la méthode radio-immunologique.

2 Les patients ont été divisés en trois groupes en fonction de l'état de leur fonction rénale, c'est-à-dire des taux de clairance de la créatinine de 45–80, 15–45 et moins de 15 ml/min.

3 La demi-vie moyenne d'élimination a été de 6,9–8,15 h, les pics de concentration et la demi-vie d'élimination ayant présenté des variations considérables dans les insuffisances rénales légères à moyennes. Il n'y a pas eu de retard d'élimination dans l'insuffisance rénale grave ni non plus d'accumulation de la substance.

4 Il n'est pas nécessaire d'ajuster la dose de brotizolam dans l'insuffisance rénale.

Farmacocinética de brotizolam en la insuficiencia renal

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1 Se estudió la cinética de brotizolam (0,25 mg) en pacientes con diverso grado de insuficiencia renal tras ingestión única y repetida. Los niveles en suero se analizaron mediante radio-inmunoensayo.

2 Los pacientes fueron distribuidos en 3 grupos según su función renal, es decir, con valores de depuración de creatinina de 45–80, 15–45 o menos de 15 ml/min.

3 La vida media de eliminación promedio fue de 6,9–8,15 h, con variación considerable de la concentración máxima y de la vida media de eliminación en los casos de insuficiencia renal leve a moderada. No hubo retardo de la eliminación en la insuficiencia renal grave y no existió tampoco acumulación del fármaco.

4 No se requiere una adaptación de la dosis de brotizolam en la insuficiencia renal.