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Pharmacokinetics of Diltiazem in Severe Renal Failure

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Summary. The acute effects of a single dose of diltiazem (Tildiem®), a calcium antagonist, were studied in 9 patients with severely impaired renal function (GFR between 0.03 and 0.87 ml/s/1.73 m^2). Control measurements were made of inulin and PAH clearance, creatinine, blood pressure, heart rate and ECG. Following administration of diltiazem 120 mg, 7 blood samples were collected in the first 12 h and after 24 h, 32 h, 48 h; urine was collected for the first 12 h, 12–24 h and 24–48 h, and blood pressure, heart rate and ECG were recorded after 6 h. Diltiazem and its main metabolite, desacetyldiltiazem, had a pharmacokinetic profile similar to that in patients with normal renal function (peak plasma concentration, half-life and urinary excretion). Diltiazem is normally eliminated in the urine to a small extent, because it is metabolized, and this also applies to desacetyldiltiazem, which is probably further metabolized.

Key words: calcium antagonist, diltiazem, renal failure; pharmacokinetics, desacetyldiltiazem, metabolism

Diltiazem (Tildiem®) is a new calcium flux antagonist, which has been widely studied experimentally (Cavero et al. 1978). Its efficacy in patients suffering from different types of angina pectoris is well-known (Grolleau et al. 1979; Guermonprez et al. 1980). The present study was carried out to evaluate its pharmacokinetic profile and tolerance in patients with severely impaired renal function.

Material and Methods

Selection of Patients (Table 1)

Nine informed patients, 4 males and 5 females, mean age 42 ± 16.6 years, mean weight 59.1 ± 11.9 kg, were studied. They all had evolving nephropathy and/or severely impaired renal function, with glomerular filtration (inulin clearance) under 50% of normal in 7 of the subjects. Two had terminal renal insufficiency and were on chronic dialysis. None showed impaired sinus node function in a standard ECG. None was given any other drug.

Table 1. Details of the patients

Patient	Age [years]	Sex	Diagnosis	Inulin clearance [ml/s/1.73 m^2]
1	58	F	Single kidney, pyelonephritis	0.52
2	29	F	Terminal renal insufficiency	0.12
3	29	M	Renal and ureteral malformations, unilateral nephrectomy	0.52
4	69	F	Diabetes, lithiasis, unilateral nephrectomy	0.82
5	28	M	Terminal renal insufficiency, chronic dialysis	–
6	59	F	High blood pressure	0.83
7	43	M	Polycystic kidney	0.03
8	41	F	Chronic glomerulonephritis, chronic dialysis	–
9	22	M	Nephrotic syndrome	0.87

Table 2. Plasma levels [ng/ml] of diltiazem (DTZ) and desacetyl diltiazem (DAD)

	Patient	0 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	32 h	48 h
DTZ	1	0	57.7	111.2	98.3	49.7	35.1	26.1	15.6	0	0	0
	2	0	206.6	158.5	79.6	57.8	32.2	19.1	9.3	0	0	0
	3	0	154.0	215.0	105.0	77.0	39.0	28.0	15.0	0	0	0
	4	0	63.7	63.7	55.0	33.4	29.3	21.0	15.1	4.2	0	0
	5	0	215.53	228.20	159.67	81.53	43.77	24.91	11.07	0	0	0
	6	0	153.94	–	140.82	139.90	21.42	15.34	17.39	8.12	2.55	1.09
	7	0	303.96	406.39	315.76	112.00	74.58	45.43	34.35	3.37	0	0
	8	0	133.53	118.70	50.06	16.58	8.01	8.86	6.37	0	0	0
	9	6.69	25.41	31.88	26.74	–	8.54	4.55	3.97	0.94	0	0
DAD	1	0	38.53	33.45	28.81	16.32	14.57	–	0	0	–	–
	2	0	26.37	27.17	29.38	16.43	traces	traces	0	0	–	–
	4	0	4.93	8.33	9.44	8.60	3.17	0	0	0	–	–
	7	0	45.49	17.77	–	23.14	22.41	13.56	9.43	0	–	–

Table 3. Plasma level of diltiazem as a function of dose and renal function

Patient	Inulin Cl [ml/s]	Dose [mg/kg]	Peak concentration [ng/ml]	$t_{½}$ [h]	Ke [h^{-1}]	Renal elimination [%] of ingested dose
1	0.52	2.24	111.2	3.20	0.217	0.64
2	0.12	3.12	206.6	2.70	0.257	0.34 (24 h)
3	0.52	1.91	215	2.80	0.248	0.51
4	0.82	1.82	108.1	4.90	0.142	0.97
5		1.75	228.2	2.12	0.327	–
6	0.83	2.42	153.9			6.94 (24 h)
7	0.03	1.79	406.4	3.59	0.193	2.39
8		2.40	133.5	4.34	0.159	–
9	0.87	1.58	31.9			0.70

Procedure

At time t_0 a control blood sample was taken and an ECG was recorded. Then a single oral dose of diltiazem 2×60 mg was administered. Blood samples were collected at 2, 3, 4, 6 (+ECG), 8, 10, 12, 24, 32 and 48 h. The first blood sample was not taken before 2 h, because anaemia in the patients did not permit too frequent blood collection. Urine was collected from 0–12, 12–24 and 24–48 h.

Diltiazem and desacetyldiltiazem, its principal metabolite, were analysed by gas chromatography (Rovei et al. 1977).

Results

The peak plasma levels of diltiazem and desacetyldiltiazem were reached within 2 or 3 h (Tables 2, 3; Fig. 1). The peak plasma concentration ranged from 31.88 to 406.39 ng/ml. The large interindividual variability had previously been observed in clinical practice.

The level of the metabolite in 4 patients was 26% of that of the parent compound for the first 6 h. No metabolite could be detected at 24 h, confirming the lack of accumulation. After a relatively short distribution phase, plasma diltiazem concentrations decayed monoexponentially, with an apparent plasma half-life $t_{½}$ ranging from 2.12 to 4.90 h, average 3.38 h (Fig. 1).

The elimination rate constant, $Ke = \frac{0.693}{t_{½}}$, calculated in 7 patients, ranged from 0.142 to $0.327 \cdot h^{-1}$ (average $0.220 \cdot h^{-1}$). 1.35% of the dose of diltiazem was recovered unmetabolized in the 24 h urine (Table 4).

The general tolerance of diltiazem was excellent, and there was no change in blood pressure. A moderate but significant increase in heart rate was seen (*t* test for paired data), but no change in PR interval in the ECG.

Table 4. Renal excretion of diltiazem

	Patient						
	1	2	3	4	6	7	9
Urine 0–12 h:							
amount eliminated [μg]	571.1	360.7	549.6	721.2	3863.5	2561.5	377.8
% of ingested dose	0.48	0.30	0.46	0.60	3.22	2.13	0.31
Urine 12–24 h:							
amount eliminated [μg]	130.1	50	33.2	309.5	4460.7	244	425.1
% of ingested dose	0.11	0.04	0.03	0.26	3.72	0.20	0.35
% cumulative 24 h	0.59	0.34	0.49	0.86	6.94	2.33	0.66
Urine 24–48 h:							
amount eliminated [μg]	57	0	19	102.9		77.4	46.6
% of ingested dose	0.05		0.02	0.09		0.06	0.04
% cumulative – 48 h	0.64		0.51	0.97		2.39	0.70

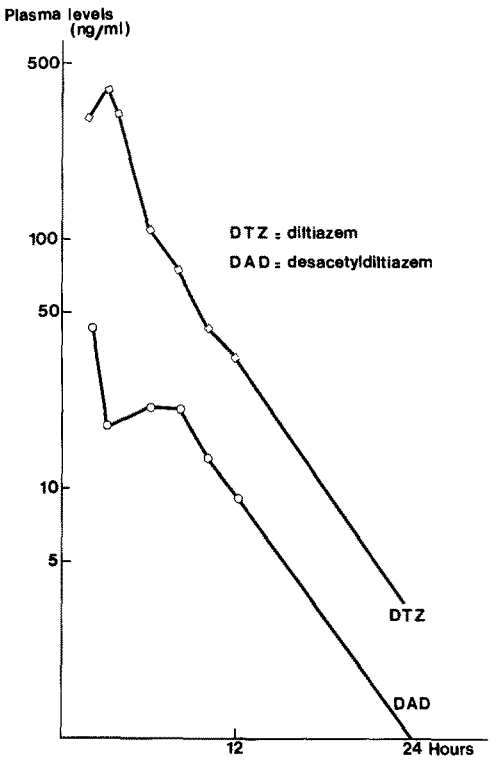

Fig. 1. Comparative plasma concentration of diltiazem (DTZ) and desacetyldiltiazem (DAD) in Patient 7

Discussion

The pharmacokinetics of diltiazem was studied by Morselli et al. (1978) in healthy volunteers and in patients suffering from angina pectoris without renal failure: the oral route of administration was used, as in our patients, since this is the commonly used route.

Absorption of the drug did not appear to be substantially different in those subjects or in the present series. The peak plasma concentration occurred a little later in the present patients (2 to 3 h instead of 1 h), but this time is too variable from one subject to another to permit a strict comparison between the 2 series. The levels reached were even more variable.

Perhaps because of its protein binding (80 to 86%), the amount of diltiazem found in the urine was very small. The disappearance of its effects is due to metabolism of the drug to desacetyldiltiazem in the first instance. The proportions of this metabolite and of the parent compound were identical in patients with (26%) and without renal failure (15 to 30%), and the lack of accumulation of desacetyldiltiazem in the former case suggests that it undergoes further metabolism as in the latter subjects. It is known that desacetyl-O-demethyldiltiazem and desacetyl-N-demethyldiltiazem and conjugation products on the hydroxy groups of all these derivatives originate from diltiazem.

The metabolism of diltiazem is consistent with a half-life which does not appear to be prolonged by renal insufficiency. If anything, the half-life might even be slightly shorter when renal function is impaired: a mean of 3.38 h as compared to 4 to 8 h.

Thus, from the pharmacokinetic data obtained from 9 patients with severely impaired function, the following conclusions can be drawn; a single oral dose of diltiazem 2×60 mg is partly absorbed; there is wide interindividual variability in the kinetics, as shown in previous studies; the compound is extensively metabolized; and, the apparent plasma half-life is similar to that in patients with normal renal function.

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