Haemodialysis does not affect the pharmacokinetics of nifedipine

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To establish dosage recommendations in patients with end-stage renal disease undergoing chronic haemodialysis, nifedipine kinetics were studied between and during haemodialysis sessions. In eight patients, during the interdialytic period, peak plasma concentrations of nifedipine (29–332 ng/ml) were reached 0.5–1.0 h after administration of a single 10 mg oral dose. Elimination half-life and oral plasma clearance were respectively 2.6 ± 0.5 h and $1\,176 \pm 412$ ml/min. Nifedipine plasma protein binding was decreased in uraemic patients ($88.8 \pm 0.3\%$ vs $94.4 \pm 0.1\%$) but not affected by haemodialysis. Removal by haemodialysis was low: the dialyser extraction ratio and the dialysis clearance were respectively $2.3 \pm 0.8\%$ and 2.8 ± 0.9 ml/min.

Keywords nifedipine pharmacokinetics haemodialysis

Introduction

Nifedipine is a calcium blocking agent with vasodilating properties (Robinson *et al.*, 1980); this drug is being increasingly used in the treatment of angina pectoris and hypertension in uraemic patients, predisposed to cardiovascular disease (Kubo *et al.*, 1983; Lewin & Trautman, 1971).

To our knowledge, no data are available in the literature on nifedipine pharmacokinetics in renal disease. Our study was designed to characterize nifedipine kinetics during haemodialysis and to provide a basis for appropriate dosage adjustments in haemodialysed patients.

Methods

Ten patients, seven men and three women (37–75 years; 43–78 kg) with end-stage renal disease undergoing routine maintenance haemodialysis were studied after having obtained their written informed consent. All had residual renal creatinine clearance under 7 ml/min. Associated drugs, except for diazepam (analytical interference) were maintained; however, ant-

acid drugs were administered at least 2 h after nifedipine to avoid interference with absorption. The patients were divided into two groups: *group 1*, eight patients (numbers 1 to 8) were studied during the 48 h interdialytic period. Their renal residual creatinine clearance was between 0.0 and 6.0 ml/min (mean 2.2 ml/min); *group 2*, five patients (numbers 9 and 10, and patient numbers 1, 2 and 3 from group 1 in a second investigation) were studied during haemodialysis. Their renal residual creatinine clearance was between 0.0 and 2.8 ml/min (mean 1.5 ml/min).

Four hour haemodialysis was performed with a double needle access in arterio-venous fistulas, using a 1.2 m² cuprophane membrane dialyser (CF 1511, Travenol Laboratories) and a single-pass dialysate delivery system with a constant dialysate flow rate of 500 ml/min; blood flow entering the dialyser, as determined by bubble transit time, was approximately 200 ml/min.

Ten patients were given a single oral dose of 10 mg nifedipine capsule with 50 ml of water. Venous blood samples (5 ml on dry heparin) were collected in patients from group 1 before

and 0.5, 1, 1.5, 2, 4, 6 and 10 h after drug intake. For the patients from group 2, nifedipine was administered 3 h before starting haemodialysis. Arterial and venous blood samples entering and leaving the dialyser, were simultaneously obtained at mid-dialysis to compute the haemodialysis clearance. Since nifedipine is photosensitive (Jakobsen *et al.*, 1979), blood samples were collected into tubes protected from light by aluminium foil; during the haemodialysis, tubings and artificial kidney were also protected from light. Blood samples were immediately centrifuged; the plasma was separated and stored at -30°C until analysed.

Nifedipine plasma levels were determined by gas liquid chromatography, using an electron capture detector, according to the method described by Jakobsen *et al.* (1979).

Plasma protein binding of nifedipine was measured by equilibrium dialysis (Dianorm® system); no significant binding of nifedipine occurred either on dialysis membrane (Visking®) or cell walls. At a temperature of 37°C and a speed of 8 rev/min, equilibrium was achieved between 2 and 3 h and so a dialysis time of 3 h was used for all determinations. Protein binding was determined at a concentration of 100 ng/ml on pooled blank plasma for healthy subjects and on pooled plasma from unmedicated uraemic patients, obtained before and after dialysis. Albumin concentrations were determined by the single radial immunodiffusion method (Nor-Partigen®—Hoechst Behring).

Data were analysed by model independent methods (Rowland & Tozer, 1980). The 4 h haemodialysis clearance (CL_{HD}) was calculated by the formula proposed by Gotch (1976):

$$\text{CL}_{\text{HD}} = \left[\frac{C_i - C_o}{C_i} \cdot Q_p \right] + \left[\frac{C_o}{C_i} \cdot Q_{\text{UF}} \right]$$

where C_i and C_o are respectively the plasma concentrations entering and leaving the dialyser; Q_p is the plasma flow entering the dialyser derived from the blood flow Q_b and the haematocrit Ht : $Q_p = Q_b \cdot (1 - \text{Ht})$; Q_{UF} is the ultrafiltration rate, as displayed on the dialyser.

Dialyser extraction ratio (E) was determined by the formula:

$$E (\%) = \frac{\text{CL}_{\text{HD}}}{[Q_p + (Q_p - Q_{\text{UF}})]/2} \times 100,$$

where the denominator represents the mean plasma flow in the dialyser.

Results

The plasma kinetics of nifedipine in the eight patients during the interdialytic period are illustrated in Figure 1. There were large inter-individual variations: the mean plasma concentration ($\pm$ s.e. mean), obtained in the first or second sample, was 124 ± 36 ng/ml (range 29–332). The half-life varied between 0.7 and 4.3 h (mean 2.6 ± 0.5 h) and the mean oral clearance was $1\,176 \pm 412$ ml/min.

The results obtained during haemodialysis in the five patients from group 2 are summarized in Table 1; elimination by haemodialysis was low; the extraction ratio through the dialyser was $2.3 \pm 0.8\%$ and the 4 h dialysis clearance was 2.8 ± 1.0 ml/min.

Nifedipine plasma protein binding (mean $\pm$ s.e. mean of five determinations) in blank plasma was $94.4 \pm 0.1\%$ (albumin concentration, 39 g/l); in uraemic plasma samples collected before and after haemodialysis, nifedipine binding was respectively $88.6 \pm 0.3\%$ (albumin concentration, 26 g/l) and $89.0 \pm 0.1\%$ (albumin concentration, 30 g/l).

Discussion

Our results show large interindividual variations of plasma concentrations and pharmacokinetic parameters as already described in healthy subjects (Kleinbloesem *et al.*, 1984).

Figure 1 Plasma concentrations of nifedipine in the eight patients from group 1 during the interdialytic period, after oral administration of 10 mg.

Table 1 Parameters during haemodialysis in the five patients from group 2

Patient	Dialyser blood flow Q_b (ml/min)	Haematocrit (Ht)	Ultrafiltration rate Q_{UF} (ml/min)	Nifedipine concentrations (ng/ml)		Haemodialysis clearance CL_{HD} (ml/min)	Extraction rate E (%)
				in	out		
1	200	0.25	9.8	4.7	5.0	0.8	0.6
2	240	0.25	12.6	10.5	11.0	4.6	2.6
3	168	0.34	10.0	10.5	11.0	4.9	4.6
9	170	0.36	10.0	60.8	66.8	0.3	0.2
10	198	0.39	14.3	80.0	88.0	3.6	3.2
Mean	195	0.32	11.3	—	—	2.8	2.3
s.e. mean	13	0.03	0.9	—	—	1.0	0.8

Peak plasma concentration (124 ± 36 ng/ml) was close to that of 160 ± 49 ng/ml reported by Raemsch & Sommer (1983) in 10 normal volunteers, 0.5 to 1 h after oral administration of 10 mg nifedipine capsule.

Likewise, in our uraemic patients, the terminal half-life (mean 2.6 h) was similar to the values reported by Kleinbloesem *et al.* (1984) and Raemsch & Sommer (1983) in healthy subjects after oral administration of 10 or 20 mg nifedipine capsule (2–3 h).

Due to the first pass metabolism of nifedipine (Waller *et al.*, 1984), the oral clearance of nifedipine (1 176 ml/min) is greater than the true clearance after intravenous administration. Absolute bioavailability of nifedipine could not be measured in our study. Forster *et al.* (1983) reported for the capsule formulation a bioavailability of 0.45. If we assume in our patients an identical bioavailability (AUC, t_{max} and C_{max} are similar to values measured in healthy subjects), nifedipine plasma clearance becomes about 500 ml/min, a value close to that calculated in healthy subjects after intravenous infusion (Forster *et al.*, 1983; Kleinbloesem *et al.*, 1984; Waller *et al.*, 1984).

These results may be explained by the fact that the elimination of nifedipine is essentially extra-renal. However, it must be pointed out that among the eight patients studied, there was a large difference in AUC and also in oral clearance values. Such a variability in hepatic extraction might be related to hepatic blood flow modifications, as frequently observed in patients with kidney disease.

Protein binding of nifedipine in normal plasma was $94.4 \pm 0.1\%$, a value in close agreement with the data of Rosenkranz *et al.* (1974). Protein binding was decreased in uraemic plasma (89%). Such a decrease has already been reported for many drugs (Reidenberg, 1976). Nifedipine protein binding was not modified during haemodialysis; thereby, the decrease in protein binding was probably not a competitive interaction between drug and dialysable endogenous compounds which accumulate in uraemic patients (Andreasen, 1974; Dromgoole, 1973; Sjöholm *et al.*, 1976). This decrease could be the consequence of an alteration of plasma albumin concentration or binding capacity (Boobis, 1977); in our study, albumin concentration in normal plasma was 39 g/l, whereas in uraemic plasma, it was respectively 26 and 30 g/l before and after haemodialysis.

Nifedipine haemodialysis clearance (2.8 ml/min) and its extraction ratio (2%) were very low. Due to the haemodilution in the artificial kidney, nifedipine plasma concentration leaving

the dialyser was higher than that entering the dialyser (Table 1), so ultrafiltration rate must be taken into account in the clearance calculations.

In these patients, plasma concentrations measured 5 h after drug administration varied greatly (5 to 80 ng/ml) as in the patients from group 1. Haemodialysis clearance was not dependent upon concentration gradient. The low haemodialysis elimination of nifedipine was probably the consequence of its lipid solubility and high protein binding.

References

- Andreasen, F. (1974). The effect of dialysis on the protein binding of drugs in the plasma of patients with acute renal failure. *Acta Pharmac. Tox.*, **34**, 234–294.
- Boobis, S. (1977). Alteration of plasma albumin in relation to decreased drug binding in uremia. *Clin. Pharmac. Ther.*, **22**, 147–153.
- Dromgoole, S. H. (1973). The effect of hemodialysis on the binding capacity of albumin. *Clin. Chim. Acta*, **46**, 469–472.
- Forster, T. S., Hamman, S. R., Richards, V. R., Bryant, P. J., Graves, D. A. & McAllister, R. G. (1983). Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects. *J. clin. Pharmac.*, **23**, 161–170.
- Gotch, F. A. (1976). Hemodialysis; technical and kinetic considerations. In *The kidney*, eds Brenner, C. & Rector, P. Vol. 2: 1672–1704.
- Jakobsen, P., Lederballe Pedersen, O. & Mikkelsen, E. (1979). Gas chromatographic determination of nifedipine and one of its metabolites using electron capture detection. *J. Chromatogr.*, **162**, 81–87.
- Kleinbloesem, C. H., Van Brummelen, P., Van de Linde, J. A., Voogd, P. J. & Breimer, D. D. (1984). Nifedipine: kinetics and dynamics in healthy subjects. *Clin. Pharmac. Ther.*, **35**, 742–749.
- Kubo, K., Shiraishi, K., Muto, H., Suzuki, T. & Sugino, N. (1983). Treatment of hypertension in hemodialysis patients with nifedipine. *Hypertension*, **5**, S109–S112.
- Lewin, K. & Trautman, L. (1971). Ischaemic myocardial damage in chronic renal failure. *Br. med. J.*, **4**, 151–152.
- Raemisch, K. D. & Sommer, J. (1983). Pharmacokinetics and metabolism of nifedipine. *Hypertension*, **5**, S18–S24.
- Reidenberg, M. (1976). The binding of drugs to plasma proteins from patients with poor renal function. *Clin. Pharmacokin.*, **1**, 121–125.
- Robinson, B. F., Dobbs, R. J. & Kelsey, C. R. (1980). Effect of nifedipine on resistance vessels, arteries and veins in man. *Br. J. clin. Pharmac.*, **10**, 433–438.
- Rosenkranz, H., Schlossman, K. & Sholtan, W. (1974). Die Bindung von 4-(2' nitrophenyl)-2,6 dimethyl-1,4 dihydropyridine-3,5 dicarbon saure dimethyl ester (Nifedipin) sowie bon anderen kronarwirksamen Stoffen an die Eiweisokoerper des Serums. *Arzneim. Forsch. Drug Res.*, **24**, 455–466.
- Rowland, M. & Tozer, T. M. (1980). *Clinical pharmacokinetics; concepts and applications*. Philadelphia: Lea & Febiger.
- Sjöholm, A., Kober, I., Odar-Cederlof, I. & Borge, O. (1976). Protein binding of drugs in uremia and normal serum; the role of endogenous binding inhibitors. *Biochem. Pharmac.*, **25**, 1205–1213.
- Waller, D. G., Renwick, A. G., Gruchy, B. S. & George, C. F. (1984). The first pass metabolism of nifedipine in man. *Br. J. clin. Pharmac.*, **18**, 951–954.

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