KINETICS OF NIFEDIPINE IN PATIENTS TREATED WITH MAINTENANCE HAEMODIALYSIS


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Summary

The pharmacokinetics of Nifedipine were studied in 10 patients with end-stage renal failure treated with maintenance haemodialysis. After administration of a single 10mg oral dose on an inter-dialytic day, the mean values of peak concentration (124±36ng/ml), time to peak concentration (0.68±0.09 hours), elimination half-life (2.6±0.5 hours) and area under curve (308±87.5ng · hr/ml) are similar to those reported in subjects with normal renal function. The haemodialysis clearance of Nifedipine through a cuprophan membrane hollow fibre dialyser (2.8±1.0ml/min) as well as its extraction ratio (2.3±0.8%) are low, due to the high protein binding of the drug (89±0.3%). End-stage renal insufficiency and haemodialysis have little effect on the pharmacokinetics of Nifedipine, whose dose need not be reduced in uraemic patients but adjusted according to clinical results because of the wide inter-individual variability of kinetic parameters.

Introduction

Nifedipine is a calcium blocking agent which is currently widely used in treating patients with angina pectoris or arterial hypertension, including those with advanced chronic renal failure, prior to or during maintenance haemodialysis therapy [1,2]. Pharmacokinetic studies of Nifedipine have been performed hitherto in healthy volunteers and in patients with various cardiovascular diseases and normal renal function [3–6]. This paper evaluates the kinetics of Nifedipine in 10 patients with chronic renal failure on maintenance haemodialysis to define the appropriate dosage adjustments that might be required for this category of patient.

Patients and methods

Ten patients on haemodialysis gave their informed consent before the study. There were seven males and three females with a mean age of 56 years (range
37–75 years). Their underlying renal disease was primary chronic glomerulonephritis (5 patients), polycystic renal disease (2), chronic interstitial nephritis (2) and diabetic nephropathy (1). Five patients had no residual renal function, and in the other five the mean creatinine clearance was 3.6ml/min (range 2 to 6.8ml/min).

The study was conducted in two parts:

1) Eight patients were given a single capsule of 10mg of Nifedipine with 50ml of water, in a fasting state on the morning of an inter-dialytic day. Blood samples (5ml on dry heparin) were drawn first prior to and 0.5, 1, 1.5, 2, 4, 6 and 10 hours after drug intake. The other medications usually taken by the patients were maintained on the day of the study with the exception of diazepam (due to analytical interference). To avoid possible alterations in drug absorption, administration of antacids was delayed for at least two hours after the intake of Nifedipine.

2) Haemodialysis clearance and extraction ratio of Nifedipine were determined in five patients after intake of a 10mg capsule three hours prior to the start of haemodialysis performed with a 1.25m² surface area hollow fibre cuprophan dialyser (CF 1511, Travenol Laboratories) and a single pass dialysate delivery system. The dialysate flow rate was 500ml/min and the blood flow entering the dialyser determined by the air bubble transit time was kept around 200ml/min. Nifedipine being sensitive to light, the dialyser and blood lines were protected from daylight during the whole dialysis session with aluminium foil. Arterial and venous blood samples were collected at 120 minutes after the start of haemodialysis in equally light-protected tubes and immediately centrifuged, the separated plasma remaining stored at a temperature of −30°C until analysed.

 Plasma Nifedipine was determined by gas-liquid chromatography using an electron capture detector according to the method described by Jakobsen et al [7], which detects a minimum concentration of 1ng/ml. Plasma protein binding of Nifedipine was measured by equilibrium dialysis at 37°C (Diannorm System) at a concentration of 100ng/ml on pooled blank plasma from healthy subjects and on pooled plasma collected before and after haemodialysis in unmedicated patients.

Pharmacokinetic data were analysed by model independent methods [8]. The terminal phase rate constant (β) was determined by the least square method as the slope of the monoexponential decline in plasma concentration over time. The terminal plasma half-life was expressed as \( T_\frac{1}{2} = 0.693/\beta \). The area under the plasma concentration curve against time (AUC) was calculated with the trapezoidal rule from time 0 to time t of the last sample and extrapolated to infinity according to the formula \( AUC_{\infty} = C \frac{t}{\beta} \) where \( C_t \) is the plasma concentration of the drug in the last sample taken at time t. Haemodialysis clearance was calculated with the formula:

\[
\text{Cl}_{HD} = \frac{Q_p \cdot C_i - (Q_p - Q_U) \cdot C_0}{C_i}
\]

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and the extraction ratio as:

\[ E = \frac{C_{lHD}}{\left[ Q_p + \left( Q_p - Q_{uf} \right) \right]/2} \times 100 \]

where \( Q_p \) is the plasma flow entering the dialyser derived from the blood flow \( Q_B \) and the haematocrit \( H_t \), as \( Q_p = Q_B \cdot (1 - H_t) \), \( C_I \) and \( C_O \) the concentrations of Nifedipine at the blood inlet and outlet of the dialyser and \( Q_{uf} \) the ultrafiltration rate (in ml/min) measured with the ultrafiltration controller of the dialysis monitor.

Results

The plasma Nifedipine recorded in the eight investigated patients during an inter-dialytic day, as well as the values of peak concentration (\( C_{max} \)), time to peak concentration (\( T_{max} \)), \( T_{1/2} \) and AUC are depicted in Figure 1 and Table 1.

![Figure 1. Plasma levels of Nifedipine versus time after oral intake of 10mg in eight uraemic patients during an inter-dialytic day](image-url)
TABLE I. Pharmacokinetic parameters of Nifedipine in eight patients during an inter-dialytic day after oral intake of 10mg

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Nifedipine dose</th>
<th>C_{max}</th>
<th>T_{max}</th>
<th>T_{1/2}</th>
<th>AUC₀⁻ᴴ</th>
<th>ng/hr/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/kg</td>
<td>ng/ml</td>
<td>Hr</td>
<td>Hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.20</td>
<td>29.5</td>
<td>0.5</td>
<td>0.7</td>
<td>47.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.16</td>
<td>123.0</td>
<td>0.5</td>
<td>1.4</td>
<td>132.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.13</td>
<td>29.3</td>
<td>1.0</td>
<td>1.1</td>
<td>70.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.18</td>
<td>120.0</td>
<td>0.5</td>
<td>3.8</td>
<td>355.7</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.13</td>
<td>201.0</td>
<td>0.5</td>
<td>3.4</td>
<td>331.4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.23</td>
<td>67.0</td>
<td>1.0</td>
<td>2.0</td>
<td>201.4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.13</td>
<td>331.6</td>
<td>0.5</td>
<td>4.2</td>
<td>712.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.16</td>
<td>90.0</td>
<td>1.0</td>
<td>4.3</td>
<td>613.8</td>
<td></td>
</tr>
</tbody>
</table>

| Mean | 0.16 | 123.9 | 0.68 | 2.6 | 308.1 |
| Mean | 0.01 | 35.8  | 0.09 | 0.5 | 87.5  |

TABLE II. Haemodialysis clearance and extraction ratio of Nifedipine in five patients treated with maintenance haemodialysis

<table>
<thead>
<tr>
<th>HTC %</th>
<th>Q₀</th>
<th>Qₙf</th>
<th>Plasma concentration of Nifedipine (ng/ml)</th>
<th>HD clearance ml/min</th>
<th>Extraction ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(ml/min)</td>
<td>ml/min</td>
<td>CA</td>
<td>CV</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>32</td>
<td>195</td>
<td>11.3</td>
<td>33.3</td>
<td>36.3</td>
</tr>
<tr>
<td>SEM</td>
<td>2.9</td>
<td>13</td>
<td>0.9</td>
<td>15.5</td>
<td>17.2</td>
</tr>
</tbody>
</table>

All parameters show wide inter-individual variations. The average clearance of Nifedipine across the dialyser was found at 2.8±1.0ml/min and the extraction ratio was 2.3±0.8 per cent (Table II). Plasma protein binding of Nifedipine was 94.4±0.1 per cent in healthy subjects, 88.6±0.3 per cent and 89.0±0.1 per cent, pre- and post-haemodialysis respectively, in patients submitted to maintenance haemodialysis.

**Comments**

Pharmacokinetic studies of Nifedipine performed in subjects with normal renal function have shown that the drug is rapidly absorbed by the digestive tract, is heavily bound to plasma proteins, is eliminated mainly through hepatic metabolism, has a short plasma half-life (2 to 4 hours) and no pharmacologically active metabolites [3,5,6]. From the present study, it can be stated that, despite wide inter-individual variations, the average pharmacokinetic parameters of the drug are comparable in patients with end-stage renal failure to those in healthy subjects:
the mean peak plasma concentration (125±36ng/ml) is close to the level reported by Raensch (160±49ng/ml) in 10 normal volunteers after administration of a 10mg capsule [6]. The elimination half-life of Nifedipine is similar in the uraemic patients (2.6±0.5 hours) to the value found by Kleimbloesem et al after oral administration of 20mg in six healthy volunteers [5]. These results are well in accordance with the mainly extra-renal mode of elimination of the drug [4]. The wide differences observed for AUC values might be related to individual variations in hepatic blood flow and/or the decrease in the protein binding of Nifedipine as it is the case for many drugs administered to patients with chronic failure [9, 10]. A significant decrease of protein-binding of Nifedipine has indeed been confirmed in our uraemic patients versus values recorded in normal subjects (88.6±0.3% versus 94.4±0.1%, p<0.01). This modification may be due either to an intrinsic alteration of plasma albumin or to the lower concentration of albumin in uraemic than in blank plasma (26g/L versus 39g/L).

The clearance of Nifedipine across a cuprophan membrane hollow fibre dialyser, as well as its extraction ratio are very low (2.8±1.0ml/min and 2.3±0.8%, respectively). Plasma concentrations of Nifedipine five hours after drug intake vary to a very wide extent: 5 to 80ng/ml. In contrast, the quite homogenous values of haemodialysis clearances (2.8±0.1ml/min) show that this parameter is not heavily dependent upon the plasma/dialysate concentration gradient of the drug. The very low elimination of Nifedipine by haemodialysis is the consequence of its liposolubility and high protein-binding.

In conclusion, terminal renal insufficiency as well as haemodialysis have little to no effect on the pharmacokinetics of Nifedipine. Hence, the dose of Nifedipine need not be reduced in patients with advanced renal failure, but has to be adjusted according to the clinical results, considering the wide inter-individual variability of the kinetic parameters of the drug.

References
6. Raensch KD, Sommer J. Hypertension 1983; 5: S18

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