Does Alpha₁-Acid Glycoprotein Reduce the Unbound Metabolic Clearance of Disopyramide in Patients with Renal Impairment?

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Summary. The pharmacokinetics of disopyramide was studied in 15 patients with renal dysfunction (4 with pyelonephritis, 7 with glomerular nephritis and 4 with interstitial nephritis).

The elimination rate constant of unbound disopyramide was 0.094 h⁻¹ and CLu/f (unbound clearance divided by bioavailability) was 245 ml/min. Both the unbound renal clearance (CLR) and CLu/f were highly correlated with the creatinine clearance (CLCR). The apparent unbound metabolic clearance in the patients was approximately two-fold lower than that previously reported in normal subjects. The estimated unbound metabolic clearance in the renal dysfunction patients showed a significant negative correlation with the α₁-acid glycoprotein (AAG) concentration and only a weak, non-significant correlation with CLCR.

As AAG in the renal dysfunction subjects was increased in comparison with normal values, it is possible that AAG is a factor in the decrease in the apparent unbound metabolic clearance.

Key words: disopyramide, alpha₁-acid glycoprotein; renal dysfunction, pharmacokinetics

Material and Methods

Patients

A total of 15 patients, 7 women and 8 men, with renal dysfunction were entered into the study, 7 with glomerulonephritis, 4 with interstitial nephritis, and 4 with pyelonephritis. Their ages ranged from 27 to 70 years (average 50±12 years), body weight from 51 to 93 kg (average 65±10 kg) and surface area from 1.54 to 1.98 m² (average 1.74±14 m²). Renal dysfunction, expressed as creatinine clearance, ranged from severe (3.4 ml/min) to mild (56 ml/min); 5 patients had a creatinine clearance <10 ml/min, 5 between 10 and 25 ml/min.
Table 1. Average (± SD) pharmacokinetic parameters of unbound and total disopyramide in patients with renal dysfunction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients</th>
<th>CL/f (ml/min)</th>
<th>CLR (ml/min)</th>
<th>CLM (ml/min)</th>
<th>k (h⁻¹)</th>
<th>kₙ (h⁻¹)</th>
<th>tₙag (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unbound drug</td>
<td>15</td>
<td>244 ± 106²</td>
<td>35 ± 29³</td>
<td>156 ± 75</td>
<td>0.093 ± 0.029⁴</td>
<td>0.48 ± 0.17</td>
<td>21 ± 18</td>
</tr>
<tr>
<td>Total drug</td>
<td>15</td>
<td>49 ± 28⁴</td>
<td>7.0 ± 5.7⁶</td>
<td>32 ± 19</td>
<td>0.054 ± 0.032⁸</td>
<td>0.78 ± 0.41</td>
<td>32 ± 17</td>
</tr>
</tbody>
</table>

¹ Estimated using an bioavailability of 0.809
² Correlated with CLCR: CL_u/f (ml/min) = 159 + 4.04·CLCR (ml/min), r = 0.65, p < 0.01
³ Correlated with CLCR: kₙ (h⁻¹) = 0.074 - 0.00094·CLCR (ml/min), r = 0.55, p < 0.05
⁴ Correlated with CLCR: CL/f (ml/min) = 28.6 + 0.965·CLCR (ml/min), r = 0.88, p < 0.001
⁵ Not statistically significantly correlated with CLCR and 5 > 25 ml/min. All patients gave informed consent prior to acceptance into the study, which was approved by the Ethics Committee at the University of Erlangen-Nürnberg. All patients had normal liver function and none had severe congestive heart failure (< NYHA III and IV). With the exception of antidiabetic therapy, antibiotics and β-blockers, all medication was discontinued 24 h prior to the study and it was withheld for its duration. Antacid medication was withheld for the first 2 h after administration of disopyramide.

After an overnight fast the patients were given 300 mg disopyramide (2 tablets of Diso-duriles, ASTRA Chemicals, Wedel/Holstein, FRG) together with 150 ml bottled water. In the 48 h after administration, fourteen to sixteen blood samples 6 ml were obtained from a cubital vein. The blood was transferred to 10 ml plastic tubes containing 75 U ammonium heparin and centrifuged at 5000 x g for 10 min. Plasma was harvested and kept frozen at −20 °C until assayed.

Urine was collected hourly for 4 h, followed by bihourly collection for the next 8 h. The urine samples over the next 40 h were pooled at 12-h intervals. Volume and pH were measured and two 5-ml aliquots were frozen at −20 °C until assayed.

**Assay Methods**

**Disopyramide.** Disopyramide was assayed using the HPLC method described by Kabra et al. [12].

**AAG.**
AAG was measured using an immunodiffusion kit (NOR-Partigen™, Behring, La Jolla, Ca).

**Protein Binding**
Protein binding was measured by equilibrium dialysis [13].

**Data Analysis**

The total and unbound plasma concentrations were fitted to a one compartment model with lag-time, using a nonlinear fitting routine [14]. The area under the concentration-time curve was determined from the fitted curve, using the trapezoidal rule from the estimated lag-time to the last concentration time point. The residual area was determined using the last concentration-time point divided by the estimated terminal rate constant. The extrapolated area accounted for 2 to 30% of the total area (average 11 ± 10). Renal clearances were determined from the total amount eliminated unchanged divided by the area under the unbound or total plasma concentration-time curve (unbound renal clearance and total renal clearance, respectively). The apparent unbound metabolic clearance was obtained from the difference between the dose divided by unbound area under the curve (CL_u/f) multiplied by the average bioavailability found previously in 10 normal volunteers [13] and the measured unbound renal clearance. The apparent total metabolic clearance was determined by a similar method using the areas under the total concentration-time curves. The latter calculations assume that the bioavailability is the same in patients with renal impairment as in normal volunteers (see Discussion).

**Results**

The average pharmacokinetic parameters for disopyramide using unbound and total plasma concentrations are given in Table 1. The correlations between the various parameters and creatinine clearance (CLCR) are also given in Table 1. As expected, the values of CL_u/f and the unbound renal clearance (CLR) were strongly correlated with renal function, measured as creatinine clearance (Table 1). Similar correlations were found using the total concentration data (Table 1).