The Effects of Aging on the Pharmacokinetics of Nelfinavir and M8 in HIV-1-infected individuals

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BACKGROUND

In the elderly, clearance of omeprazole (a CYP2C19 substrate) is significantly decreased suggesting reduced CYP2C19 activity with aging; Nelfinavir (NLF) is primarily metabolized by CYP2C19 tb its active metabolite M8. M8 is then metabolized by CYP3A4;

We hypothesize that aging may increase and decrease NLF and M8 exposure, respectively, and cause a decrease in the M8/NLF metabolic ratio.

STUDY OBJECTIVE

To investigate the effects of aging on the steady-state pharmacokinetics (PK) of nelfinavir, M8 and the metabolic ratio in HIV-1-infected individuals.

METHODS

Steady-state 12 hour intensive PK study
Inclusion criteria
  Patients on nelfinavir 1250 mg BID (625 mg tablet formulation) and 2 NRTIs for more than 2 weeks
  Signed written informed consent
  ≥ 18 years of age
  Stable medical condition

Exclusion criteria
  Concomitant medications known or thought to interact with nelfinavir or M8 (2C19/3A4 inhibitors or inducers, acid-modifying agents)
  Acute illness
  Pregnant, breastfeeding or at risk of becoming pregnant during study
  Suspected non adherence

Pharmacokinetic sampling and analysis
  Standardized breakfast (617 kcal, 18g fat)
  PK sampling pre-dose and at 1, 2, 3, 4, 5, 6, 8 and 12 hours post-dose
  Analytical method: validated LC/MS/MS assay (Ottawa, Canada)
  PK parameters calculated using non compartmental methods
  Molecular weight adjusted AUC0-t, MB/AUC0-t, NLF metabolic ratio

STATISTICAL ANALYSIS

Sample size needed: 24 patients, 6 patients per age group (< 39, 40-49, 50-59, ≥ 60 years)
Linear regression between age and each PK parameter and metabolic ratio
ln-transformed PK parameters compared using T-tests for patients < 50 years and ≥ 50 years of age
S-Plus® 8.0 for Windows

RESULTS

PATIENT DEMOGRAPHICS BY AGE GROUP (n=10)

<table>
<thead>
<tr>
<th>Age group</th>
<th>&lt; 39 (n=4)</th>
<th>40-49 (n=4)</th>
<th>50-59 (n=3)</th>
<th>≥ 60 (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>29.2 ± 2.1</td>
<td>45.8 ± 3.5</td>
<td>57.6 ± 3.0</td>
<td>61.8 ± 3.0</td>
</tr>
<tr>
<td>Mean weight ± SD</td>
<td>73.5 ± 7.9</td>
<td>70.3 ± 17.5</td>
<td>66.0 ± 10.3</td>
<td>64.0 ± 14.1</td>
</tr>
<tr>
<td>Mean BMI ± SD</td>
<td>25.6 ± 2.1</td>
<td>24.5 ± 3.5</td>
<td>22.4 ± 3.1</td>
<td>22.7 ± 2.9</td>
</tr>
</tbody>
</table>

Race (%)
- Black: 100%
- Caucasian: 0%
- Other: 0%

% male
- 75%

PK PARAMETERS NELFINAVIR (geometric mean)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age group</th>
<th>AUC0-t</th>
<th>Cmax</th>
<th>Cmin</th>
<th>CL/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 39 (n=4)</td>
<td>39.0±2</td>
<td>5.68</td>
<td>1.06</td>
<td>32.02</td>
<td></td>
</tr>
<tr>
<td>40-49 (n=4)</td>
<td>48.73</td>
<td>6.65</td>
<td>1.57</td>
<td>25.65</td>
<td></td>
</tr>
<tr>
<td>50-59 (n=3)</td>
<td>32.53</td>
<td>4.87</td>
<td>0.95</td>
<td>38.43</td>
<td></td>
</tr>
<tr>
<td>≥ 60 (n=4)</td>
<td>69.83</td>
<td>10.10</td>
<td>3.85</td>
<td>17.90</td>
<td></td>
</tr>
</tbody>
</table>
| Sample size needed: 24 patients, 6 patients per age group (< 39, 40-49, 50-59, ≥ 60 years)

The PK parameters and metabolic ratio were not statistically associated with age;
If we remove the outlier in the 50 to 59 year age group, the AUC0-t (p=0.046) and CL/F (p=0.036) are associated with age;
The geometric means of the PK parameters for the < 50 versus the ≥ 50 age groups were not significantly different.

DISCUSSION / CONCLUSIONS

Small sample size limits the results;
Trend towards increased AUC0-t and decreased CL/F with aging, but not statistically significant;
High interpatient variability that may be explained in part by pharmacogenetics;
The present results do not support the hypothesis of decreased CYP2C19 activity with aging and subsequent increased NLF concentrations, decreased M8 concentrations and decreased M8/NLF metabolic ratio;
Recruitment is ongoing to validate these results.

ACKNOWLEDGMENTS

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