Study Days in Blue are days with intensive PK sampling.

BID

600 mg

BID

400 mg

300 mg

RTV

500 mg

300 mg

RTV

Arm

Control

Day14 15 16 17 13 12 11 10 9 8 7 6 5 4 3 2 1

Day14 13 12 11 10 9 8 7 6 5 4 3 2 1

Study 1 Design

• Subjects were confined throughout the study.
• To assess the effect of mild or moderate HI on the single- and multiple-dose pharmacokinetics of RTV.

CONCLUSIONS

Based on PK observations, there appears to be no need to reduce the ritonavir dose in mild or moderate HI.

It would be prudent to monitor hepatic transaminases in patients with HI that are receiving RTV.

REFERENCES


OBJECTIVE

To assess the effect of mild or moderate HI on the single- and multiple-dose pharmacokinetics of RTV.

STUDY DESCRIPTION

Two Phase I, open label, single center studies.

• Study 1: HIV-infected subjects with normal hepatic function (control, n=6) and subjects with mild HI (Child-Pugh score 5-6, n=6).
• Study 2: HIV-negative subjects with normal hepatic function (control, n=6) and subjects with moderate HI (Child-Pugh score 7-9, n=6).
• Subjects were confined throughout the study.
• RTV was dosed with food; dose was administered shortly after breakfast on intensive PK study days.
METHODOLOGICAL DETAILS

- On Study Day 1 (Period I), plasma samples were collected pre-dose and through 48 hours post dose for RTV.
- On the last study day of Period II (after at least 10 days of multiple dosing), plasma samples were collected during a 12-hour dosing interval in both Studies 1 and 2.
- RTV concentrations were measured by LC/MS/MS. Lower limit of quantitation (LLOQ)=1.0 ng/mL.
- Plasma protein binding was determined by ultrafiltration using (HCl) RTV.
- Noncompartmental methods were used for PK and analysis of variance (ANOVA) or analysis of covariance (ANCOVA) for statistical comparisons, with dose normalization to 500 mg BID for HI arms at steady state.

DEMOGRAPHIC DATA

- Study 1: 12 Subjects (6 control and 6 mild HI) completed.
- Study 2: 12 Subjects (6 control and 6 moderate HI) completed.

RESULTS

Protein Binding Results

At steady state, mean % free RTV ranged from 1.2 to 1.8 (% bound 98.2 to 98.8) with no difference between HI and control arms within each study (p>0.14), therefore RTV PK was analyzed using total concentrations.

Table 1. Effect of Mild Hepatic Insufficiency on Ritonavir PK (Mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cmax (µg/mL)</th>
<th>AUC0–24 (µg•h/mL)</th>
<th>Cmin (µg/mL)</th>
<th>C%F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>13.8 ± 3.0</td>
<td>127.8 ± 23.9</td>
<td>3.88 ± 1.43</td>
<td>70.2 ± 4.9</td>
</tr>
<tr>
<td>Mild HI</td>
<td>12.3 ± 1.9</td>
<td>114.6 ± 19.5</td>
<td>4.85 ± 1.79</td>
<td>73.4 ± 1.99</td>
</tr>
</tbody>
</table>

Figure 1. Protein Binding: Individual and Mean ± SD

Figure 2. Protein Binding: Individual and Mean ± SD

Figure 3. Mild Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 500 mg Single Dose

Figure 4. Mild Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 500 mg BID

Table 2. Effect of Moderate Hepatic Insufficiency on Ritonavir PK (Mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cmax (µg/mL)</th>
<th>AUC0–24 (µg•h/mL)</th>
<th>Cmin (µg/mL)</th>
<th>C%F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8.11 ± 2.93</td>
<td>144.4 ± 4.92</td>
<td>68.1 ± 23.3</td>
<td>76.8 ± 35.3</td>
</tr>
<tr>
<td>Moderate HI</td>
<td>13.9 ± 1.02</td>
<td>161.6 ± 1.28</td>
<td>85.1 ± 29.1</td>
<td>78.6 ± 35.3</td>
</tr>
</tbody>
</table>

Figure 5. Moderate Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 500 mg Single Dose

Figure 6. Moderate Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 500 mg BID

Figure 7. Mean (SD) AUC, Single Dose and Multiple Dose

Figure 8. Mean (SD) Cmin, Multiple Dose
METHODS

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Table 1. Effect of Mild Hepatic Insufficiency on Ritonavir PK (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Study Day 1 Single Dose</th>
<th>Study Day 14 Multiple Dose (BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild HI</td>
<td>Control</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>13.0 ± 3.0</td>
<td>12.7 ± 3.9</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>2.06 ± 0.94</td>
<td>–</td>
</tr>
<tr>
<td>Cmin (µg/mL)</td>
<td>13.9 ± 4.13</td>
<td>–</td>
</tr>
<tr>
<td>AUC0-∞ (µg•h/mL)</td>
<td>68.1 ± 23.3</td>
<td>–</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>4.9 ± 1.0</td>
<td>6.2 ± 1.1</td>
</tr>
<tr>
<td>Cmax/F+</td>
<td>4.9 ± 1.0</td>
<td>6.2 ± 1.1</td>
</tr>
<tr>
<td>Ctrough (µg/mL)</td>
<td>59.8 ± 17.6</td>
<td>–</td>
</tr>
<tr>
<td>% Free Ritonavir</td>
<td>3.6 ± 1.8</td>
<td>3.5 ± 1.8</td>
</tr>
</tbody>
</table>

* Statistically significantly different from Control (ANOVA or ANCOVA, p<0.05).
† Parameter not tested statistically.

Figure 3. Mild Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 400 mg Single Dose

Figure 4. Mild Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 500 mg BID

Table 2. Effect of Moderate Hepatic Insufficiency on Ritonavir PK (Mean ± SD)

<table>
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* Statistically significantly different from Control (ANOVA or ANCOVA, p<0.05).
† Parameter not tested statistically.
**Discussion**

- Protein binding of RTV appeared to be unaffected by mild or moderate HI.
- It has been reported that liver disease has a differential effect on P450 isoenzymes. The protein amount and activity of CYP3A4 are somewhat preserved in patients with mild to moderate disease, which may explain the observed results in the current two studies.
- The somewhat lower RTV concentrations and prolonged T_{max} at steady state in moderate HI group may be due to the reduced absorption of RTV.
- C_{min}, an important PK parameter that is associated with sustained anti-viral effects of RTV, was not statistically different between HI subjects and those with normal hepatic function with or without dose normalization.

**Conclusions**

- Based on PK observations, there appears to be no need to reduce the RTV dose in patients with mild or moderate HI.
- It would be prudent to monitor hepatic transaminases in patients with HI that are receiving RTV.

**References**


**Acknowledgments**

Thank you to Gondi Kumar, John Darbyshire, Sonja Kemmis and Janet Lamm for their contributions.