Natural and Conventional Drug Interactions: Important Determinants of Drug Disposition and Effects in Target Tissues and Cells

Weibin Zha, Ph.D.
zhaw@uw.edu
DDI 2016
June 20, 2016
**Natural products (NPs) in the United States**

- Nature products (NPs) are defined as:
  - Vitamins and minerals
  - Herbal remedies
  - Homeopathic medicines
  - Traditional medicines such as traditional Chinese medicines
  - Probiotics
  - Other products like amino acids and essential fatty acids

- The most common and fastest growing NPs modality is **herbal medicine**.
- The combined use of NPs and conventional drugs is widespread in United States.

<table>
<thead>
<tr>
<th>United States</th>
<th>Combined use of NPs and conventional drugs</th>
<th>references</th>
</tr>
</thead>
</table>
The deleterious vs. beneficial effects of the combined use of NPs and HIV antiretroviral drugs

Beneficial effects

- Perceived additional efficacy
- An increase in quality of life
- A reduction of adverse effects of conventional drugs
- A feeling of control

Deleterious effects

- Treatment failure
- The emergence of viral resistance
- Increasing risk of toxicity
- Hyperlipidemia

The pharmacokinetic interactions between NPs and HIV drugs

THE LANCET
Volume 355, Issue 9203, 12 February 2000, Pages 547–548
Research Letters

Indinavir concentrations and St John's wort

Dr Stephen C Piscitelli, PharmD, Aaron H Burstein, PharmD, Doreen Chaith, MPH, Raul M Alfaro, MS, Judith Falloon, MD

a Department of Pharmacy, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD 20892, USA
b Warren G Magnuson Clinical Center and Laboratory of Immunoregulation, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD 20892, USA

After St. John’s Wort
Identification of key constituents responsible for the NP-HIV drug pharmacokinetic interaction

St. John’s Wort
Hyperforin
“Inducer”

PXR binding site

HIV protease inhibitors
“Substrate”

CYP3A

HO-HIV PIs
Excreted

CYP3A4
β-actin

NP-HIV drug pharmacokinetic interaction: Therapeutic Drug Monitoring

No plasma pharmacokinetic interaction = ? Desired therapeutic and safety outcomes
Two studies of NPs-HIV protease inhibitors (PIs) interactions

- Pharmacokinetic interaction between 20(S)-ginsenoside Rh2 and the HIV PI ritonavir

- Pharmacokinetic interaction between berberine and HIV PIs
Influence of ginseng extracts on pharmacokinetic profile of HIV PIs in healthy volunteers


Table 2: PK parameter estimates of IDV before and after co-administration with AG (1 gram every 8 hours), n = 13

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IDV alone (Day 7)</th>
<th>IDV + AG (Day 22)</th>
<th>Day 7/Day 22 Geometric Mean Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>C&lt;sub&gt;min&lt;/sub&gt; (ng/mL)</td>
<td>t&lt;sub&gt;max&lt;/sub&gt; (hours)</td>
</tr>
<tr>
<td></td>
<td>5623 (4027-7853)</td>
<td>61.97 (42.72-89.88)</td>
<td>0.98 (0.7189-1.3403)</td>
</tr>
</tbody>
</table>


Table 1. Lopinavir and Ritonavir Pharmacokinetic Parameter Values Before and After 14 Days of Panax ginseng Administration (12 Healthy Volunteers)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preadministration Ginseng</th>
<th>Postadministration Ginseng</th>
<th>Geometric Mean Ratios (90% CI) Postadministration Ginseng/Preadministration Ginseng</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12&lt;/sub&gt; (μg·hr/ml)</td>
<td>108 (92–125)</td>
<td>103 (88–117)</td>
<td>0.95 (0.85–1.05)</td>
<td>0.34</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</td>
<td>12.3 (10.8–13.8)</td>
<td>11.5 (10.1–12.9)</td>
<td>0.94 (0.84–1.04)</td>
<td>0.35</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>2.4 (1.7–3.2)</td>
<td>2.5 (1.7–3.4)</td>
<td>1.05 (0.62–1.48)</td>
<td>0.55</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>8.4 (6.5–10.2)</td>
<td>10.0 (6.8–13.2)</td>
<td>1.19 (0.92–1.46)</td>
<td>0.06</td>
</tr>
<tr>
<td>CL/F&lt;sub&gt;ss&lt;/sub&gt; (L/hr)</td>
<td>3.70 (3.19–4.20)</td>
<td>3.89 (3.47–4.32)</td>
<td>1.05 (0.94–1.17)</td>
<td>0.55</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12&lt;/sub&gt; (μg·hr/ml)</td>
<td>13.9 (10.5–17.2)</td>
<td>13.10 (10.09–16.13)</td>
<td>0.95 (0.80–1.09)</td>
<td>0.38</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</td>
<td>1.81 (1.40–2.22)</td>
<td>1.66 (1.24–2.09)</td>
<td>0.92 (0.70–1.14)</td>
<td>0.50</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>2.37 (1.58–3.17)</td>
<td>2.70 (2.01–3.38)</td>
<td>1.14 (0.20–2.08)</td>
<td>0.67</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>7.55 (6.23–8.86)</td>
<td>7.71 (5.45–9.97)</td>
<td>1.02 (0.60–1.44)</td>
<td>0.58</td>
</tr>
<tr>
<td>CL/F&lt;sub&gt;ss&lt;/sub&gt; (L/hr)</td>
<td>7.22 (5.23–9.20)</td>
<td>7.63 (6.32–8.93)</td>
<td>1.06 (0.89–1.23)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

CI = confidence interval.

<sup>a</sup>The paired 2-tailed Student t-test was used for statistical comparisons except for T<sub>max</sub>, for which the Wilcoxon signed rank test was used.
Pharmacokinetic interaction between ginsenosides and HIV PIs

Ginsenosides
Rb₁, Rb₂, Rc, Rd, Re, Rf, Rg₁, Rg₂, Rg₃, Rh₁, Rh₂, and Rh₃
Pharmacokinetic interaction of 20(S)-ginsenoside Rh2 and the HIV PI ritonavir in animal model


Table II. Plasma Radioactivity (ng/ml Tissue) in mdr1a (+/+ ) and (-/-) Mice at 4 h after Oral Administration of [3H]-Indinavir (6 mg/kg), [3H]-Nelfinavir (6 mg/kg), or [3H]-Saqvinavir (6 mg/kg)

<table>
<thead>
<tr>
<th>Drug</th>
<th>mdr1a (+/+ )</th>
<th>mdr1a (-/-)</th>
<th>Ratio (-/-)/(+/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir</td>
<td>34±7.4</td>
<td>69±11*</td>
<td>2.03</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>2.3±0.8</td>
<td>11±4.4*</td>
<td>4.78</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>5.4±1.6</td>
<td>22±2.1†</td>
<td>4.07</td>
</tr>
</tbody>
</table>
Pharmacokinetic interaction of 20(S)-ginsenoside Rh2 and the HIV PI ritonavir in animal model

Metabolic effects of 20(S)-ginsenoside Rh2 in animal model receiving the HIV PI ritonavir

20(S)-ginsenoside Rh2 enhances the distribution of ritonavir into liver

The effect of 20(S)-ginsenoside Rh2 on the tissue/plasma distribution ratios of ritonavir

Inhibition of P-glycoprotein transport enhances the distribution of HIV PIs into brain and testes

**Fig. 2.** Tissue levels of [14C]nelfinavir (5 mg/kg) in mdr1a wild-type mice given 25 mg/kg LY-335979 [plasma (○), brain (●)] or vehicle [plasma (△), brain (▲)] 30 min before and simultaneously with [14C]nelfinavir.

Each point represents three mice, except at 2 h (n = 5).

**Fig. 4.** Brain/plasma distribution ratios determined 2 h after radiolabeled HIV-protease inhibitor administration (mean ± S.E., n = 3 or greater) in vehicle control mice (open column) and LY335959 (50 mg/kg) treated (filled column) mdr1a(+/+) wild type (WT) and mdr1a(-/-) knockout (KO) mice.

<table>
<thead>
<tr>
<th>mdr1a(+/+) mice</th>
<th>Plasma</th>
<th>Brain</th>
<th>Brain/Plasma Ratio</th>
<th>Testes</th>
<th>Testes/Plasma Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY-335979</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle control</td>
<td>84 ± 4.9</td>
<td>6.6 ± 1.7</td>
<td>0.08 ± 0.02</td>
<td>47 ± 3.7</td>
<td>0.48 ± 0.07</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>74 ± 14</td>
<td>9.4 ± 1.7</td>
<td>0.11 ± 0.04</td>
<td>56 ± 1.7</td>
<td>0.81 ± 0.15*</td>
</tr>
<tr>
<td>4 mg/kg</td>
<td>72 ± 4.8</td>
<td>24 ± 4.5***</td>
<td>0.33 ± 0.04***</td>
<td>95 ± 18*</td>
<td>1.4 ± 0.33**</td>
</tr>
<tr>
<td>12.5 mg/kg</td>
<td>71 ± 11</td>
<td>60 ± 5.4***</td>
<td>0.89 ± 0.16***</td>
<td>108 ± 27*</td>
<td>1.6 ± 0.44*</td>
</tr>
<tr>
<td>25 mg/kg</td>
<td>89 ± 8.1</td>
<td>89 ± 17***</td>
<td>1.1 ± 0.28**</td>
<td>168 ± 61*</td>
<td>2.0 ± 0.48**</td>
</tr>
<tr>
<td>50 mg/kg</td>
<td>171 ± 12***</td>
<td>243 ± 19***</td>
<td>1.4 ± 0.08***</td>
<td>187 ± 17***</td>
<td>1.2 ± 0.19**</td>
</tr>
</tbody>
</table>

Rh2 increased the accumulation and inhibited the efflux of ritonavir in MDCK-MDR1 cells

NPs-HIV drugs interaction: Target tissues

• Inhibition of P-gp by Rh2 may enhance the distribution of ritonavir into liver, brain, testes, kidney, lung and fat with no effect on plasma concentration.

Current understanding of NPs-HIV drug interactions
• The monitoring of the plasma concentration of HIV drugs is used to ensure that antiretroviral therapy efficacy is maintained and drug side effects are avoided.

The missing part of NPs-HIV drugs interactions
• The concentration of NPs and HIV drugs at the site of action in physiologically relevant cells or tissues is also needed to help improve HIV drug efficacy and prevent drug side effects.
Berberine, a natural product, prevents HIV protease inhibitor-induced chronic inflammatory response

**Berberine**
- Goldenseal root
- Oregon grape root
- Barberry bark

- Antimicrobial action against various infectious disorders
- Beneficial effects on hyperlipidemia, obesity, diabetes and cardiovascular diseases
- Treating inflammatory bowel disease (IBD)
- Reduction of inflammation

**HIV protease inhibitors (PIs)**
- A key component of anti-retroviral therapies for HIV/AIDS (Current PIs)
- HIV PI-induced inflammatory response plays an important role in HIV PI-associated metabolic disorders and GI side effects.

Pharmacokinetic interaction between berberine and the HIV PI ritonavir

- Berberine and HIV PIs are P-gp substrates as well as inhibitors.


**Plots:**

- **Plasma BBR Concentration vs Time (hours):**
  - BBR (50 mg/kg)
  - BBR + RITV

- **Plasma RITV Concentration vs Time (hours):**
  - RITV (50 mg/kg)
  - RITV + BBR

**Table:**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Parameter (mean±SD) (n=5)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$T_{max}$ (h)</td>
</tr>
<tr>
<td>RITV alone</td>
<td>4.20±1.10</td>
</tr>
<tr>
<td>RITV and BBR</td>
<td>3.12±2.65</td>
</tr>
<tr>
<td>BBR alone</td>
<td>5.00±0.00</td>
</tr>
<tr>
<td>BBR and RITV</td>
<td>4.00±2.65</td>
</tr>
</tbody>
</table>

Berberine inhibits HIV PI-induced macrophage inflammatory response by reducing ERK activation

HIV PIs increase intracellular accumulation of berberine in macrophages

**Macrophages**

Berberine-HIV PIs PK interaction

HIV PIs increase intracellular accumulation of berberine in macrophages

HIV PIs increase intracellular accumulation of berberine in macrophages

Murine macrophages

Human macrophages

Identification of P-gp as a major player in HIV PI-mediated intracellular accumulation of BBR

![Graph showing intracellular concentration of berberine (pmol/mg protein)](image)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBR (5 μM)</td>
<td></td>
<td></td>
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<tr>
<td>Verapamil (100 μM)</td>
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<tr>
<td>Haloperidol (50 μM)</td>
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<tr>
<td>MK571 (10 μM)</td>
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<tr>
<td>Bromosulfalein (80 μM)</td>
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</table>

*Statistically significant difference

Identification of P-gp as a major player in HIV PI-mediated intracellular accumulation of BBR

HIV PIs increase intracellular accumulation of berberine by inhibiting the transport activity of P-gp in macrophages

NPs-HIV drug interaction: Target cells

• Inhibition of P-gp by HIV PIs increases intracellular accumulation of berberine in macrophages.

Current understanding of NPs-HIV drug interactions

• The interactions between NPs and HIV drugs involve induction and/or inhibition of the P-gp, MRPs, and CYPs and thus can result in an increase/decrease of the amount of HIV drugs in the blood stream and physiologically relevant cells or tissues.

NPs ← ONE WAY → HIV drugs

The missing part of NPs-HIV drugs interactions

• The effect of HIV drugs on the concentration of bioactive natural products in the blood stream and physiologically relevant cells or tissues.

NPs ← TWO WAY → HIV drugs
NPs-HIV drugs interaction: Overall Summary

No plasma pharmacokinetic interaction \(=\) ? Desired therapeutic and safety outcomes

- The interaction between NPs and HIV drugs at the site of action in physiologically relevant cells or tissues.

- The effect of HIV drugs on the concentration of NPs in the blood stream, physiologically relevant cells or tissues.
Acknowledgements

VCU school of medicine
Huiping Zhou Ph.D.
Phillip Hylemon Ph.D.
Beth Shoshana Zha M.D., Ph.D.

China Pharmaceutical University
Guangji Wang Ph.D.
Jiye A Ph.D.
Jian Shi Ph.D.

UW School of Pharmacy
Joanne Wang Ph.D.

$$$ National Institute of Health (NIH) grant R01AT004148 (H.Z.), R21AI068432 (H. Z.)
China National Science Foundation (Grants 30973583 and 30801411 to G. W.)
China “Creation of New Drugs” Key Technology Projects (Grants 2009ZX09304-001 and 2009ZX09103 to G.W.)
Questions