Toxicity and drug interactions of psychotropic agents in HIV-infected patients

1st International Symposium on Psychiatry & HIV
Barcelona, May 22, 2008

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Telephone call (Monday May 12, 2008)

• Patient A. is on a NVP containing regimen and being treated with citalopram (40mg/day) for depression
• NVP plasma levels are subtherapeutic (< 3.0 mg/L), though viral load remains < 40 copies/mL
• Psychiatrist wants to increase citalopram dose to 60mg/day because of insufficient response

• Questions:
  • can dose of citalopram safely increased?
  • can citalopram reduce NVP plasma levels?
Outline of my presentation

- Toxicity of psychotropic agents
- Drug interactions between ARVs and hypnotics/anxiolytics
- Drug interactions between ARVs and antidepressants
- Drug interactions between ARVs and antipsychotics
Toxicity of psychotropic agents in HIV-infected patients

• No data that adverse events are different from HIV-negative patients (except because of drug interaction)

• Some adverse events may be less acceptable in HIV-infected patients:
  • Weight gain (lipodystrophy)
  • Hyperlipidemia (PIs, EFV)
  • Diabetes (PIs)
  • Sexual disorders
Benzodiazepines

• Some are CYP3A substrates (triazolam, midazolam, alprazolam)
  • NNRTIs induce CYP3A: less sedative effect
  • PIs inhibit CYP3A: more sedative effect

• Alternative agents less affected by drug interactions:
  • Temazepam, lorazepam, oxazepam
  • Zolpidem, zopiclone
Midazolam - saquinavir drug interaction study

**Intravenous Midazolam**

- AUC: +148%

**Oral Midazolam**

- AUC: +418%

Triazolam/zolpidem + RTV drug interaction study

AUC: +1939%

AUC: +28%

Antidepressants

• All agents are substrates of CYP450, so interactions with NNRTIs and PIs are likely to occur

• Many antidepressants are CYP3A substrates (trazodone, (es)citalopram, venlafaxine, mirtazepine, sertraline)
  • PIs inhibit CYP3A
  • NNRTIs induce CYP3A

• Many antidepressants are CYP2D6 substrates (TCADs, paroxetine, fluoxetine, fluvoxamine)
  • RTV is strong inhibitor of CYP2D6
  • Effect NNRTIs may be difficult to predict:
    • SPC Sustiva®: no effect on paroxetine
    • De Maat et al. (Clin Drug Inv 2003): NVP reduces fluoxetine levels; no effect on fluvoxamine
Fluoxetine (CYP2D6) – ARV drug interaction

Table 2. Case series summary, Atlanta Veterans Affairs Medical Center.

<table>
<thead>
<tr>
<th>Case</th>
<th>Serotonergic medications (mg/day)</th>
<th>P450 inhibitor added</th>
<th>Symptoms developed</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fluoxetine (40)</td>
<td>Ritonavir 600 mg bid</td>
<td>Confusion, agitation, fever, anxiety, diarrhea, nausea, vomiting</td>
<td>Discontinue ritonavir</td>
</tr>
<tr>
<td>1a</td>
<td>Fluoxetine (40)</td>
<td>Ritonavir 400 mg bid</td>
<td>None</td>
<td>Decrease fluoxetine to 20 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saquinavir 400 mg bid</td>
<td></td>
<td>Discontinue ritonavir</td>
</tr>
<tr>
<td>2</td>
<td>Fluoxetine (40)</td>
<td>Ritonavir 400 mg bid</td>
<td>Paranoia, hypomania, diaphoresis, diarrhea, nausea, vomiting</td>
<td>Discontinue ritonavir</td>
</tr>
<tr>
<td></td>
<td>Bupropion (300)</td>
<td>Saquinavir 400 mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Fluoxetine (40)</td>
<td>Efavirenz 600 mg q pm</td>
<td>Anxiety, akathisia, diaphoresis, restlessness</td>
<td>Decrease fluoxetine to 20 mg/day</td>
</tr>
<tr>
<td>4</td>
<td>Fluoxetine (20)</td>
<td>Grapefruit</td>
<td>Confusion, dizziness, syncope</td>
<td>Discontinue grapefruits</td>
</tr>
<tr>
<td>5</td>
<td>Fluoxetine (20)</td>
<td>Ritonavir 200 mg bid</td>
<td>Mania, myoclonus, diarrhea</td>
<td>Discontinue trazodone, decrease ritonavir to 100 mg bid</td>
</tr>
<tr>
<td></td>
<td>Trazodone (200)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lithium (1200)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Rechallenge. bid, twice daily; q pm, once daily at night.*
Trazodone (CYP3A) – RTV drug interaction study

AUC: +137%

Escitalopram (various CYPs) – RTV drug interaction study

N.B. single dose RTV!

AUC: +8%

Gutierrez et al. Clin Ther 2003
Paroxetine (CYP2D6) – FPV/r drug interaction study

AUC: -55%

Van der Lee et al. AAC 2007
Possible explanations for unexpected decrease in paroxetine levels by FPV/r

- Effect of FPV/r on absorption of paroxetine
- FPV/r induces CYP2D6
- Paroxetine is a substrate of CYP3A (and FPV/r induces CYP3A)
- FPV/r displaces paroxetine from plasma proteins

Van der Lee et al. AAC 2007
Evidence-based recommendations for use of antidepressants in HIV-infected patients

• (Es)Citalopram may be preferred in patients on RTV-boosted PIs (based on single-dose RTV study)

• Paroxetine is an alternative option for RTV-boosted PIs; titrate to effective dose

• Avoid use of trazodone, fluoxetine

• NNRTIs may reduce antidepressant activity (case)
  • Limited effect expected on CYP2D6 substrates (paroxetine, fluoxetine, TCADs)
Antipsychotic agents: pharmacokinetics

- Olanzapine, clozapine: CYP1A2 substrate
  - RTV & NNRTIs induce CYP1A2

- Risperidone: CYP2D6 substrate
  - RTV is a strong inhibitor of CYP2D6
  - NNRTIs may have little impact on CYP2D6

- Quetiapine, aripiprazole: CYP3A substrates
  - PIs inhibit CYP3A
  - NNRTIs induce CYP3A
Risperidone case report in HIV-infected patients

Reversible Coma Caused By Risperidone-Ritonavir Interaction

Francisco Jover, José-Maria Cuadrado, Lucio Andreu, and Jaime Merino

Infectious Diseases Division, Internal Medicine Department, Hospital of San Juan, Alicante, Spain
Olanzapine – RTV drug interaction study

AUC: -53%

Evidence-based recommendations for use of antipsychotics in HIV-infected patients

• Avoid use of risperidone with RTV-boosted PIs

• Olanzapine & RTV-boosted PIs or NNRTIs: titrate to effective dose

• SPC Aripiprazole: reduce dose with 50% with PIs (no data)

• SPC Quetiapine: PIs are contra-indicated
What about newer ARVs and psychotropic agents?

• Maraviroc is CYP3A substrate but does not influence CYP450 enzymes

• Raltegravir is not a substrate of CYP450 nor influences CYP450

Figure 1. Single oral doses of 2 mg of midazolam with or without administration of 400 mg of raltegravir twice daily to young, healthy, male and female subjects (inset = semilog scale; error bars = SEM).

Conclusions

• Limited data available on combined use of ARVs and psychotropic agents

• Consider both increased toxicity AND reduced efficacy

• Consult expert advice to optimize individual patient care

• New ARVs with less drug interaction potential (maraviroc, raltegravir) are highly welcome; no clinical data available yet