Overview of pharmacokinetic drug interactions

Gary Maartens
Importance

• Drug interactions increase exponentially with the number of drugs used:
  – 6% with 2 drugs, 50% with 5, 100% with 10

• Some interactions are beneficial

• Other interactions will reduce a drug’s action or increase it’s toxicity, both of which can be life-threatening

• Importance of drug-herb interactions increasingly recognised (minimal data on SA traditional meds)
Two mechanisms of interactions

- Pharmacodynamic (what the drug does to the body) interactions are shared effects (either toxic or therapeutic)

- Pharmacokinetic (what the body does to the drug) interactions alter the concentrations & distribution of drugs
Calls to UCT MIC HIV Hotline by Topic

- Therapy: 38%
- ADR: 27%
- Interaction: 20%
- Pregnancy: 8%
- Other: 7%

Chisholm, SA AIDS Conf Durban 2005
Patients taking NNRTI & other chronic Rx
(24% had significant interactions)

Regensberg L. 14th Int AIDS Conf, Barcelona 2002
Patients taking PIs & other chronic Rx
(34% had significant interactions)

- Antidepressants 21.6%
- Calcium Channel Blockers 19.6%
- Anticonvulsants 15.7%
- Antihistamines 7.8%
- Theophylline 7.8%
- Neuroleptics 5.9%
- Azole antimycotics 3.9%
- Benzodiazepines 3.9%
- Beta blockers 3.9%
- HMGCoA Reductase Inhibitors 3.9%
- Warfarin 2.0%
- Clarithromycin 2.0%
- Omeprazole 2.0%

Regensberg L. 14th Int AIDS Conf, Barcelona 2002
Absorption interactions

• Some drugs require low gastric pH, so acid-lowering drugs reduce absorption (eg atazanavir, itraconazole)

• Divalent cations in antacids chelate some drugs (eg dolutegravir, ciprofloxacin, tetracyclines)
Drug transporters (eg P-glycoprotein)

• P-gp expressed mostly in GIT & blood-tissue barriers (CNS & testis)

• Co-localises with the CYP450 isoenzyme CYP3A4 – most drugs that are substrates of P-gp are also CYP3A4 substrates

• Transporters can be inhibited (eg ritonavir, cobicistat) or induced (eg rifampicin, phenytoin)
Substrate

Intestinal lumen

Intestinal wall

Plasma

Pgp

Intestinal lumen

Intestinal wall

Plasma

↑ risk of toxicity

Inhibitor

Pgp
Metabolism: CYP450 drug interactions

Substrates (lipid soluble)

Inducers
- Rifampicin
- Efavirenz
- Phenytoin
- Carbamazepine

Reduce levels of substrate, may cause sub-therapeutic concentrations

Cytochrome P450

Metabolites (water soluble)

Increase levels of substrate, may cause toxic concentration

Inhibitors
- Ritonavir
- Macrolides
- Cimetidine
- Azoles
CYP450 enzymes induced or inhibited by ARVs

CYP3A4/5
CYP2E1
CYP2D6
CYP2C19
CYP2C8/9
CYP2B6
CYP2A6
CYP1B1
CYP1A1/2
OTHERS

EFV
NVP
RTV
EFV
RTV
EFV
RTV
NVP
EFV
RTV
RTV
Inhibition of CYP450

• Inhibition may be reversible or irreversible

• Irreversible inhibitors (e.g. ritonavir):
  – Reactive intermediate metabolite binds irreversibly to enzyme causing inactivation
  – More potent inhibition than reversible
  – Duration of inhibition is longer (5-10 days compared with about 48 hours after stopping) as new enzyme needs to be synthesised

• Severe toxicity may occur if a P450 substrate is co-administered
## Effect of boosted PIs on statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>% change to AUC</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>+390 to +590</td>
<td>Low dose</td>
</tr>
<tr>
<td>Pravastatin*</td>
<td>-50 to +180</td>
<td>Same dose</td>
</tr>
<tr>
<td>Rosuvastatin*</td>
<td>+148 to +313</td>
<td>↓effect – avoid</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>+3159</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

*Not substrates of CYP3A4

http://www.hiv-druginteractions.org/
Exploiting PK interactions: PI boosting

- PIs are substrates of CYP3A4 & P-gp
- Ritonavir & cobicistat potently inhibit CYP3A4 & P-glycoprotein
- Co-administered of ritonavir/cobicistat with PIs:
  - PI absorption increased & elimination reduced
  - PI metabolism decreased
- Resulting higher concentrations of PI
  - Dosing less frequent
  - Low-level resistance can be overcome
  - More toxicity
Effect of ritonavir on saquinavir

- Saquinavir SGC 1600 mg / ritonavir 100 mg
- Saquinavir SGC 1200mg tid
Induction of metabolism

• Many drugs & exogenous substances (eg smoking, grilled food, garlic) can induce
• Several (2 main) pathways to turn on regulatory gene that affects MANY downstream genes that have the net effect of reducing exposure to a xenobiotic/drug
PXR-RXR mechanism of enzyme induction

Phase I
CYP2B6
CYP2C8/9
Phase II
UGT
GST
Transporters
P-glycoprotein

Rifampin
Phenytoin
Ritonavir
St. John’s wort

Calcium-channel blockers
Cyclosporine
Triazolam
Lovastatin
Erythromycin
HIV-protease inhibitors
Sildenafil

Drug S

Increased CYP3A4 activity

Metabolite

OTHERS →

NEJM 2005;352:2211
Chen 2006
Time course of induction

Max at about 2 weeks - wanes in 2 weeks
Nevirapine concentrations in adult patients before and after stopping rifampicin-based TB therapy

Cohen, JAC 2008

Off rifampicin

On rifampicin

p=0.005
Individual variability of induction & inhibition

Omeprazole (CYP2C19 induced)            Midazolam clearance (CYP3A4 inhibited)

Lopinavir/r interactions

Yeh R JAIDS 2006
Interaction case

- 32 year old man with background of depression. On fluoxetine 40mg daily long term, with good response. Failed AZT 3TC nevirapine.

- ART switched to AZT ddI indinavir ritonavir

- Within a week, developed severe anxiety, headache and sweating.
  - Serotonin syndrome due to inhibition of CYP3A4 metabolism of fluoxetine by Pis
  - Settled on withdrawal
  - Fluoxetine later reintroduced at 10 mg
Therapeutic drug monitoring

Ideal to measure concentrations of ARVs and the potentially interacting drug, where available

Need to use clinical judgement if no drug assays available
Drug interaction resources

- Package inserts
- SAMF
- UCT Medicines Information Centre
- Software in pharmacies
- Internet & apps

http://www.mic.uct.ac.za/
HIV Drug Interaction Checker

Access our comprehensive, user-friendly, free drug interaction charts. Providing clinically useful, reliable, up-to-date, evidence-based information

Start Now ➔

<table>
<thead>
<tr>
<th>Drug</th>
<th>Atazanavir</th>
<th>Darunavir</th>
<th>Dolasetravir</th>
<th>Elvitegravir</th>
<th>Raltegravir</th>
<th>Rilpivirine</th>
<th>Tenofovir-DF</th>
</tr>
</thead>
</table>

http://www.hiv-druginteractions.org/

Site News & Twitter Updates

Follow @hivdruginteractions

Discover Our HIV Mobile Apps

HIV iChart gives easy access to our drug interaction information on mobile devices. Click the links below for further details and to download the HIV iChart app.
Conclusions

• When using strong inhibitors or inducers
  ALWAYS check for drug interactions with all
  drugs you prescribe
• Lots of information resources
• Review all meds when switching to 2\textsuperscript{nd} line