Clinical Case Presentations
Pharmacists perspective

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Radboudumc

Content

Introduction

Patient 1

- Darunavir/ritonavir, etravirine, daclatasvir

Patient 2

- Simeprevir, daclatasvir, phenytoin

Patient 3

- Daclatasvir, sofosbuvir, oxcarbazepine

Take home messages

Introduction

- 5 P's of drug-drug interactions

- Problem presentation
  - *e.g. e-mail from physician about direct-acting antivirals (DAAs) and co-medication*
- Prediction of outcome
  - *e.g. recommendations based on literature*
- Pharmacokinetic sampling
  - *Validating our prediction*
- Patient evaluation
  - *e.g. sustained virological response (SVR), adverse events*
- Publication
  - *N = 1, but others can learn from our cases*

Patient 1 – Problem presentation

- 54 year old male
- >20 years HIV infected
- HCV infection genotype 4
  - Liver cirrhosis Child-Pugh B
  - ALT 37 UI/L, AST 27 UI/L, yGT 54 UI/L
  - Peg-interferon + ribavirin 2006 → relapse
- Pulmonary hypertension
- Ascites
  - Diuretics → kidney function loss
- Initiation DAA therapy

Patient 1 – Problem presentation

- Etravirine
- Darunavir/r
- Amlodipine
- Atenolol
- Ciprofloxacine
- Lisinopril
- Fosinopril
- Furosemide
- Insuline
- Levothyroxine
- Omeprazol
- Paracetamol
- Prednisolon
- Valaciclovir
- Tamsulosine

- Interaction between HCV and HIV drugs?
- Which HCV therapy is possible?

Patient 1 – Prediction

- Etravirine
- Darunavir/r
- Amlodipine
- Atenolol
- Ciprofloxacine
- Lisinopril
- Fosinopril
- Furosemide
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- Levothyroxine
- Omeprazol
- Paracetamol
- Prednisolon
- Valaciclovir
- Tamsulosine

- Options: simeprevir, daclatasvir, sofosbuvir, ribavirin

- Proposed DAA therapy → minimal interactions:
  - Daclatasvir
  - Sofosbuvir
  - Ribavirin
  - For 12 weeks

Patient 1 – Prediction

- Daclatasvir
  - CYP3A4 and P-gp substrate
  - Inhibitor P-gp, OATP1B1
- Sofosbuvir
  - P-gp and BCRP substrate
- Etravirine
    - CYP3A4, CYP2C9, CYP2C19, UGT substrate
    - CYP2C9, CYP2C19 inhibitor
    - CYP3A4 inducer
- Darunavir/ritonavir
    - CYP3A4 and CYP2D6 substrate
    - CYP3A4 inhibitor

Patient 1 – Prediction

- Daclatasvir + Etravirine
  - Etravirine induces CYP3A4
    - Expectation: *decreased daclatasvir concentration (not studied)*
    - Recommendation: increase daclatasvir dose: 90 mg/day

- Daclatasvir + darunavir/ritonavir
  - Ritonavir inhibits CYP3A4
    - Expectation: *increased daclatasvir concentration*
    - Recommendation: normal dose daclatasvir: 60 mg/day

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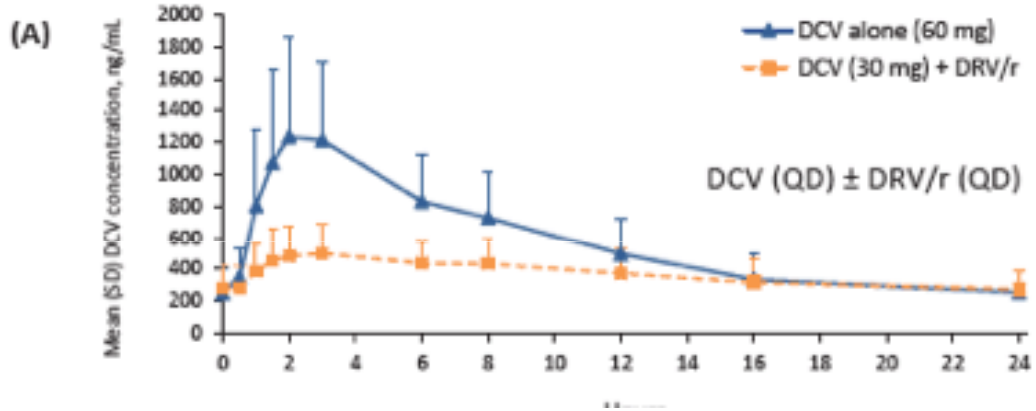
Concentration-time profile for daclatasvir administered alone (60 mg) and daclatasvir(30 mg) with DRV/r (800/100 mg)



Conclusion: daclatasvir 60 mg is right dose

Gandhi Y et al, 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. Washington DC, May 26-28, 2015

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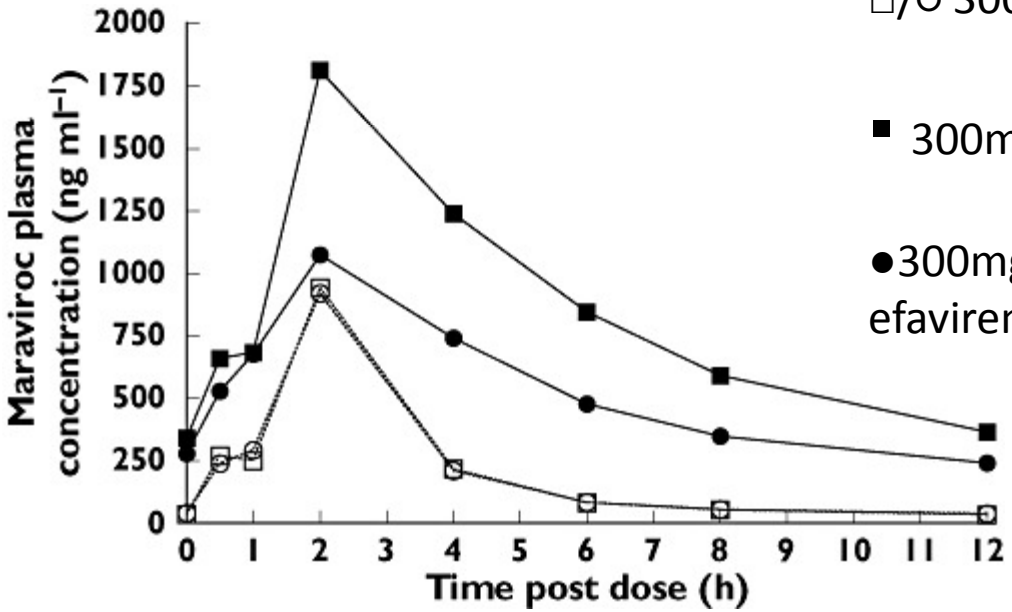
Patient 1 – Prediction

Ritonavir CYP3A4 inhibition compensates etravrine CYP3A4 induction

→ Daclatasvir 60 mg is the right dose

Maraviroc, lopinavir/ritonavir, efavirenz

- Maraviroc: CYP3A4 substrate
- Lopinavir/ritonavir: CYP3A4 inhibitor
- Efavirenz: CYP3A4 inducer



□/○ 300mg maraviroc + placebo

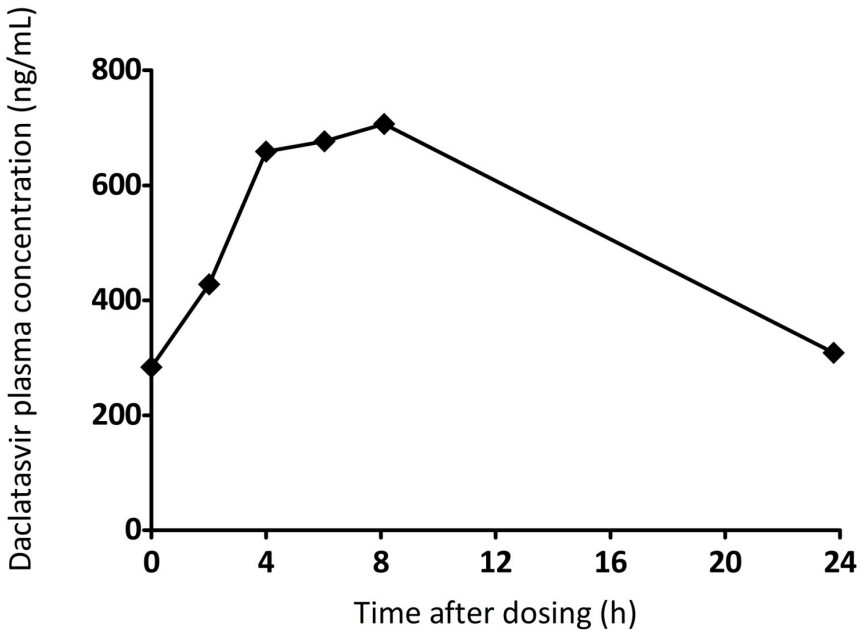
■ 300mg maraviroc + lopinavir/ritonavir

●300mg maraviroc + lopinavir/ritonavir + efavirenz

S Abel et al, Br J Clin Pharmacol, 2008

Patient 1 – Pharmacokinetic sampling

- Patient was treated with daclatasvir 60 mg, sofosbuvir 400 mg, and ribavirin 1200 mg
- 12 weeks
- PK curve was recorded at steady-state



Patient 1 – Pharmacokinetic sampling

	Daclatasvir 60 mg QD	Reference value Daclatasvir 60 mg QD [1]
T_{max} (h)	8.00	1.0 to 2.0
C_{max} (ng/mL)	707	1726
C_{trough} (ng/mL)	284	255
$T_{1/2}$	12.57	12.81
$AUC_{0\text{-}tau}$ (h·ng/mL)	12037	15121

1:Nettles, R.E., et al. Hepatology, 2011.

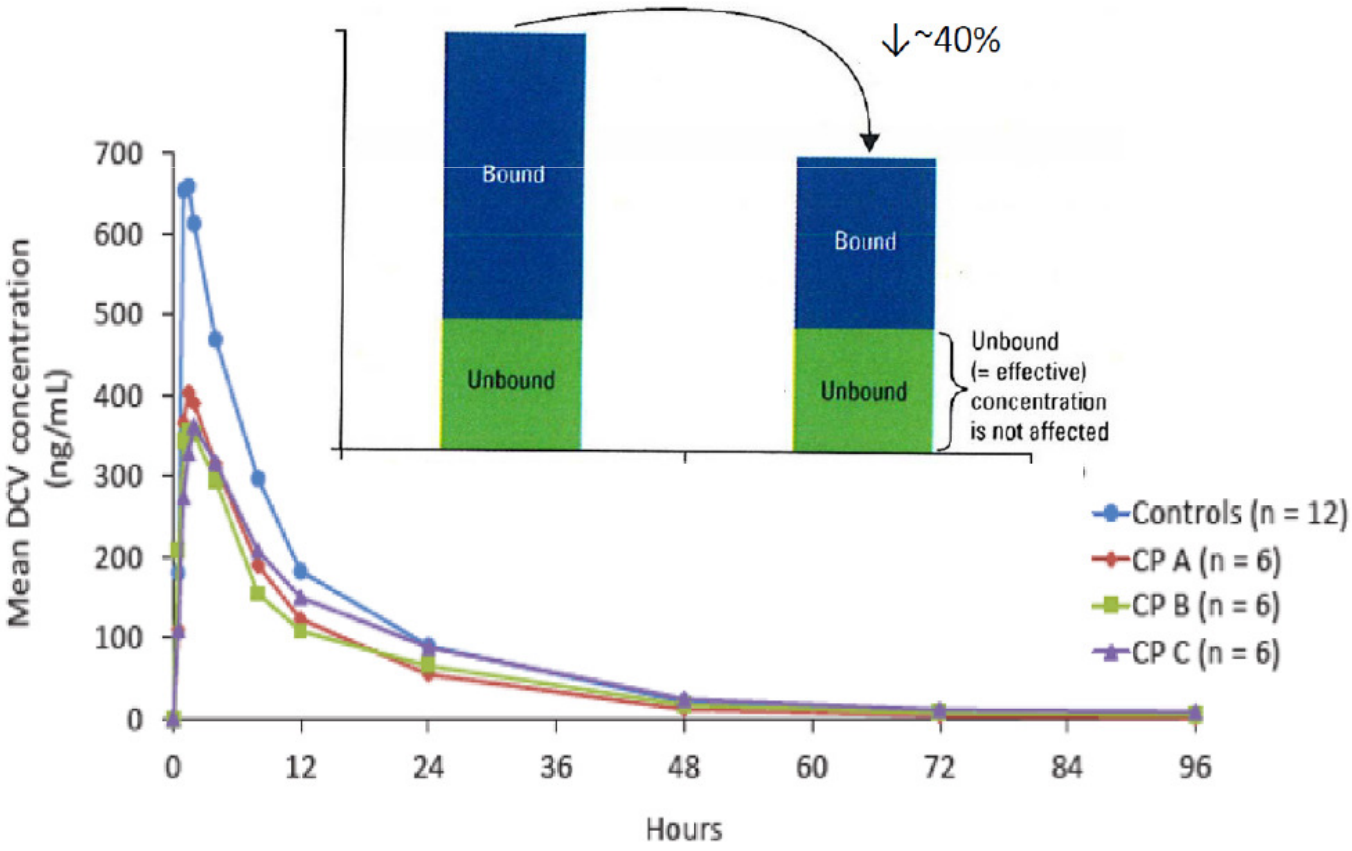
Patient 1 – Patient evaluation

- Patient achieved SVR12

- C_{trough}
  - Ctrough high enough to maintain viral inhibition throughout the complete dose interval
- AUC slightly decreased and C_{max} decreased
  - Is this a problem?

Patient 1 – Patient evaluation

- Total daclatasvir concentrations were decreased, but free amount was unaffected



M Bifano, 62nd AASLD 2011

Patient 1 – Patient evaluation

- Despite the lower total AUC and C_{max} we believe the patient was treated with the right dose
- The inducing effect of etravirine can be mitigated by darunavir/ritonavir

Patient 1 - Publication

Sixty milligram daclatasvir is the right dose for hepatitis C virus treatment in combination with etravirine and darunavir/ritonavir

The HIV and hepatitis C virus (HCV) share the same routes of transmission and HCV coinfection is therefore often prevalent in HIV-infected patients [1]. With the introduction of the direct-acting antivirals (DAAs), HCV treatment success became independent of coinfection with HIV [2]. Indeed, more than 90% of patients reached a sustained virologic response (SVR) after 12–24 weeks of treatment [2,3]. However, concomitant treatment of HIV and HCV increases the risk of drug–drug interactions.

The case report describes an HIV–HCV coinfected patient who received simultaneous treatment for HCV with sofosbuvir, daclatasvir, plus ribavirin while on etravirine and darunavir/ritonavir for his HIV infection.

In May 2015, a 54-year-old Ethiopian man with a 20-year history of HIV infection presented with progressive pulmonary hypertension and ascites. These symptoms were attributed to his liver cirrhosis [Child–Pugh score B (CP-B); alanine transaminase 37 UI/l; aspartate

AIDS 2016, 30:1487–1493

Patient 2 – Problem presentation

- Female
- HCV monoinfection
  - Genotype 1b
  - No cirrhosis
  - Previously failed on peg-interferon + ribavirin
- Severe, treatment resistant epilepsy

Patient 2 – Problem presentation

- Comedication
  - **Clobazam 10 mg**
  - **Phenytoin 92 mg**
  - **Phenytoin 46 mg**
  - **Levetiracetam 500 mg**
  - Cetirizine 10 mg
  - Folic acid 5 mg
  - Potassium supp 500 mg/800E
  - Macrogol electrolyte

- Which HCV treatment is possible?
- February 2015 (sofosbuvir, daclatasvir, simeprevir, ribavirin available in the Netherlands)
- Sofosbuvir: only reimbursed for cirrhotic patients (F3/F4)

Patient 2 – Prediction

- No interactions with clobazam and levetiracetam
- Phenytoin
  - CYP2C9 and CYP2C19 substrate
  - CYP3A4 and P-gp inducer
- Daclatasvir
    - CYP3A4 and P-gp substrate
    - Inhibitor P-gp, OATP1B1
- Simeprevir
  - CYP3A4 substrate
  - CYP1A2, CYP3A4, P-gp, and OATP1B1/3 inhibitor

Patient 2 – Prediction

- Daclatasvir/simeprevir + phenytoin
  - Phenytoin induces CYP3A4
  - Expectation: *decreased daclatasvir/simeprevir concentration*
  - Recommendation: Contra-indicated *not studied*

Patient 2 – Prediction

- Switching phenytoin → lamotrigine, valproic acid
  - Not possible….
- Phenytoin
  - CYP3A4 induction: can be manipulated with strong CYP3A4 inhibitor
    - Ritonavir
- Patient is treated with: simeprevir 150 mg QD, daclatasvir 60 mg QD, and ritonavir 100 mg QD
- Concept comparable with patient 1

Patient 2 – Pharmacokinetic sampling

- Phenytoin concentration did not alter during HCV therapy
  - CYP2C19 induction ritonavir

- Simeprevir concentrations higher than reference values
  - (C_{max} 10-fold, C_{trough} 11-fold, $AUC_{0\text{-}tau}$ 13-fold)
- Daclatasvir concentrations were higher than reference values
  - (C_{max} 1.5-fold, C_{trough} 7-fold, $AUC_{0\text{-}tau}$ 3-fold)

Patient 2 – Patient evaluation

- Adverse events
  - Severe rash

- Based on toxicity and high drug levels. Simeprevir dose changed.
  - Simeprevir 150 mg + ritonavir 100 mg every 3 days

Patient 2 – Patient evaluation

- Adverse events
  - Severe rash

- Based on toxicity and high drug levels. Simeprevir dose changed.
  - Simeprevir 150 mg + ritonavir 100 mg every 3 days

- The patient did not achieve SVR12

- Comments
  - Due to miscommunication, the patients was treated without ritonavir for the first two weeks of treatment
  - Simeprevir nonlinear pharmacokinetics might explain the high exposure to simeprevir
  - Treatment experienced patient: Sofosbuvir? Ribavirin? Other DAAs?
  - To many uncertainties to publish a case-report?