UMC St Radboud

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

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

David M. Burger, PharmD, PhD
Ass. Professor of Clinical Pharmacology
Radboud University Nijmegen Medical Center
The Netherlands
D.Burger@akf.umcn.nl

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?

UMC St Radboud

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)

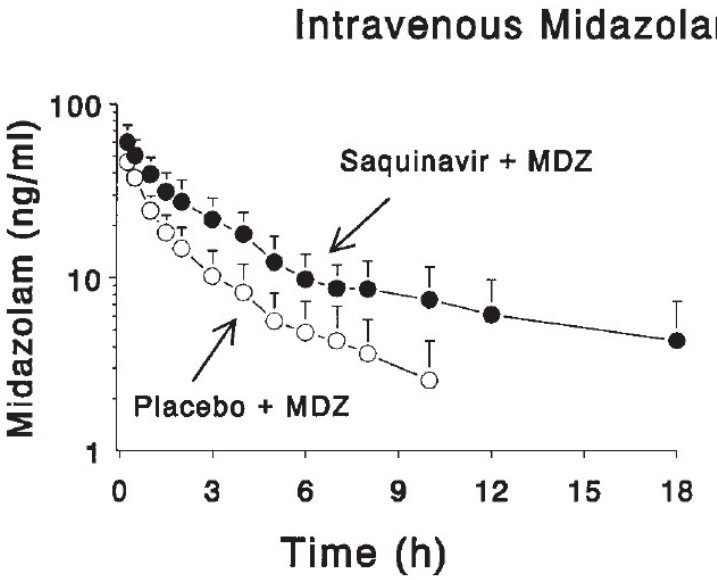
- Some adverse events may be less acceptable in HIV-infected patients:
  - Weight gain (lipodystrophy)
  - Hyperlipidemia (PIs, EFV)
  - Diabetes (PIs)
  - Sexual disorders

Benzodiazepines

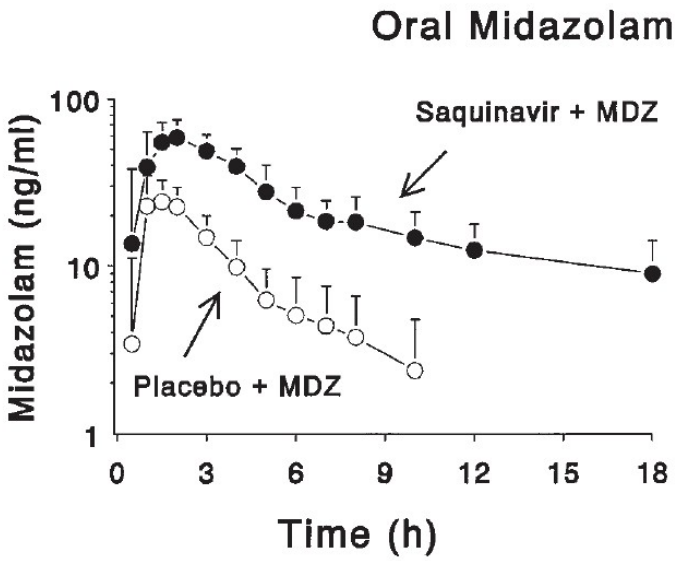
- Some are CYP3A substrates (triazolam, midazolam, alprazolam)
  - NNRTIs induce CYP3A: less sedative effect
  - PIs inhibit CYP3A: more sedative effect

- Alternative agents less affected by drug interactions:
  - Temazepam, lorazepam, oxazepam
  - Zolpidem, zopiclone

Midazolam - saquinavir drug interaction study



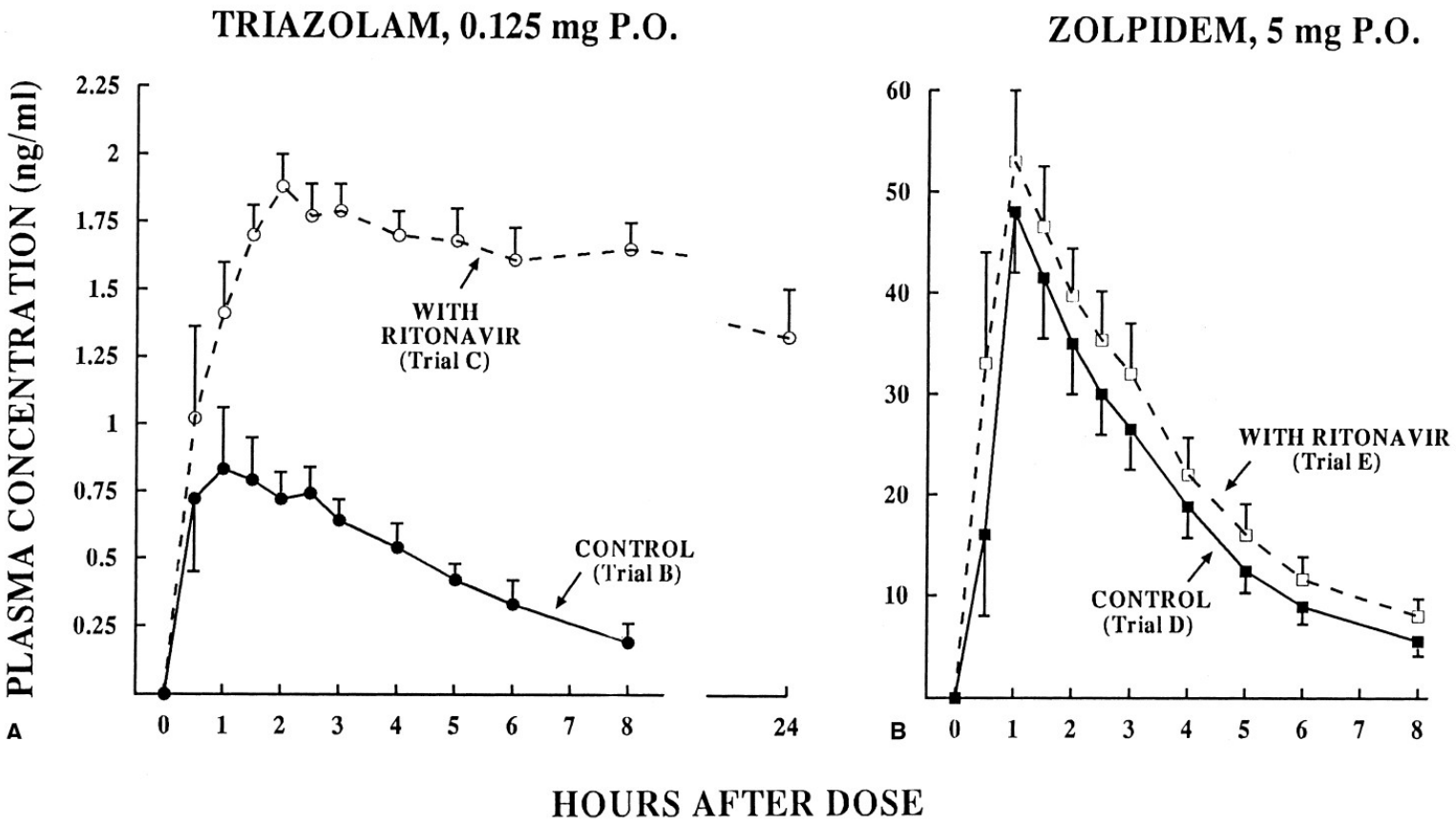
AUC: +148%



AUC: +418%

Palkama et al. Clin Pharmacol Ther 1999

Triazolam/zolpidem + RTV drug interaction study



AUC: +1939%

AUC: +28%

Greenblatt et al. J. Clin Pharmacol 2003

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

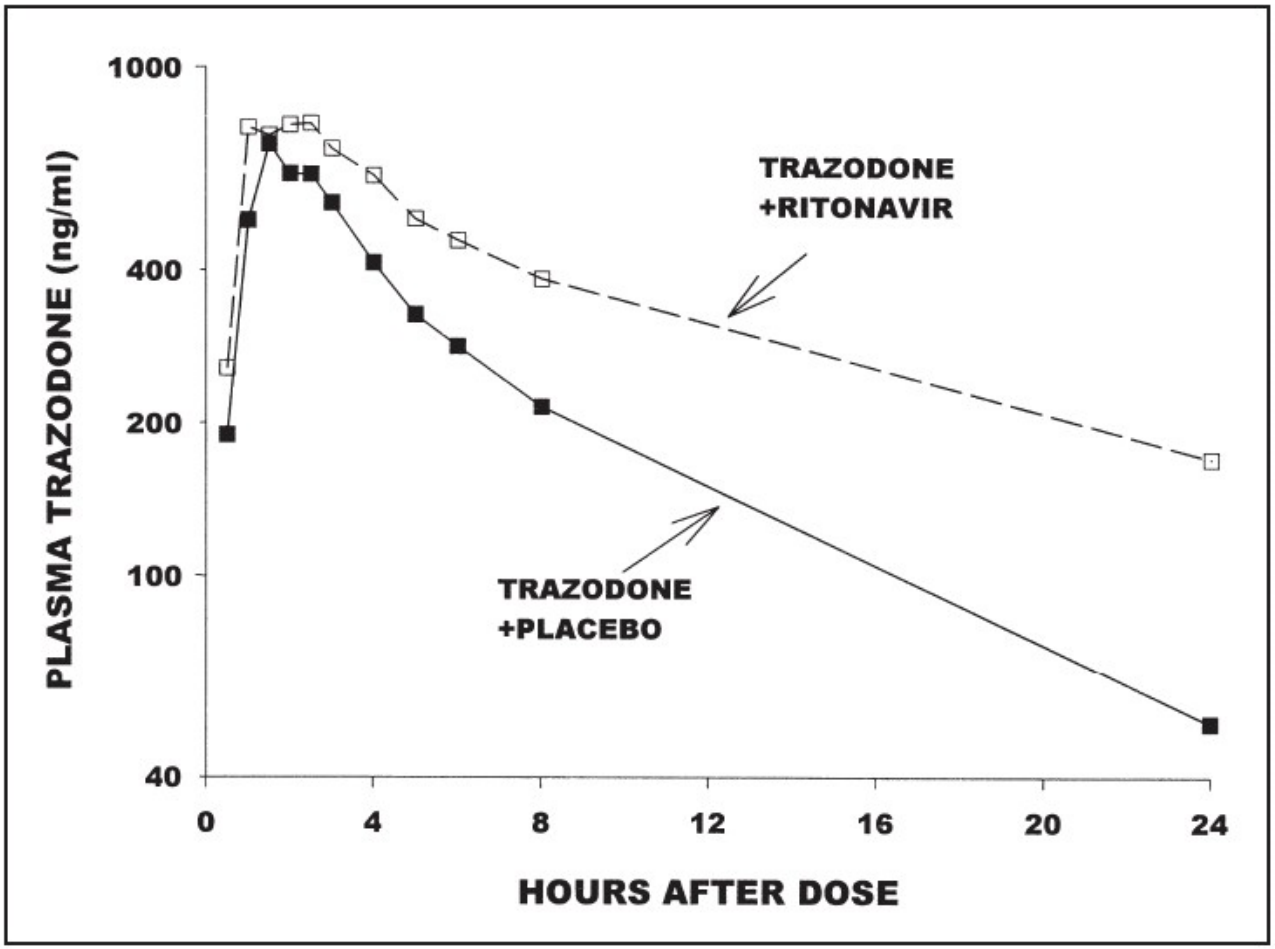
Table 2. Case series summary, Atlanta Veterans Affairs Medical Center.

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

[a]Rechallenge. bid, twice daily; q pm, once daily at night.

DeSilva et al. AIDS 2001

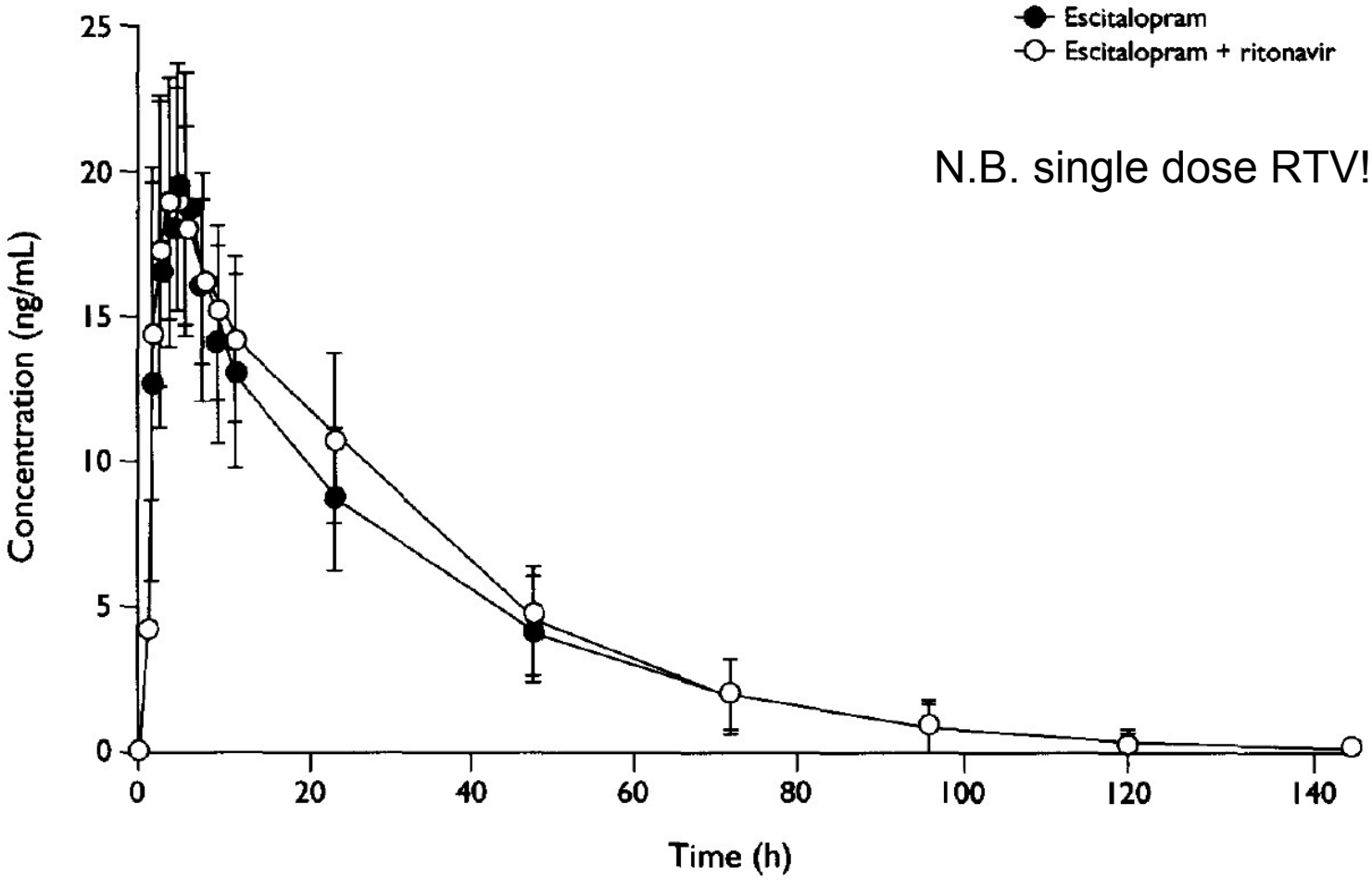
Trazodone (CYP3A) – RTV drug interaction study



AUC: +137%

Greenblatt et al. J Clin Pharmacol 2003

Escitalopram (various CYPs) – RTV drug interaction study

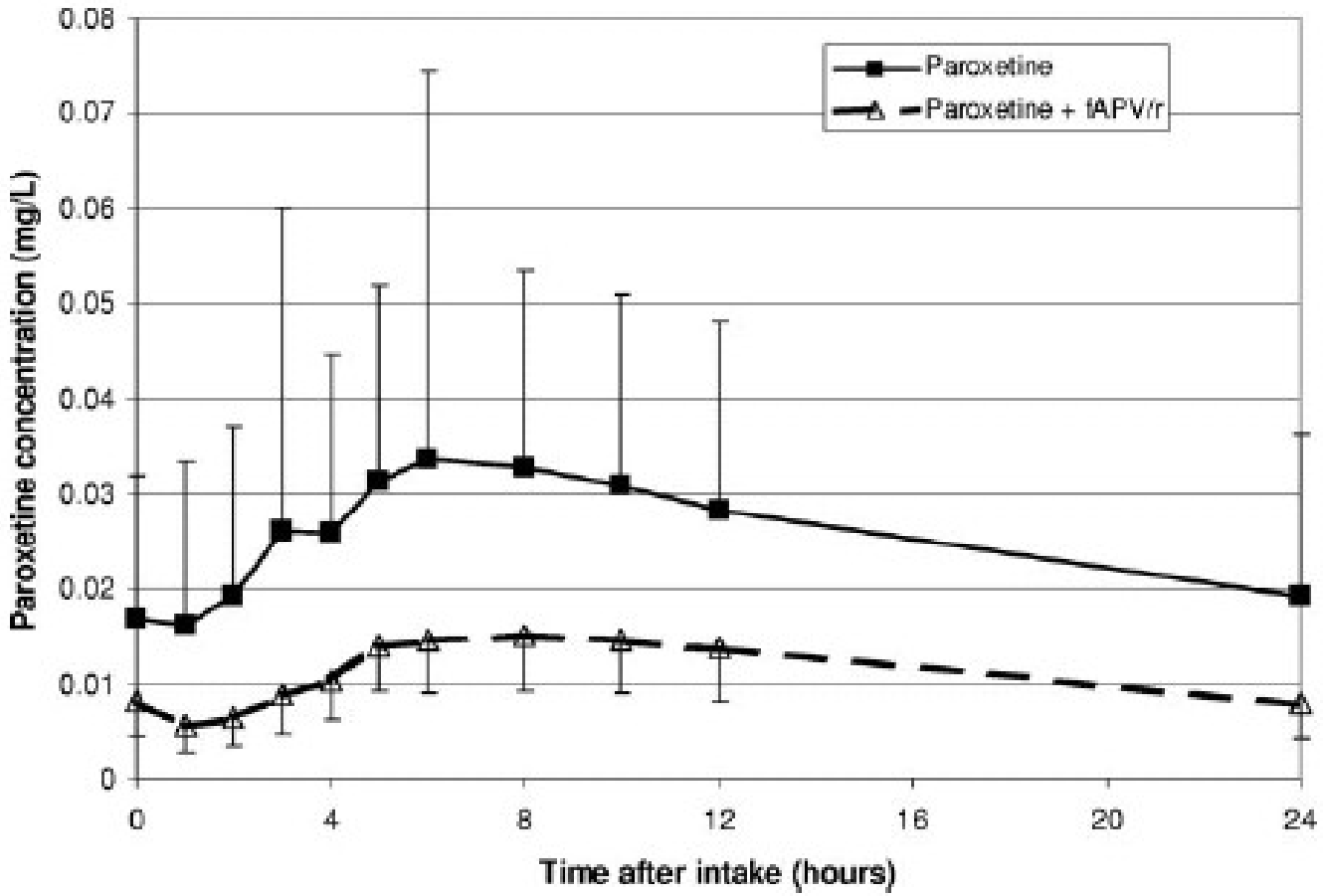


N.B. single dose RTV!

AUC: +8%

Gutierrez et al. Clin Ther 2003

Paroxetine (CYP2D6) – FPV/r drug interaction study



AUC: -55%

Van der Lee et al. AAC 2007

UMC St Radboud

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

UMC St Radboud

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

UMC St Radboud

Risperidone case report in HIV-infected patients

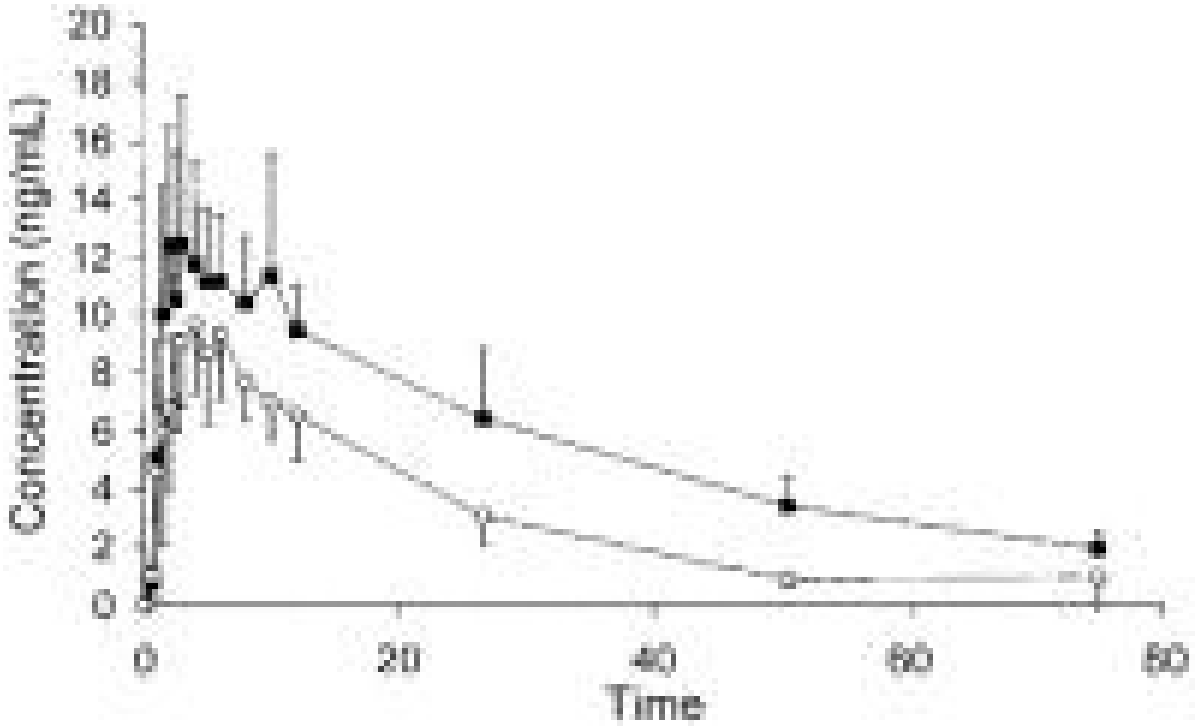
Clinical Neuropharmacology
Vol. 25, No. 5, pp. 251–253

Reversible Coma Caused By Risperidone-Ritonavir Interaction

Francisco Jover, José-María 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%

Penzak et al. J Clin Psychopharmacol 2002

UMC St Radboud

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

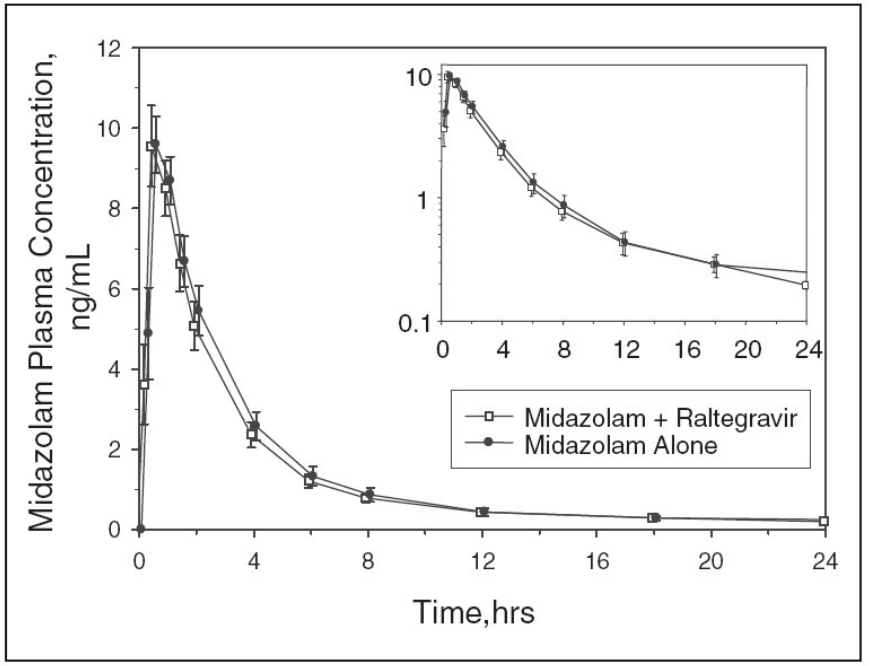


Figure 1. Single oral doses of 2 mg of midazolam with or without administration of 400 mg of raltegravir twice daily to young, healthy, male and female subjects (inset = semilog scale; error bars = SEM).

Iwamoto et al. J Clin Pharmacol 2008

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