A European regulatory perspective

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The views expressed in this presentation are mine and may not represent those of either EMA, the PKWP, or MPA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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CPMP/EWP/560/95/Rev. 1 Corr. 2**
Committee for Human Medicinal Products (CHMP)

Guideline on the investigation of drug interactions

Adopted	June 2012
Coming into effect	January 2013

Transporter highlights in the guideline

- Recommend identifying transporters important for absorption and elimination in vivo and performing relevant DDI studies.
- Published a living list of transporters for which inhibition should be screened
- and cut-offs for in vivo relevance of in vitro inhibition signals based on available data (Pgp) or estimations from the enzyme experience
- Provide recommendations on in vitro study design

Initial issues in applications

- Transporters not identified although there was significant metabolism (OATPs) or biliary excretion
- Problems interpreting mass-balance data and worst-case thinking (without iv data)
- Lack of in vivo DDI or PGx studies
- Lack of justification of chosen in vitro system and probe drug / inhibitor
- Too high concentrations in substrate assays
- DDI risk/study with inducer in vivo not considered
- Stability, adsorption in assays
- Controls in in vitro study (inhibitors, untransfected cells, etc)

Initial issues

almost solved
solved

- ~~Transporters not identified although there is significant metabolism (OATPs) or biliary excretion~~
- ~~Problems interpreting mass-balance data and worst-case thinking (without iv data)~~
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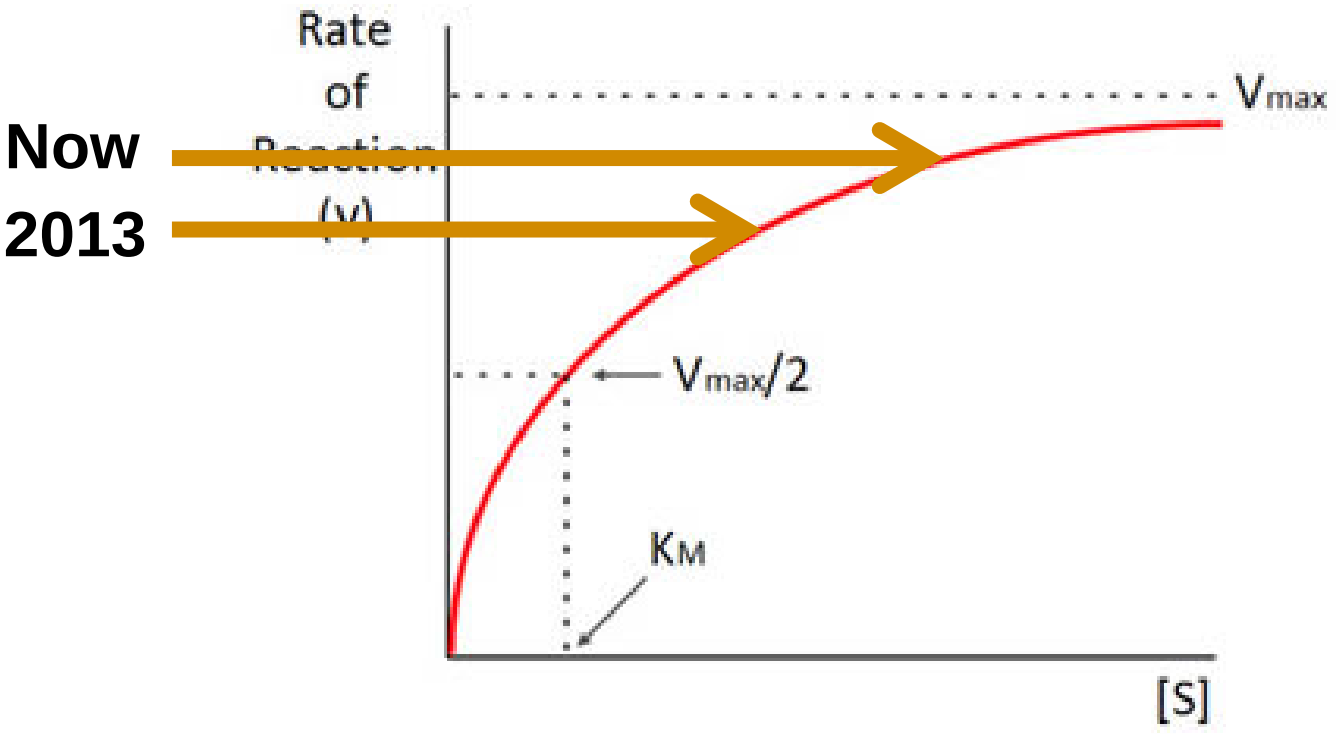
The applications have markedly improved!

The guideline was applied more flexibly in the beginning.



We are also learning with the applications

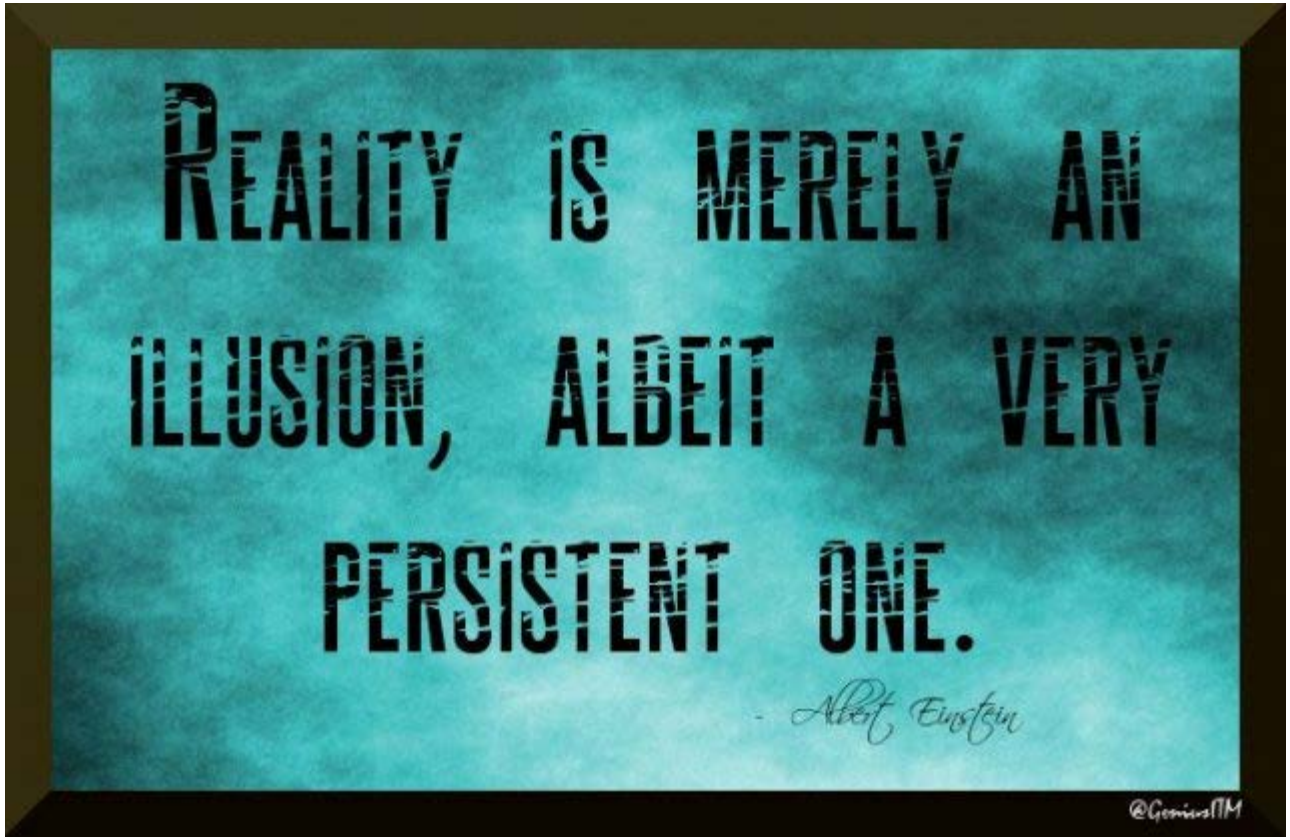
Missing information in today´s applications

- **Caco-2 cell studies with inhibited/saturated transporters, controls**
- **Double systems for inhibition of Pgp**
- **Justify *in vitro* system and probe drug / inhibitor**
- **Justify using EC_{50} (time and conc. independent)**
- **DDI risk/study with inducer in vivo not considered**
- **Use dabigatran etexilate instead of digoxin for intestinal Pgp inhibition**
- **i.v data (bioavailability) supporting estimation of biliary excretion from mass-balance data**
- **PGx, stratified studies**

Additional knowledge: rate limiting step

- The uptake to the hepatocyte may be rate limiting for the elimination
- Inhibition of a major metabolism pathway may not affect drug exposure, only metabolite exposure – parent drug may be misleading in elimination investigations.
- **Useful to check metabolites!**
- **In vitro metabolite formation data important.**
- (The effect of inhibition of uptake transport is not influenced by these considerations. Inhibition will always have an effect on elimination ruled by its contribution as compared to passive permeation.)

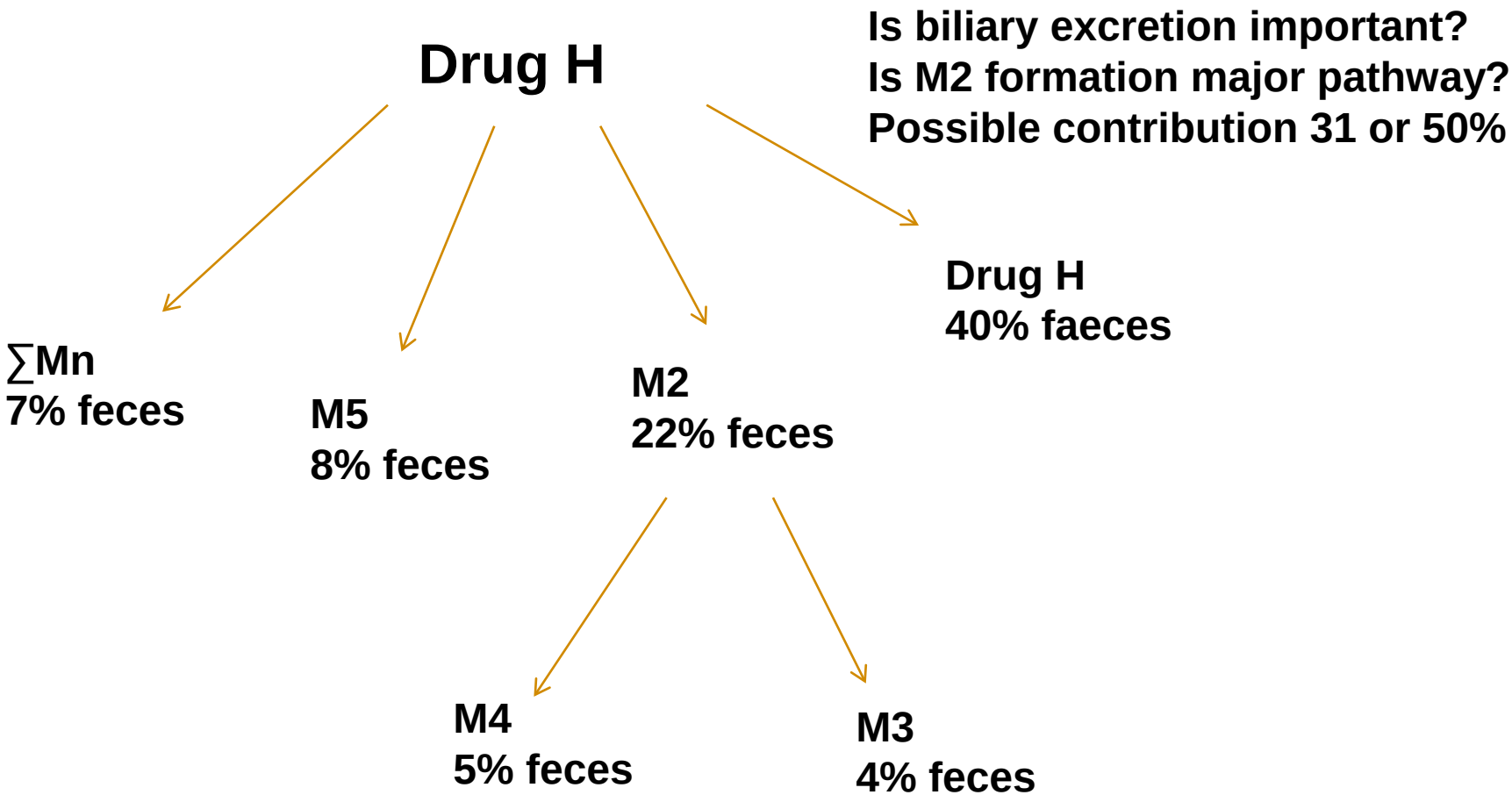
See Maeda et al, CPT 2011



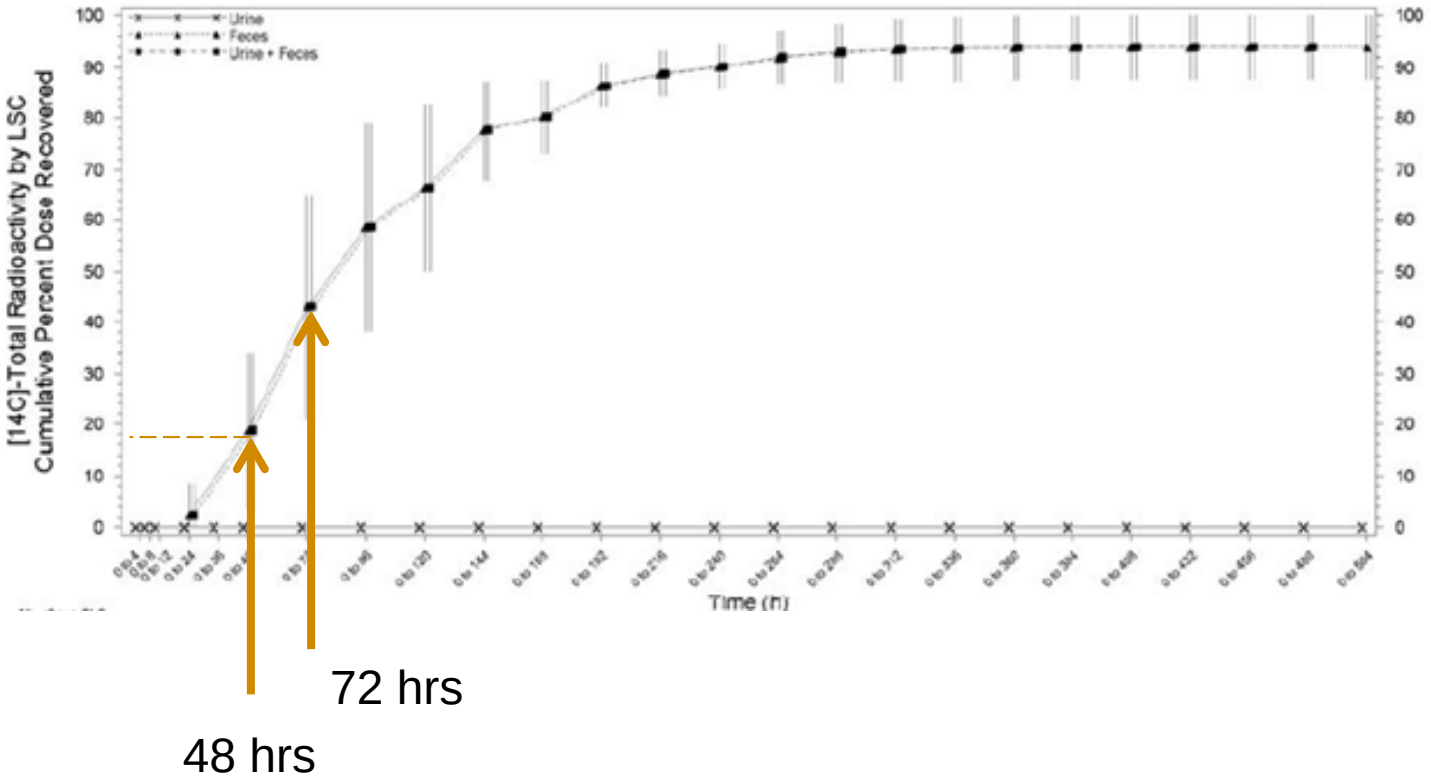
Time for more data and less text

Illustrative data in recent submissions

Discussed last week - Importance of i.v. data



Supportive data

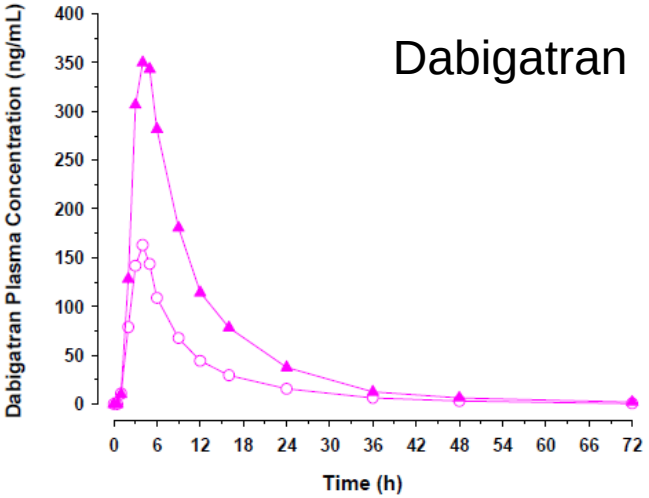


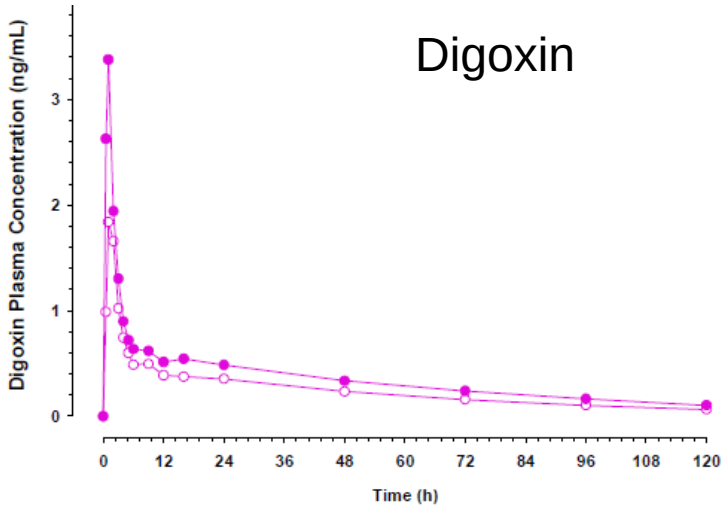
Food interaction (other formulation) rather high on other formulation indicating a quite low Fabs.

Dabigatran vs digoxin

Drug X/Y, Pgp/BCRP inhibitor in intestine

Dabigatran	Cmax 105%↑
150 mg, caps	AUC 138%↑
fed	t1/2 9,9 to 13 hrs
Digoxin	Cmax 72%↑
0.5 mg, tablet	AUC 48%↑
fed	t1/2 37 to 42hrs
	CLR ↔

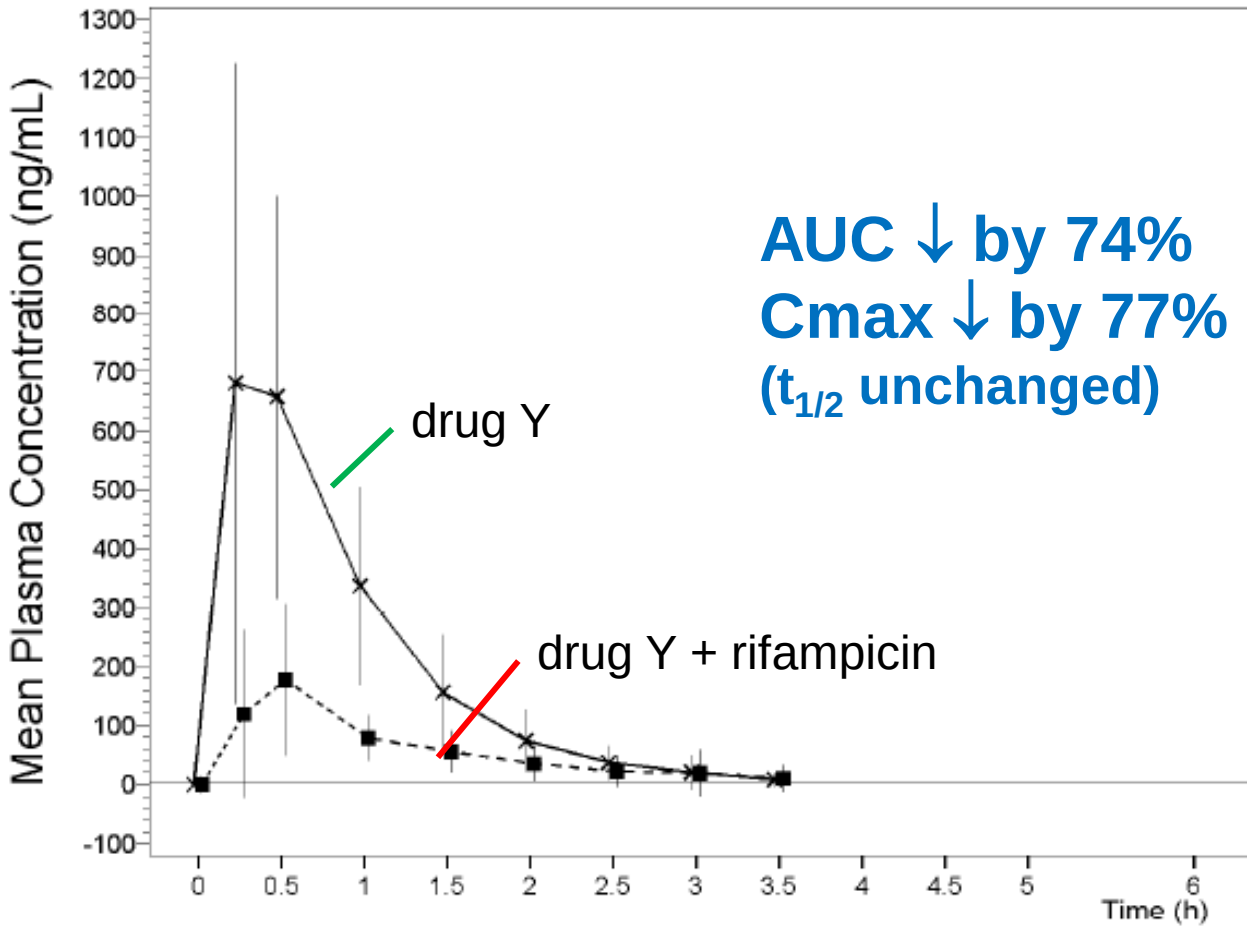




Why making a (sensitive) in vivo study?

Support labelling of intestinal Pgp substrates: dabigatran, sofosbuvir, tenofovir alafenamide, coming NCEs (digoxin TDM)

Remember DDIs with inducers on drugs with significant intestinal Pgp/BCRP transport



AUC ↓ by 74%
Cmax ↓ by 77%
($t_{1/2}$ unchanged)

7 days OK here

Other examples: Inducers on intestinal Pgp

- **Dabigatran - RIF: AUC↓ by 67 %.**
- **Drug X - RIF: Cmax ↓ by 79%, AUC ↓ by 87%**
- **TAF – efavirenz: Cmax ↓ by 22%, AUC ↓ by 14%**

  (No RIF study, labelled “Not recommended”)

- **(Digoxin - RIF staggered Cmax ↓ by 22%, AUC ↓ by 19%, CLR ↔ (other transporter inhibited))**

Kirby et al DMD 2012

Assessment time

Some recent questions

We look a lot on the half-lives in DDI studies trying to get information on the site of the DDI (intestine or liver).

Why is the half-life sometimes unchanged by OATP1B1/3 inhibition?

OATP inhibition and $t_{1/2}$

Rifampicin <u>single dose</u> on drug Y

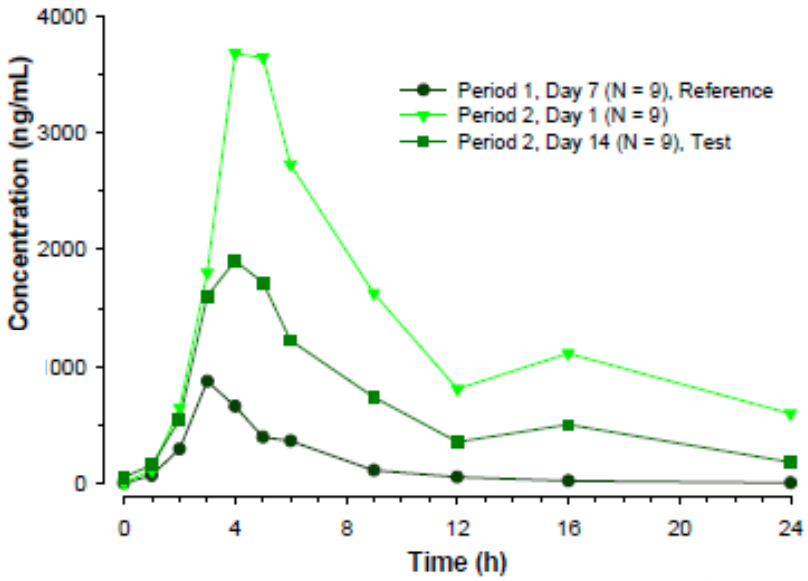
(OATP1B1/3, BCRP/Pgp substrate, fu 2.7%, Vd?)

AUC 8.55-fold ↑

$t_{1/2}$ ↓ from 5.70 to 3.80 hrs

Effect also on Vd?

Drug Y, lopinavir/r



CyA gave AUC 8.5-fold ↑ and $t_{1/2}$ ↑ fr. 5.5 to 11.4 hrs and

Darunavir/r 800/100 qd gave AUC 5-fold ↑ and C_{trough} ↑ 8-fold

Lopinavir/r 400/100 bid gave AUC 4.4-fold ↑ and C_{trough} ↑ 19-fold

Atazanavir/r 300/100 qd gave gave AUC 6.5-fold ↑ and C_{trough} ↑ 14-fold

Effect by OATP1B1/3, Pgp and BCRP inhibitory combination

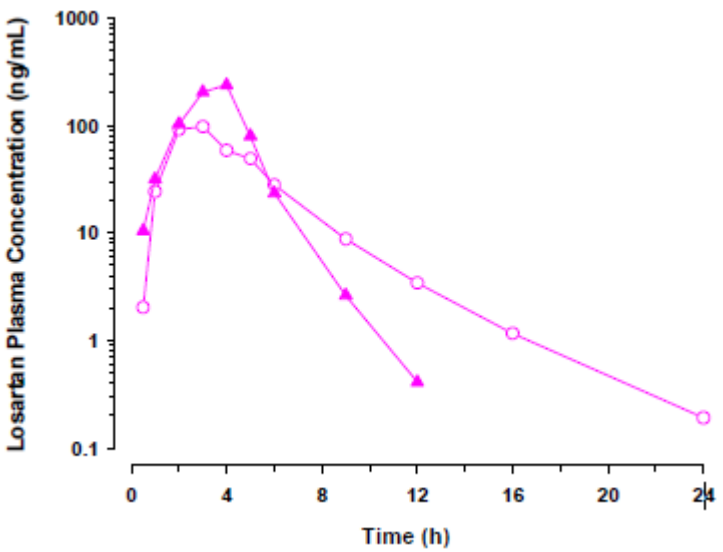
Losartan

50% biliary elimination, OATP1B1/3 substrate, Vd 17L, low fu

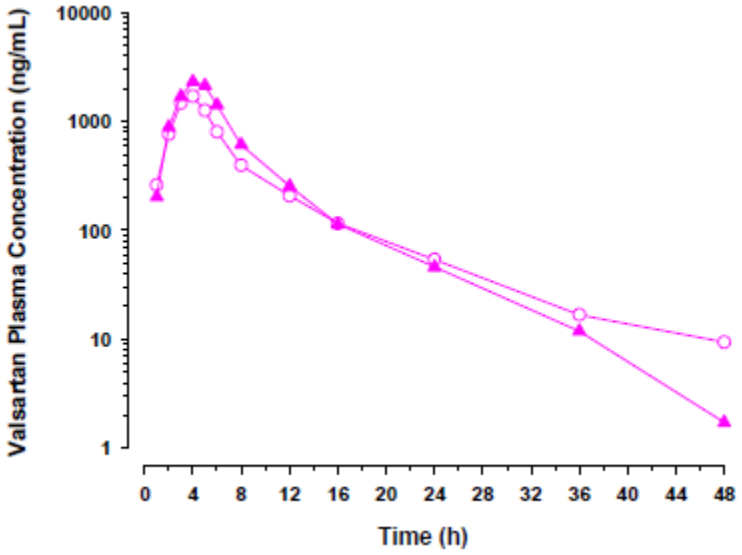
Valsartan

biliary excretion main pathway, OATP substrate, Vd 34L, low fu

Losartan
AUC 1.56, t1/2 2.1 to 0.9hrs



Valsartan
AUC 1.31, t1/2 8.9 to 5.9

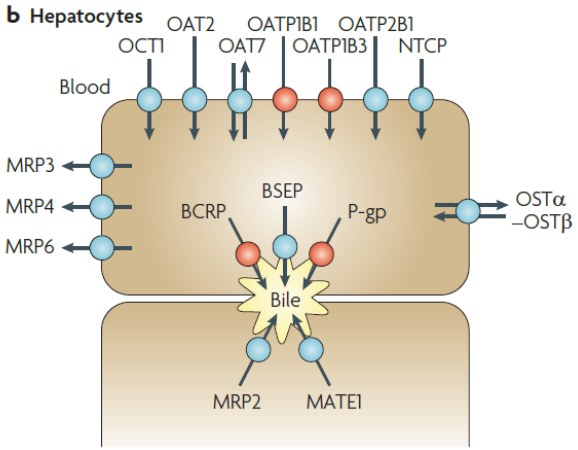


Filled = with inhibitor

How are the hepatocyte concentrations affected?

By induction?

By inhibition of the efflux transporters?



Can we do anything to know more? (Post-marketing follow up, KO, etc)

ITC paper 2010

Up, down, tox or what?

- **Difficult to extrapolate DDI effects to other scenarios when multiple transporters involved.**

  Identified for HIV drugs in the DDI guideline :

… most drug-drug interaction can be predicted. However, it is acknowledged that there are remaining scientific uncertainties. In the area of HIV there have been cases of unexpected interactions. When developing a drug in such an area, *in vivo* interaction studies should be considered with commonly combined drugs having a relatively narrow therapeutic window while more knowledge is gained on the mechanism behind the unsuspected interactions in the field.

This can be applied to other fields/situations with complex DDI mechanisms, especially involving transporters.

Time for a guideline update

PKWP workplan 2017
EU Guidelines under revision

Guideline on the investigation of drug interactions, EMEA/CHMP/EWP/147013/2004

Target date
Concept paper to be released for public consultation **Q1 2017**
Under preparation for publication.

Not a major update but
Proposed changes includes

- **Specific recommendations for in vitro studies on**
  - Transport
  - TDI
  - Induction
- **Update of transporter list (for inhibition screening)**
- **Update on cut-offs for transporter inhibition**
- **Transport as rate limiting step**
- **Clarifications of guideline text**
- **Discussion of DDI study requirement with contraceptive steroids**

Public consultation

- **Q1 2017 – aimed for publication at 1st of April**
- **3 months consultation period**

Thank you for listening!

Are there any clarifying questions?