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Antivirals and nuclear receptor activation of CYP3A4 and 2B6

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Purpose of the study

The orphan nuclear receptors PXR (pregnane × receptor) and CAR (constitutive androstane receptor) are xenosensors that mediate drug-induced transcription of genes involved in drug metabolism, clearance and disposition. Early studies indicate that ritonavir (RTV), saquinavir (SQV) and efavirenz (EFV) modulate CYP3A4 expression via PXR, albeit at non-clinical concentrations. However, little information is available regarding newer antiretroviral agents or the effects on transcriptional regulation of CYP2B6. This study investigates the role of PXR and CAR in the transcriptional regulation of CYP3A4 and CYP2B6 by ART.

Methods

HepG2 cells were transfected with the nuclear receptor plasmids, luciferase reporter gene constructs and an internal standard (pRL-TK), and incubated in medium supplemented with RTV, TFV (Tenofovir), NFV (Nelfinavir), IDV (Indinavir), NVP (Nevirapine), SQV, EFV or FOS (Fosamprenavir) for 48 hrs. Rifampicin and CITCO were positive controls. Transcriptional activation was measured using a dual-luciferase reporter assay and data normalised to the internal standard, and expressed relative to the untreated controls.

Summary of results

The rank order for PXR-mediated transcriptional activation of CYP3A4 was FOS = LPV, > NFV = EFV> SQV (Table 1). None of these drugs altered CYP3A4 through a CAR dependent mechanism. LPV strongly induced transcriptional activation of CYP2B6 via PXR, while NFV, FOS, EFV and RTV were weak activators (<3 fold). Only LPV and NVP induced CAR-mediated activation of CYP2B6, albeit weakly.

Conclusion

In conclusion, the results indicate that inductive effects of PIs and NNRTIs on the CYP-P450 superfamily are due to PXR rather than CAR regulatory mechanisms. Newer PIs such as LPV and FOS are as likely to induce CYP3A4 and 2B6 expression by this pathway as older ARV agents and may affect plasma levels of co-administered through altered metabolism. Clinically relevant combinations and all new drugs should be screened for PXR and CAR activation.

Table 1:

	Fold Induction			
Approx. Clinical Conc	**PXR/CYP3A4**	**CAR/CYP3A4**	**PXR/CYP2B6**	**CAR/CYP2B6**
IDV (15 μM)	1.3	<1	1.5	<1
NFV (6 μM)	6.1	<1	3.0	<1
LPV (16 μM)	9.1	<1	8.6	1.6
RTV (1 μM)	1.9	<1	2.1	<1
TFV (1 μM)	<1	1.2	ND	ND
SQV (4 μM)	3.2	<1	ND	ND
NVP (7.5 μM)	<1	1.1	<1	1.6
EFV (10 μM)	5.8	<1	2.6	<1
FOS (13 μM)	10.4	1.4	2.9	1.3
Rifampicin (10 μM)	18.3	---	15.9	---
CITCO (100 nM)	---	3.4	---	3.5