CYP2D6 is inducible by endogenous and exogenous corticosteroids

Muhammad Farooq
CYP2D6 induction in vitro

- Biotransforms ~20% of all marketed drugs.
- Widely accepted that CYP2D6 protein is non-inducible by xenobiotics.
- Candidate drug is not screened for its CYP2D6 induction profile.
- Nor is such a profile required by regulatory agencies.
Rifampicin treatment induces CYP2D6 activity

**Fig. 1.** Mean (± SD) plasma concentration–time profiles for propafenone after a single dose of 300 mg propafenone orally (PO) before (●) and during (○) induction with rifampicin in six extensive (top) and six poor metabolizers (EM and PM, respectively) of cytochrome P4502D6.
Induction of CYP2D6 in pregnancy

Wadelius et al., 1997
## Oral and IV kinetics of metoprolol

Hogstedt et al., 1985

<table>
<thead>
<tr>
<th></th>
<th>During pregnancy</th>
<th>After delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral (100 mg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>3.42 ± 0.80</td>
<td>3.42 ± 0.31</td>
</tr>
<tr>
<td>AUC (nmol · hr/L)</td>
<td>998 ± 517</td>
<td>3562 ± 809*</td>
</tr>
<tr>
<td>$Cl_o$ (L/min)</td>
<td>9.56 ± 2.70</td>
<td>1.71 ± 0.39*</td>
</tr>
<tr>
<td>$Cl_o$ (L/min · kg)</td>
<td>0.118 ± 0.034</td>
<td>0.024 ± 0.006*</td>
</tr>
<tr>
<td>$F$</td>
<td>0.21 ± 0.06</td>
<td>0.42 ± 0.05†</td>
</tr>
<tr>
<td><strong>Intravenous (10 mg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>5.38 ± 1.36</td>
<td>5.36 ± 1.18</td>
</tr>
<tr>
<td>$Vd$ (L/kg)</td>
<td>6.87 ± 1.32</td>
<td>3.85 ± 0.43</td>
</tr>
<tr>
<td>$Cl_{iv}$ (L/min)</td>
<td>1.38 ± 0.26</td>
<td>0.65 ± 0.08</td>
</tr>
<tr>
<td>$Cl_{iv}$ (L/min · kg)</td>
<td>0.017 ± 0.003</td>
<td>0.009 ± 0.001</td>
</tr>
<tr>
<td>Plasma protein binding (%)</td>
<td>9.18 ± 1.70</td>
<td>10.86 ± 1.06</td>
</tr>
</tbody>
</table>

Data are $\bar{X}$ ± SE.

$F$ = Bioavailability.

*P < 0.05, †P < 0.01 compared with value during pregnancy.
**Hepatocyte culture conditions may mask CYP2D6 induction**

- Hepatocytes are routinely cultured in the presence of serum that contains physiologically relevant concentrations of all the endogenous hormones.

- Presence of these hormones will enhance cell survival and maintain enzyme activity.

- Supplementing the culture medium with the synthetic glucocorticoid dexamethasone (100 nM) has become a routine and established culturing method.

- We investigated if the experimental conditions routinely used in human hepatocyte studies may be a confounding factor in the lack of in vitro induction of CYP2D6.
CYP2D6 is inducible by endogenous and exogenous corticosteroids (1μM)

CYP2D6 activity relative to control

Dexamethasone concentration as a media supplement
CYP2D6 expression and activity in response to glucocorticoid treatment (1μM)

Dex-free culture conditions

CYP2D6 mRNA, protein and activity relative to control

Treatment
Cortisol, Corticosterone, Dexamethasone, Prednisolone, Rifampin
Physiologically relevant concentrations of cortisol does not influence CYP2D6 induction.

Corticotropin
Prednisolone
Rifampin
Dexamethasone
Cortisol

Cortisol concentration as a media supplement
CYP2D6 activity relative to control
Absence of dexamethasone does not influence cell morphology

24 h post plating

192 h post plating

Control

Cortisol (20 nM)

Dexamethasone (100 nM)
CYP2D6 induction dose-response

CYP2D6 mRNA relative to control

CYP2D6 activity relative to control

Concentration (nM)

Concentration (nM)

- Control
- Cortisol
- Corticosterone
- Dexamethasone
- Prednisolone
- Rifampicin
Dexamethasone influence CYP3A induction

CYP3A activity relative to control

- Control
- Cortisol
- Dexamethasone

- Control
- 20 nM cortisol
- 100 nM dexamethasone

* Dexamethasone influence CYP3A induction
Conclusions

• These data show, for the first time that CYP2D6 is inducible *in vitro* in human hepatocytes.

• The routine presence of 100 nM dexamethasone in the culture medium masks this induction.

• Our cortisol data are in agreement with the clinical observation that CYP2D6 is inducible during pregnancy where the plasma concentrations of cortisol during the third trimester increase to ~1 μM.

• These findings, if confirmed *in vivo*, have implications for predicting CYP2D6 mediated drug-drug interactions and call for re-evaluating regulatory guidelines on screening for CYP2D6 induction by xenobiotics.
Acknowledgements

Dr. Jashvant D. Unadkat
Dr. Edward J. Kelly
Dr. Bhagwat Prasad

Unadkat Team

NIDA grant P01DA032507