Drug Interaction Studies

The rational selection of drug interaction studies

Dr. Barbara S. Schug
SocraTec R&D, Oberursel/Germany
Concepts in Drug Research and Development

Regulatory Background

- FDA: Guidance for Industries: In vivo drug Metabolism/Drug Interaction Studies
  Study Design, Data Analysis and Recommendations for dosing and labelling (1999)
When are interactions clinically relevant?
- require dosage adjustment
- require any other medical interaction
  - For compounds with wide therapeutic margin, PK drug interactions are expected to have little clinical significance
- concomitant use within the therapeutic recommendation

Identification of potentially clinically relevant interactions based on:
- physicochemical properties of the drug
- full pharmacokinetic profile
- full pharmacodynamic profile

Mechanistic approach for the selection of candidates

Focus on Pharmacokinetics
- Absorption
  - Rate of absorption
  - Fraction absorbed
  - First-pass metabolism
Mechanistic approach for the selection of candidates

Focus on Pharmacokinetics

- Absorption ➔
  - Physico-chemical properties: pH-dependency, solubility, complex formation, chelation
  - PK: absorption mechanism, first-pass, biliary excretion, enterohepatic recycling
  - PD: motility, pH, bile secretion, splanchnic blood flow, GI-flora
  - Toxic effects (membranes)

- Distribution ➔
  Displacement interaction studies:
  - Non-linear protein binding
  - Small volume of distribution (<10L/70kg)
  - Narrow therapeutic index and
  - Highly bound to plasma proteins (>95%)
  - Occupies most of the binding sites
Mechanistic approach for the selection of candidates

Focus on Pharmacokinetics

- **Elimination**
  - Metabolism • Change of intrinsic clearance
  - Induction (dose/time dependent)
  - Inhibition (quick and competitive)

- **Renal Excretion**
  - Protein binding (GFR)
  - Urinary pH (pKa 7.5 – 10.5 for bases / pKa 3.0 – 7.5 for acids)
  - Urinary flow rate (passive reabsorption)
  - Active secretion (table)
Mechanistic approach for the selection of candidates

Focus on Pharmacokinetics

- Elimination
  - Hepatic/biliary Excretion
  - Competition for hepatic excretion (saturation of capacity)
  - No further advice

"...interference with enterohepatic circulation should also be considered"

Experimental design

- Cross-over design is normally appropriate
- Overall investigation of inhibition/induction/competition
  - Dosage regimen should result in maximum effekt
  - Should ensure effect over 24h
  - Pre-treatment with inducer should be sufficiently long to maximise effect
- Investigation of the effect of a specific drug...
  ...approved therapeutic regiment should be used
Evaluation Strategy

- Numbers of subjects should consider variability
- Analysis of variances (logarithmically transformed data)
- Lack of interaction: pre-specified acceptance range (80-125% or wider if medically justified)

Design Development

Choice of Study Population

- Healthy subjects: PK (seldom in PD)
- Patients: PD
- Genotyping/phenotyping recommended

“Clinically relevant interactions may only occur in a subset of the total population for instance, slow metabolisers, when an alternative route of metabolism is inhibited (CPMP)”
Design example: CYP3A4 substrat

- Roflumilast as CYP3A4 and CYP1A2 under steady state (po)
- Midazolam as CYP3A4 probe substrate administered iv and po

**Figure 1. Study design**

<table>
<thead>
<tr>
<th>Period 1 (4 days)</th>
<th>Washout (≥ 3 days)</th>
<th>Period 2 (14 days)</th>
<th>Period 3 (4 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1, Day 3</td>
<td></td>
<td>Day 1 to Day 14</td>
<td>Day 1, Day 3</td>
</tr>
<tr>
<td>Midazolam single dose</td>
<td></td>
<td>Roflumilast repeated dose</td>
<td>Midazolam single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK analysis Day 1 Day 3</td>
<td></td>
<td>Day 1 Day 3</td>
<td></td>
</tr>
</tbody>
</table>

Study performed by: Anschütz M., Blume H., Hermann R., Nassr N., Schug B., Wolf D. et al.

Intravenous administration of Midazolam (sd) with and without Roflumilast (ss)

<table>
<thead>
<tr>
<th>Time_hours (hr)</th>
<th>Concentration (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>AUC alone</th>
<th>AUC Roflumilast</th>
<th>PE</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl alone</td>
<td>36.3 µg/h/l</td>
<td>35.2 µg/h/l</td>
<td>97</td>
<td>84-113</td>
</tr>
<tr>
<td>Cl Roflumilast</td>
<td>27.5 µg/h/l</td>
<td>26.4 µg/h/l</td>
<td>103</td>
<td>89-120</td>
</tr>
</tbody>
</table>
Peroral administration of Midazolam (sd) with and without Roflumilast (ss)

Design example: cocktail approach

- Cocktail: tolbutamide (CYP2C9), caffeine (CYP1A2), dextromethorphan (CYP2D6), oral and iv midazolam (CYP3A4)
- St. John's wort short-term (sd) and long-term (2 weeks, 300mg T/D) treatment
- Cocktail is administered sd
  - Without St. John's wort
  - With short-term treatment of St. John's wort
  - With long-term treatment of St. John's wort

Results:

- No change for CYP2C9, CYP1A2, CYP2D6 (short-term and long-term)
- Highly significant increase in clearance of oral midazolam after long-term treatment (100% increase)
Blood concentration of midazolam versus time after intravenous midazolam administration before (squares) and after short-term (900mg) (circles) and long-term (300mg 3 times a day for 14 days) (diamonds) administration of St. John's wort (n = 12).


Blood concentration of midazolam versus time after oral midazolam administration before (squares) and after short-term (900mg) (circles) and long-term (300mg 3 times a day for 14 days) (diamonds) administration of St. John's wort (n = 12).

CPMP sets focus on CYP450...

Table 1: The major drug metabolizing CYP450 enzymes, examples of substrates, inhibitors, inducers and markers.

<table>
<thead>
<tr>
<th>P450 Enzyme</th>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Aromatic amines, Phenacetin, Theophyllin</td>
<td>Fluvoxamine, Furafylline</td>
<td>Charcoal-grilled Beef, Gastroesophageal reflux disease vegetables</td>
<td>Caffeine</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Cisapride, Butadiein, Nicotine</td>
<td>Ethylidithiocarbamate, 8-methoxypsoralen, Tranylcypromine</td>
<td>Barbiturates, Coumarin</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>NSAIDs, Phenylalanine, Tolbutamide, S-Warfarin</td>
<td>Sulfenpyrazone, Sulfaphenazole, Sulfapyridine</td>
<td>Rifampin, Barbiturates, S-Warfarin</td>
<td>Tolbutamide</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Clonazepam, Diazepam, Hexobarbital, Imipramine, Omeprazole, Propanolol, Propranolol</td>
<td>Tranylcypromine</td>
<td>Rifampin, Barbiturates</td>
<td>Mefenoxate, Omeprazole</td>
</tr>
</tbody>
</table>

SocraTec R&D
Seminar:
Drug Interactions AGAH

CYP2D6 | Several antidepressants, Neuroleptics, Beta-blockers, Antiarrhythmics, Codeine, Dextromethorphan, Erythromycin, Nicotine | Almataline, Clayton, Ethylidithiocarbamate, Theophylline | None known | Debrisoquine, Dextromethorphan |

CYP2E1 | Acetaminophen, Alcohols, Caffeine, Chloroxazone, Dapsone, Ethylmorphine, Theophylline | Dextromethorphan, Dexamethasone, Dimethyl sulfide, Diclofenac, Diclofenac | Ethanol, Isosorbide | Caffeine, Chloroxazone |

CYP3A4 | Acetaminophen, Carbamazepine, Cyclosporin, Diltiazem, Diazepam, Erythromycin, Felodipine, Fluoxetine, Haloperidol, Quinidine, Saquinavir, Steroids (e.g. cortisol), Terfenadine, Triazolam, Verapamil, Warfarin | Ciorimazole, Ketoconazole, Ritonavir, Triazolam, Tedizodone | Dexamethasone, Phenytoin, Ritonavir, Triazolam | Dapson, Erythromycin, Ketoconazole, Lidocaine |
and the renal elimination

Table 2: Examples of drugs actively secreted into the renal tubule.

<table>
<thead>
<tr>
<th>ORGANIC ACIDS</th>
<th>ORGANIC BASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetazolamide</td>
<td>amantadine</td>
</tr>
<tr>
<td>some cephalosporins</td>
<td>amiodarone</td>
</tr>
<tr>
<td>chlorpropamide</td>
<td>cimetidine</td>
</tr>
<tr>
<td>hippuric acid</td>
<td>dopamine</td>
</tr>
<tr>
<td>indomethacin</td>
<td>ethambutol</td>
</tr>
<tr>
<td>loop diuretics</td>
<td>meperidine</td>
</tr>
<tr>
<td>methotrexate</td>
<td>metformin</td>
</tr>
<tr>
<td>oxyphenbutazone</td>
<td>N-methylnicotinamide</td>
</tr>
<tr>
<td>penicillins</td>
<td>morphine</td>
</tr>
<tr>
<td>phenytoin</td>
<td>procainamide</td>
</tr>
<tr>
<td>probenecid</td>
<td>d-pseudo ephedrine</td>
</tr>
<tr>
<td>salicylic acid</td>
<td>quinacrine</td>
</tr>
<tr>
<td>sulphonamides</td>
<td>triamterene</td>
</tr>
<tr>
<td>sulphonic acids</td>
<td>thiourea</td>
</tr>
<tr>
<td>thiazide diuretics</td>
<td></td>
</tr>
</tbody>
</table>

Hepatic/biliary excretion

“For drugs where the biliary route is an important route of elimination and for which a saturation of the excretory capacity of the liver is possible, interactions caused by competition for hepatic excretion should be considered. The possibility for the drugs to interfere with enterohepatic circulation should also be considered. Interactions at the level of hepatic excretion have been reported for a few drugs (e.g. rifampicin).”

GMCP Guidance Interactions 1997
Seminar:
Drug Interactions AGAH

Acknowledgement:

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