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Seminar:
Drug Interactions AGAH

Drug Interaction Studies

The rational selection of drug interaction studies

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Regulatory Background

- CPMP: Note for Guidance on the Investigation of drug interactions (CPMP/EWP/560/95,1997)
- FDA: Guidance for Industries: In vivo drug Metabolism/Drug Interaction Studies
  Study Design, Data Analysis and Recommendations for dosing and labelling (1999)

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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 potentally clinically relevant interactions based on:

- physicochemical properties of the drug
- full pharmacokinetic profile
- full pharmacodynamic profile

3

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Mechanistic approach for the selection of candidates

Focus on Pharmacokinetics

- Absorption ➡
  - Rate of absorption
  - Fraction absorbed
  - First-pass metabolism

4

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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)

5

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Mechanistic approach for the selection of candidates

Focus on Pharmacokinetics

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

6

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Mechanistic approach for the selection of candidates

Focus on Pharmacokinetics

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

7

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Mechanistic approach for the selection of candidates

Focus on Pharmacokinetics

- Elimination
  - 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)

8

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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"

9

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Experimental design

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

  ...approved therapeutic regiment should be used

10

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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)

11

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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)"

12

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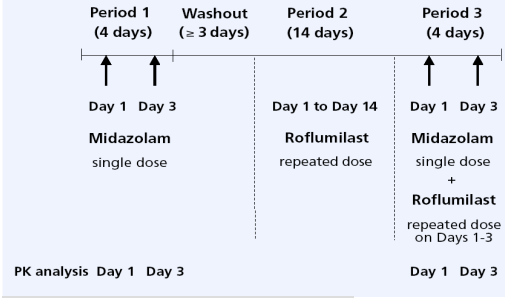
Design example: CYP3A4 substrat

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

Figure 1. Study design



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

13

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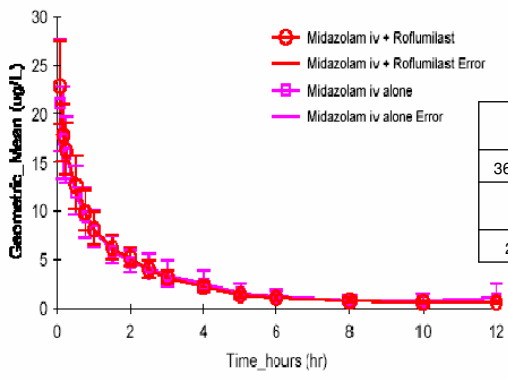
Intravenous administration of Midazolam (sd) with and without Rofluminast (ss)



AUC alone	AUC Roflumilast	PE	CI
36,3 µg·h/l	35,2 µg·h/l	97	84-113
Cl alone	Cl Roflumilast		
27,5 l/h	28,4 l/h	103	89-120

14

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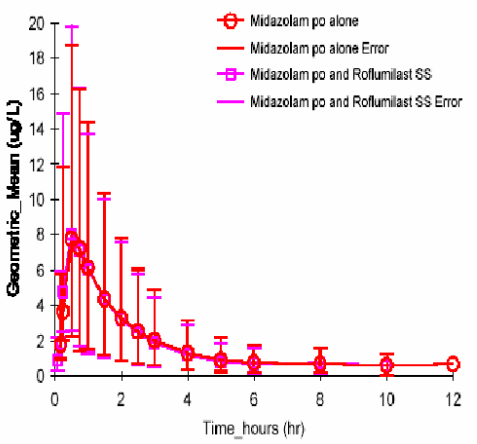
Peroral administration of Midazolam (sd) with and without Roflumilast (ss)



AUC alone	AUC Roflumilast	PE	CI
17,9 µg·h/l	17,6 µg·h/l	98	82-117
Cl alone	Cl Roflumilast		
111,5 l/h	114,0 l/h	102	85-123

15

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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)

16

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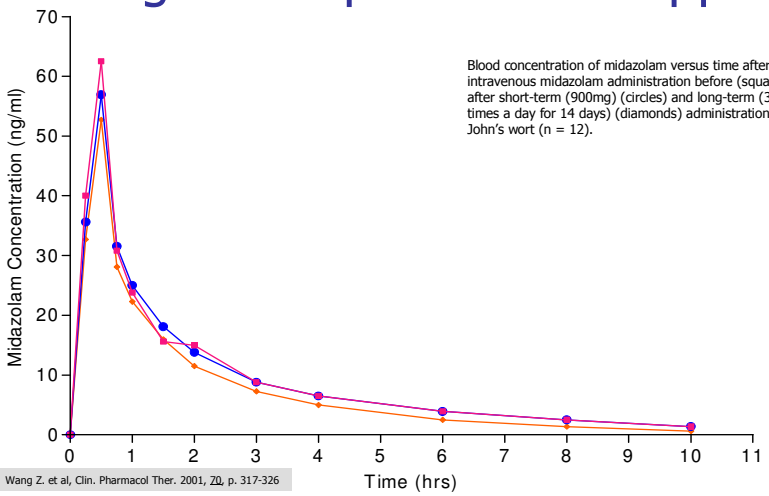
Design example: cocktail approch



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).

Wang Z. et al, Clin. Pharmacol Ther. 2001, 70, p. 317-326

17

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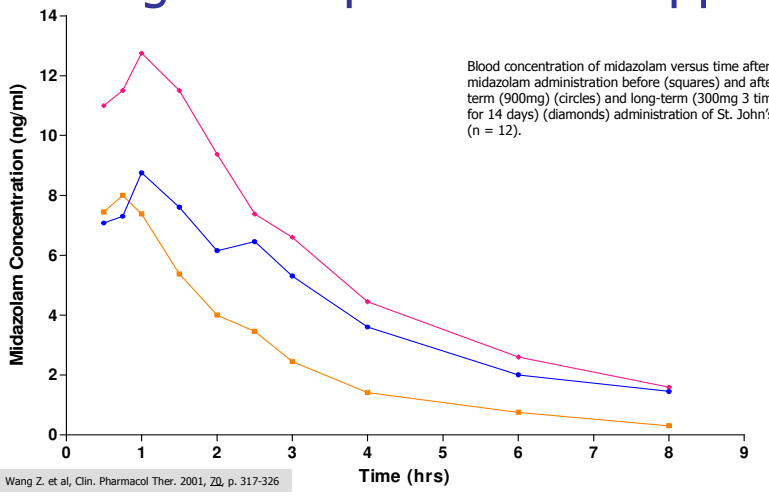
Design example: cocktail approch



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).

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18

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CPMP sets focus on CYP450…

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

P450 Enzyme	Substrates	Inhibitors	Inducers	Markers
CYP1A2	Acetaminophen Aromatic amines Caffeine Phenacetin Theophyllin	Fluvoxamine Furafylline	Charcoal-grilled Beef Cigarette smoke Cruciferous vegetables	Caffeine
CYP2A6	Coumarin Butadien Nicotine	Diethyldithiocarbamate 8-methoxypsoralen Tranylcypromine	Barbiturates	Coumarin
CYP2C9	NSAID drugs Phenytoin Tolbutamide S-Warfarin	Sulfaphenazole Sulfinpyrazone	Rifampin Barbiturates	S-Warfarin Tolbutamide
CYP2C19	Citalopram Diazepam Hexobarbital Imipramine Omeprazole Proguanil Propranolol	Tranylcypromine	Rifampin Barbiturates	Mefenytoin Omeprazole

19

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CYP2D6	Several antidepressants Neuroleptics Beta-blockers Antiarrhytmics Codeine Dextromethorphan Etylmorphine Nicotine	Ajmalicine Chinidin Fluoxetine Paroxetine Quinidine Ritonavir	None known	Debrisoquine Dextromethorphane
CYP2E1	Acetaminophen Alcohols Caffeine Chlorozoxazone Dapsone Enflurane Theophylline	Diethyldithiocarbamate Dimethyl sulfoxide Disulfiram	Ethanol Isoniazid	Caffeine Chlorzoxazone
CYP3A4	Acetaminophen Carbamazepine Cyclosporin Digitoxin Diazepam Erythromycin Felodipne Fluoxetine Nifedipine Quinidine Saquinavir Steroids (e.g. cortisol) Terfenadine Triazolam Verapamil Warfarin	Clotrimazole Ketoconazole Ritonavir Troleandomycin	Dexamethasone Phenytoin Rifampin Troleandomycin	Dapsone Erythromycin Ketoconazole Lidocaine

20

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and the renal elimination

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

ORGANIC ACIDS	ORGANIC BASES
acetazolamide	amantadine
some cephalosporins	amiloride
chlorpropamide	cimetidine
hippuric acid	dopamine
indomethacin	ethambutol
loop diuretics	meperidine
methotrexate	metformin
oxyphenbutazone	N-methyinicotinamide
penicillins	morphine
phenylbutazone	procainamide
probenecid	d-pseudo ephedrine
salicylic acid	quinacrine
sulphonamides	triamterene
sulphonic acids	
thiazide diuretics	

21

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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

22

Acknowledgement:

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