



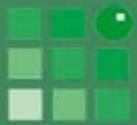
BIOTRIAL



**WELCOME
BIENVENUE**

**DRUG-DRUG
INTERACTIONS**





BIOTRIAL

DRUG-DRUG INTERACTIONS UPDATE ON THE STUDY DESIGN

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Biotrial





What we do, we do well.



INTRODUCTION

- Pharmacological responses of a drug is function of :
 - either the peak concentration (C_{max}) if there is an activity threshold,
 - either, the total exposure to the parent drug and/or its active metabolite(s) measured by AUC (more precisely the response is a function of exposure to unbound drug)
- The clearance is the main regulator of drug concentrations.
- Large differences in blood levels can occur because of individual differences in metabolism due to genetic polymorphism, age, race, gender and environmental factors (smoking, alcohol, diet e.g. grapefruit juice). Drug-drug interactions can have similarly large effects in drug disposition



Drug interactions : Definitions

- An interaction is an alteration either in the pharmacodynamics, either in the pharmacokinetics of a drug, caused by concomitant drug treatment, dietary factors or social habits (such as tobacco or alcohol).

- A clinically relevant interaction will produce in vivo changes of the magnitude and/or the duration of the pharmacological activity of the drug :
 - ✦ leading to changes in the risk-benefit ratio for patients
 - ✦ justifying a dose adjustment or a contraindication



Drug interactions : Definition

- Conventionally, a drug interaction is regarded as the modification of the effect of one drug by prior or concomitant administration of another (could require a dosage adjustment).
 - A better definition would insist that the pharmacological outcome when 2 or more drugs are used in combination is not just a direct function of their individual effects. If the resultant response is greater than the sum of their separate actions than potentiation may be seen to have occurred, while if the overall result is less than expected this can be regarded as antagonism.
- 



Examples of Drugs Withdrawn from the U.S. Market or Not Approved between 1998 and 2003

Withdrawn	Year of Approval	Drug name ^a	Use	Risk
1998	1997	Mibefradil	High blood pressure/ chronic stable angina	Drug-drug interactions , torsades de pointes
1998	1997	Bromfenac	NSAID	Acute liver failure
1998	1985	Terfenadine	Antihistamine	Torsades de pointes, drug-drug interactions
1999	1998	Astemizole	Antihistamine	Torsades de pointes, drug-drug interactions
1999	1997	Grepafloxacin	Antibiotics	Torsades de pointes
1999 (NA)		Drug A		Torsades de pointes, drug-drug interactions
2000	2000	Alosetron ^b	Irritable bowel syndrome in women	Ischemic colitis, complications of constipation
2000	1993	Cisapride	Heartburn	Torsades de pointes, drug-drug interactions
2000	1997	Troglitazone	Diabetes	Acute liver failure
2001	1997	Cerivastatin	Cholesterol lowering	Rhabdomyolysis, drug-drug interactions
2001	1999	Rapacuronium bromide	Anesthesia	Bronchospasm
2001 (NA)		Drug B		Drug-drug interactions

- **NA, not approved.**
- **a. Trade names are in parentheses.**
- **b. Reintroduced to the market in 2002 with use restricted to patients severely affected with irritable bowel syndrome.**



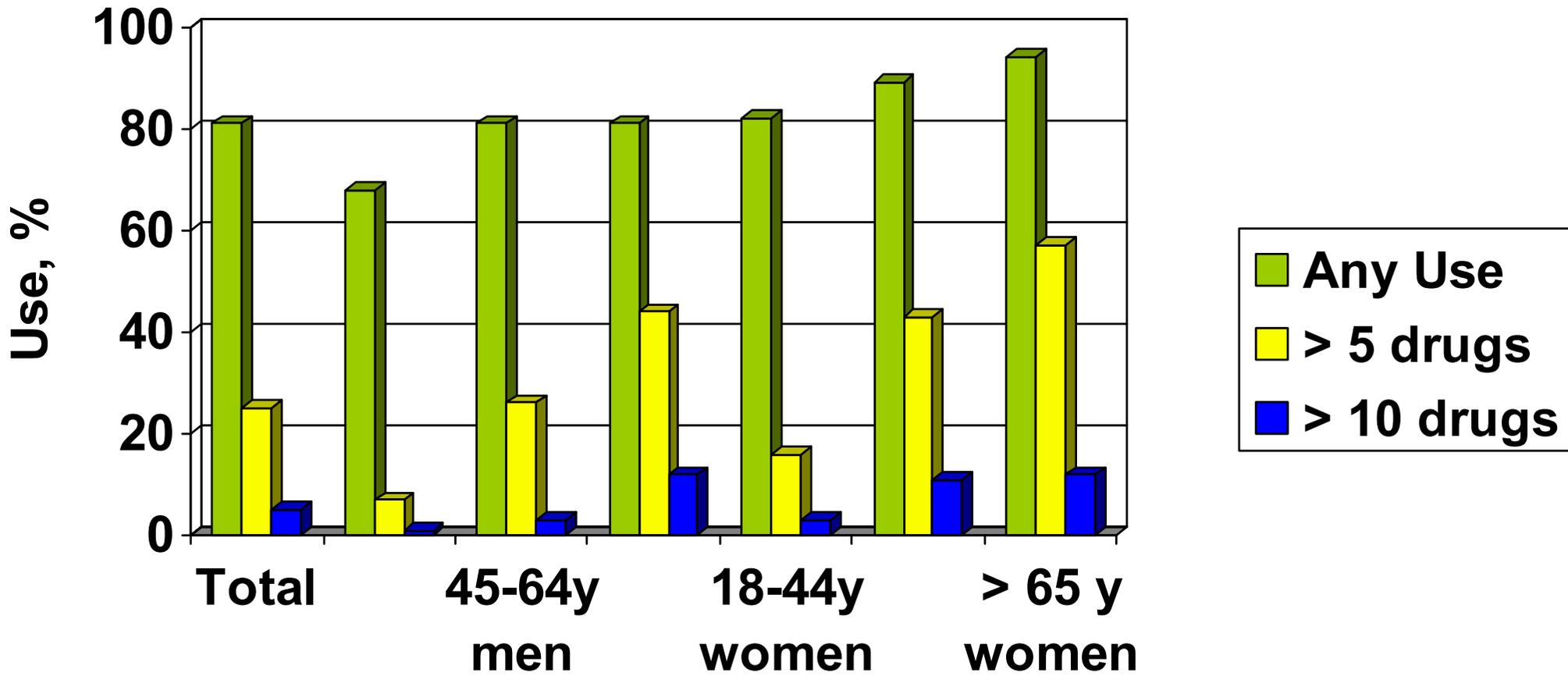
Safety aspect : Adverse drug reactions

- 10-30 % of hospital admissions.
- ADRs are between the 4th & 6th leading cause of death in hospitalized patients in the U.S. (Lazarou et al, JAMA; 1998: 12:1200-5) causing an estimate 100.000 deaths annually in the US alone.
- Often due to drug-drug interactions (5% - 22%).



Why are there so many ADRs?

Use of Medications by Sex and Age



Drug-drug interaction: Criteria to identify drug 'at risk' of interaction

- Pharmacodynamic properties
- Metabolism and pharmacokinetic profile:
 - ❖ transporter (Pg-P, OAT, OATP, UGT)
 - ❖ intestinal and hepatic metabolism
 - ❖ metabolic pathway(s) with identified CYP450 isoforms
 - ❖ inducing or inhibiting potential in vitro
 - ❖ protein binding
 - ❖ renal clearance
- Further use of the medication
 - ❖ widespread clinical use (even OTC)
 - ❖ high dose (with risk of saturation of a first-pass effect)
 - ❖ treatment of long duration
 - ❖ prescribed to at risk population (elderly, liver impaired, renal impaired or CHF patients, severely ill patients with polypharmacy)
- Narrow therapeutic range (warfarin, digoxin, theophylline, antiepileptic drugs)



Relevant considerations during the drug development program

- Extensive characterization of the physico-chemical properties
- Early characterization of the full pharmacodynamics and pharmacokinetics
- Based on in vitro data, undertake relevant in vivo studies required to support a claim of 'No clinically relevant interactions' in the dossier
- Preferably, both pharmacokinetic and when relevant pharmacodynamic variables, should be studied and the clinical relevance of the results in light of the dose-concentration-effect (therapeutic as well as toxic) relationships should be discussed
- Focus both reciprocal effects of the two drugs investigated
- Based on the medical recommendations take into account the frequency of the coadministration in the disease

Guidance Documents

- Europe - EMEA (European Agency for the Evaluation of Medicinal Products).

[Http://www.emea.europa.eu](http://www.emea.europa.eu)

- US - FDA - CDER: Guidance for Industry

- ✦ Drug Metabolism/ Drug Interactions in the Drug Development

- ✦ Process: Studies In Vitro: 1997

- ✦ Guidance for Industry, In vivo drug metabolism studies 1999

- ✦ Drug Interaction Studies: Study Design, Data Analysis, and Implications for Dosing and Labeling Sep 2006

[Http://www.fda.gov/cder/drug/drugInteractions/default.htm](http://www.fda.gov/cder/drug/drugInteractions/default.htm)

- Japan-MHLW (Ministry of Health, Labor and Welfare in Japan) guidance (draft 13 Apr. 2000). Available (when finalized) from URL:

[Http://www.nihs.go.jp/drug/DrugDiv-E.html](http://www.nihs.go.jp/drug/DrugDiv-E.html)



- Tucker GT, Houston JB, Huang SM. Optimizing drug development: strategies to assess drug metabolism /transporter interaction potential – toward a consensus. Clin Pharmacol Ther 2001 70 103-114. Basel conference held on Nov 13-15 2000 under the hospices of EUFEPS, FDA and AAPS.
- Bjornsson TD et al. The conduct of In vitro and In vivo drug-drug interactions studies: a PhRMA perspective. J Clin Pharmacol 2003 43 443-469
- Huang SM and all. New era in Drug interaction evaluation J Clin Pharmacol 2008; 48:662-670
- Zhao P and all. Quantitative evaluation of PK inhibition of CYP3A substrates by Ketoconazole J Clin Pharmacol 2009; 49:351-359



Drug-drug interaction studies: objective

- Possibility of PK and/or PKD interactions
- to determine whether the (PKD/PK) interaction is sufficiently large to necessitate a dosage adjustment of the drug itself or the drugs it might be used with, or whether the interaction would require additional therapeutic monitoring



Pharmacodynamic interactions

- Produce a change in the PKD response by a direct or an indirect action on the drug target without any change in drug plasma concentrations.
- May be caused by a large variety of mechanisms. It is therefore impossible to give detailed guidance. The design must be determined on a case-by-case basis.
- PKD interaction studies should be performed when drugs likely to be co-administered have:
 - similar or opposing pharmacodynamic effects
 - similar mechanism of action or potentially similar interaction mechanisms of action



Pharmacokinetic interactions

- Absorption
- Distribution
- Metabolism
- Excretion



Absorption

- In vitro studies may be helpful in investigating transport mechanisms or the potential of a drug for complex binding / chelation
- Since current in vitro absorption studies have been shown to have limited value for in vivo absorption, potential interactions should be confirmed by well-designed in vivo studies
- When designing absorption interaction studies, it must be remembered that:
- Food interactions should preferably be investigated early in drug development process so that the information obtained may be considered in the design of the Phase II and III studies. Food or other drugs may influence drug absorption for several hours. If a significant interaction is demonstrated, the dosage recommendations (i.e. timing of dose in relation to the interacting agent) should be adequately validated in the clinical situation

Absorption

- Drug-drug absorption interaction studies should be performed based on a combined knowledge of the 2 drugs properties :
 - Factors known to influence drug absorption including the effect of food
 - Physico-chemical properties of the drug substance and formulation (pH dependency, solubility, dissolution, ability for complex formulation/chelation/absorption)
 - Pharmacokinetic properties (in particular absorption mechanisms, bioavailability, extent absorbed and first pass metabolism, biliary excretion, enterohepatic recycling)
 - Pharmacodynamic properties (in particular effects on the gastrointestinal physiology such as gastric emptying and motility, gastric pH, bile secretion, splanchnic blood flow, gastrointestinal flora)
 - Toxic effects such as damage of gastrointestinal membranes

- Displacement of drug from plasma proteins is the most common explanation for altered distribution in drug interactions. However, few displacement interactions result in clinically relevant changes



- Displacement interaction studies should be performed when the investigated drug :
 - Has non-linear protein binding
 - The volume of distribution is small $<10\text{L}/70\text{ kg}$
 - Has a narrow therapeutic index and
 - Is highly bound ($> 95\%$) to proteins in human plasma at therapeutic concentrations and
 - Occupies most of the binding sites (e.g. plasma therapeutic concentrations at the highest recommended dose exceed the plasma binding capacity)
 - Is administered intravenously and possesses a high metabolic extraction ratio



- When designing displacement interaction studies, it must be remembered that :
 - Displacement studies should be preferably performed in vivo, since the metabolites of the drug may also be involved in such interactions. If such studies are performed in vitro, then the possible contribution of metabolites to an interaction should be considered
 - Changes in unbound plasma concentration may not occur in parallel with the total plasma concentration



Metabolic interactions

- The most frequent (> 50%) interaction type (80 % of those due to CYP 2C9, 2C19, 2D6 and 3A4)
- Characterize the primary metabolic pathway(s)
- Determine the proportion of the total clearance that each primary metabolic pathway constitutes and identify the enzymes responsible for the metabolism in each pathway
- Evaluate the inducing and inhibiting properties of the test drug by determining its relevant kinetic parameters with each enzymes
- Assess the influence of genetic variability on the metabolism (genotype, phenotype)
- Evaluate the effects of established inducers and inhibitors of the metabolic pathway(s) involved in the test drug metabolism

- As a general guidance, in vitro and/or in vivo metabolic interaction studies should be performed for compounds :
 - whose elimination is mainly metabolic
 - administered by the oral route and whose bioavailability is low due to a large first-pass effect
 - for which a specific enzyme is responsible for 30% or more of the total clearance
 - However, if toxic/active metabolites are formed, minor metabolites pathways may also need to be studied
- Take into account : unbound plasma concentrations and slope of the effect-concentration curve of the parent drug and its active and/or toxic metabolites



In vitro studies

- Strong correlations have been documented between well-conducted studies in vitro and in vivo so metabolism studies in vitro would be useful prior to the initiation of first into man studies
- Experiments in vitro should be conducted at concentrations similar to the relevant concentration in vivo



Reasons for conducting as early as possible metabolism studies in vitro

- To identify all of the major metabolic pathways that affect the drug and its metabolites, including the specific enzymes responsible for elimination and the intermediates formed
- To explore the effects of the test drug on the metabolism of other drugs (“CYP cocktail studies”) and the effects of the other drugs on its metabolism. Pharmacological effects should also be studied if feasible





Assessing the metabolism of a drug in vitro :

Identify the critical metabolic pathways and metabolites that are formed by these pathways

- Human liver microsomes provide the most convenient way to study CYP450 metabolism
- The metabolic pathways for a new drug can be readily demonstrated with use of human liver microsomes (from several donors) combined with selective chemical inhibitors
- Use of recombinant human enzymes provides an excellent way to confirm results identified in microsomes
- Isolated hepatocytes and liver slices provides the most complete picture for hepatic metabolism
- Do not forget other hepatic enzymes (acetylation, glucuronidation), gastrointestinal drug metabolism (CYP3A4) and carrier-mediated transport system (P-glycoprotein...)

Metabolic interaction: in vitro studies

- In vitro data should mainly be used qualitatively
- If no interaction is detected in vitro, there is no need to perform an in vivo study. However if a claim of “no clinically relevant interaction with drug X” is desired in the labeling, confirmatory data in vivo needs to be provided
- If an interaction is present in vitro, an in vivo study should be conducted whenever possible to assess the extent of the interaction or a warning statement will appear in the labeling



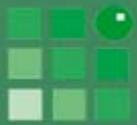
Metabolic induction

- Clinically relevant induction occurs during multiple dosing of the inducing drug and is a dose and time dependent phenomenon
 - Decide if the relevant enzyme(s), is (are) inducible or not
 - Time is required for the onset and offset of induction (2 to 3 weeks)
 - When metabolites are pharmacologically active, it should be remembered that the introduction of an inducer may result in an increase in the concentration of the metabolites, possibly resulting in an increased effect
 - The clinical effects of induction might be more serious when the inducer is abruptly withdrawn
 - Many dietary and social habits such as charcoal grilled meat or smoking or chronic alcohol use may induce drug metabolism
- 

Metabolic induction

- Exposure to an enzyme inducing agent during chronic drug administration may lead to a loss of drug efficacy because of increase drug clearance
 - Doubling of the dose is required if a pathway is induced threefold only if that pathway initially accounted for 50% or more of total drug clearance
 - In the most common case, in which the clearance associated with a particular pathway is only 20% of total clearance, then more than a six-fold induction would be required to necessitate altering the dose
 - Moreover, a need to change the dose is not anticipated even if metabolic clearance increased 20-fold if this clearance usually only contributes about 1%





Inducers

CYP1A2

Omeprazole, lansoprazole

Ritonavir

Cigarette smoke

Charcoal-broiled meat

Cruciferous vegetables

CYP2A6

Barbiturates

CYP2B

Phenobarbital, Phenytoin

Steroids (dexamethazone)

Clofibrate

CYP2C

Phenobarbital, Phenytoin

Rifampicin (2C19)

Steroids (prednisone, norethindrone)

Ritonavir

CYP2D6

Not known

CYP2E1

Ethanol (chronic use)

Isoniazid

Imidazole and derivatives

Clofibrate

CYP3A

Rifampicin (3A4)

Phenytoin, phenobarbital, carbamazepine

Steroids (dexamethazone, methylprednisolone, cortisol, estrogens, progestins)

Erythromycin

Omeprazole, lansoprazole

CYP4A

Ritonavir

Clofibrate



Metabolic inhibition

- Inhibition is a dose-dependent phenomenon but in contrast to induction, clinically relevant inhibition can occur quickly (even after a single dose). In inhibition processes, both the oxidative, the hydrolytic and conjugation pathways may be involved, inhibition of the oxidative enzymes being clinically the most common.
 - Most inhibition is competitive and disappears rapidly as soon as the inhibitor is eliminated or decreases after the dose is reduced
 - In contrast to induction, inhibition is often enzyme specific
 - When metabolites are pharmacologically active, it should be remembered that the introduction of an inhibitor may result in a decrease in the concentration of the active metabolites, thereby possibly reducing their effect
 - Some dietary constituents are known inhibitors of specific drug metabolism enzymes, e.g. grapefruit juice (CYP3A4)

Inhibitors

<p>CYP1A2</p>	<p>Fluvoxamine Quinolones (ciprofloxacin ...) Mexiletine Cimetidine Erythromycin Zafirlukast</p>	<p>CYP3A4</p>	<p>Ketoconazole, itraconazole Erythromycin (troleandomycin ...) Cimetidine Fluoxetine, nefazodone Diltiazem Estrogengestoden Zafirlukast Ritonavir, Indinavir, nelfinavir, saquinavir Grapefruit juice</p>
<p>CYP2D6</p>	<p>Quinidine, ajmaline, flecainide Cimetidine Antidepressants :SSRI (fluoxetine, paroxetine, sertraline) IMAO-A (moclobemide), tricycliques (imipramine...) Neuroleptics (thiorizadine, levopromazine , haloperidol, fluphenazine, chlorpromazine) Diphehydramine Dextropropoxyphene Ritonavir</p>	<p>CYP2E1</p>	<p>Ethanol (acute) Disulfiram</p>
<p>CYP2C</p>	<p>Cimetidine Omeprazole Fluoxetine , fluvoxamine Ritonavir Statins (fluvastatin) Ketoconazole/fluconazole Sulfaphenazole Sulfinpyrazone Zarfirlukast</p>		



- The clinical effect of a drug-drug interaction depends on the activity of the isozyme involved in a given individual : interactions is most unlikely in poor and ultrarapid metabolizers and is greatest in those with an intermediate functional catalytic capacity (heterozygous extensive metabolizers)
- This phenotype dependent susceptibility to drug interactions is important when evaluating data generated in different ethnic groups. There is also significant inter ethnic differences in the variability in drug metabolizing enzymes



Inter ethnic differences in polymorphic drug metabolism :

Percentage of poor/slow metabolizers

	CYP-oxidation		N- acetylation
	Sparteine debrisoquine (2D6)	S- mephenytoin (2C19)	Isoniazide sulfamethazine
Caucasoids	5-10	2-5	50-70
Mongoloids	1-2	18-23	10-20
Negroids	1-8*	2-6**	40-60
Arabs	1-2	1-2	60-90

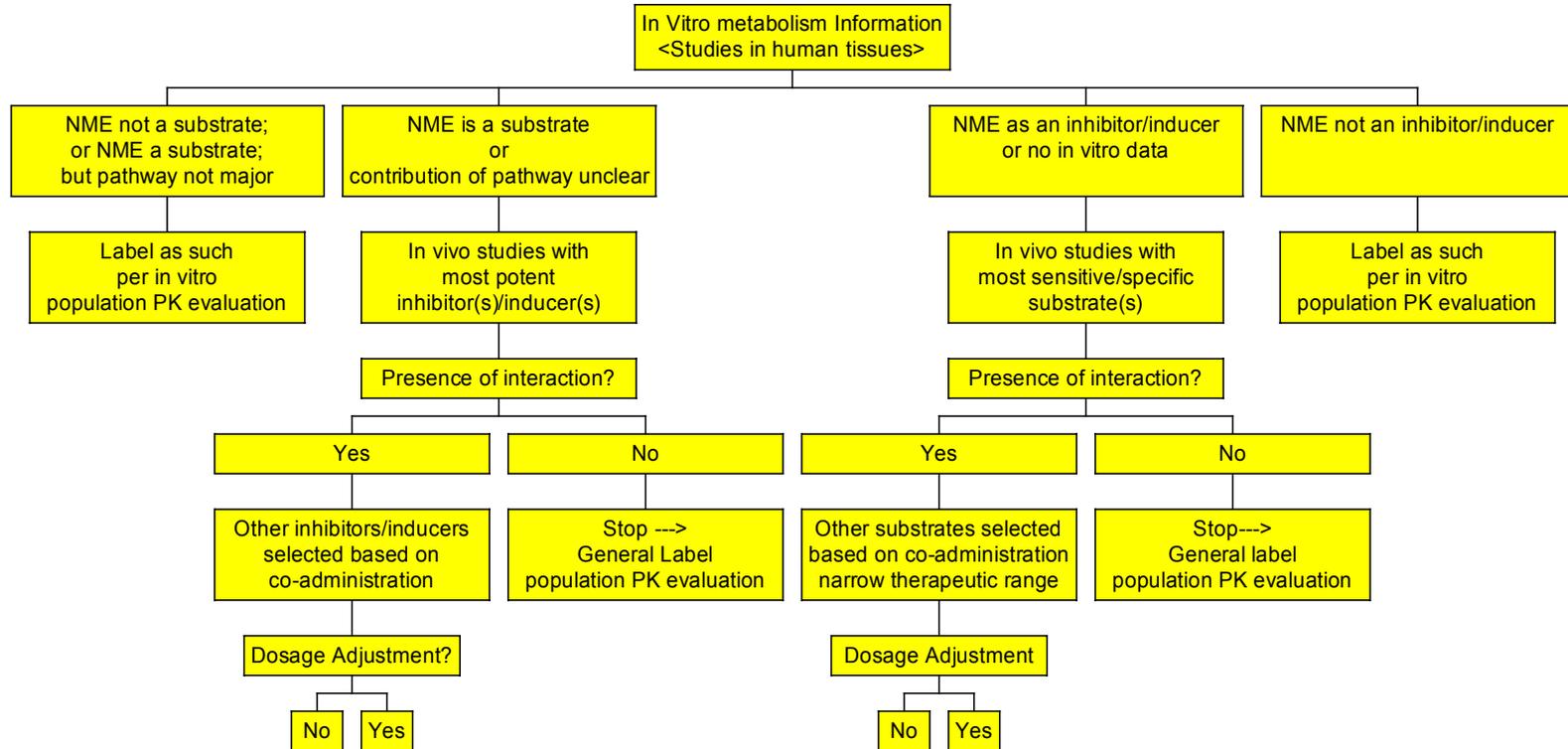
* Discordance between sparteine and debrisoquine

** No clear bimodality (poor metabolizers defined as S/R > 0.9)



Algorithm for evaluating drug-drug interactions

Chart Title



•NME, New molecular entities; PK, pharmacokinetic. (From Huang SM, Lesko LJ, Williams RL. Assessment of the quality and quantity of drug-drug interaction studies in recent NDA submissions: study design and data analysis issues. J Clin Pharmacol 1999;39:1006-14).



Experimental design

- 2x2 factorial plan : randomized, double-blind, 4-way crossover, placebo-controlled design. The only way to demonstrate a statistically significant interaction on clinical and pharmacodynamic endpoints i.e. :
 - ✦ potentiation $[(A+B) + (PLaA+PLaB)] > [(A+PLaB) + (B+PLaA)]$
 - ✦ antagonism $[(A+B) + (PLaA+PLaB)] < [(A+PLaB) + (B+PLaA)]$
- Double-blind or open, 2-way crossover design : to assess the effect of one drug (e.g. CYP inhibitor/inducer) on the other
- Open, 3-way crossover design : to assess the reciprocal pharmacokinetic interaction of both drugs

- **Sufficient time must be allowed to reach a pharmacokinetic and pharmacodynamic steady-state. To provide adequate dosage recommendations to the prescriber, the off-set of induction may be important to study as well**
- **In order to reduce variability, a cross-over design is usually appropriate. Other designs may be chosen in specific situations, but should be justified in the study protocol**



- In studies involving simple induction or inhibition, it may be adequate to investigate the effect of one drug on the pharmacokinetics of the drug in question (2-way crossover)
 - **However**, when the two drugs are substrates of the same enzyme, it is important to investigate the pharmacokinetics of both the drugs administered singly and in combination to the same cohort in order to evaluate the effect of each drug on the other (3-way crossover). The sequence of administration of both drugs also needs to be considered
- 

Study Design to Determine if a New Molecular Entity (NME) is an Inhibitor or Inducer of a Specific CYP Enzyme

Order of Drug Administration and Data Collected

Dose

1. Administer probe substrate as a SD regimen, and collect pharmacokinetic (PK) information.

1. Safe and well tolerated with minimal pharmacodynamic effects, allowing for adequate sensitivity in detecting effects on the activity of the relevant CYP pathway; common referenced doses.

2. Administer NME as a MD^c regimen until steady state is achieved (for inhibition) or at least 5 days for induction to occur (this may extend to 10-14 days, depending on the properties of the NME).

2. For inhibition and induction: highest approved dose (or highest in clinical development).^d

3. Administer probe compound as a SD + NME on the last few days (\approx 5 half-lives of NME) or last day (if half-lives of the two compounds are similar); collect PK information for the probe.

3. Same as in (1). Dosing of the NME should continue until the PK information of the probe is collected.

- This type of induction study is not mandatory; in particular, if the NME is both a substrate and an inducer of a given CYP pathway, evidence of autoinduction from a multiple oral dose study may be efficient.
- SD, single dose (e.g., oral midazolam for CYP3A. If the NME is an inhibitor or inducer of several CYPs, it is possible to combine several probe substrates in a cocktail to reduce the studies.
- MD, multiple dosing. Multiple dosing may be especially needed if a metabolite of the NME is a CYP inhibitor or if there is dose accumulation (e.g., >2-fold) with NME multiple dosing.

If the NME has a potentially narrow therapeutic index, then a low but clinically relevant dose may be appropriate.





Recommended in vivo probe substrates

for CYPs (Tucker, Houston, and Huang. Clin Pharmacol Ther
2001; 70: 103-114)

<i>CYP</i>	<i>Probe substrate</i>	<i>Comments</i>
1A2	Caffeine	Alternative: Theophylline (clinical relevance, but concern about selectivity?)
2B6	Bupropion	More validation required
2C8	Unclear	Paclitaxel cannot be given to healthy subjects
2C9	Tolbutamide	Alternatives: Flurbiprofen, diclofenac, phenytoin, warfarin (all relevant; safety issue with warfarin?)
2C19	Mephenytoin	Availability?
	Omeprazole	Potential contamination from 3A4 pathway?
2D6	Debrisoquine	Availability? Alternatives: Dextromethorphan (urine pH-dependent renal excretion; potential contamination from downstream 3A4 pathway?); metoprolol (urine pH-dependent renal excretion); desipramine (clinical relevant)
2E1	Chlorzoxazone	
3A4	Midazolam (oral)	Not selective for 3A4 versus 3A5
	Midazolam (oral and intravenous)	Separates liver versus gut contributions; need for stable-isotope labeling for concurrent oral and intravenous administration; staggered oral and intravenous dosing may avoid use of labeled drug?
	Midazolam (oral) +erythromycin (intravenous)	Liver versus gut; erythromycin marks 3A4 preferentially to 3A5, but precise mechanistic interpretation is confounded by P-glycoprotein transport, and use of radioactive compound (breast test) may be an issue in some countries
	Simvastatin or atorvastatin	Availability of metabolite standards





Study Design to Determine if a CYP Inhibitor or Inducer (Marketed Drug) Would Affect the PK of a NME

Order of Drug Administration and Data Collected	Dose
1. Administer NME as a single-dose (SD) regimen and collect PK information.	1. Standard therapeutic dose or highest dose used in development.
2. Administer the know CYP inhibitor ^a or inducer as a multiple-dose regimen until steady state is achieved or maximal induction has occurred.	2. Recommended highest dosage regimen.
3. Administer a SD of the NME + known inducer or inhibitor and collect PK information of the NME (and, perhaps, of major active metabolites).	3. Same as in (1). Dosing of CYP inhibitor or inducer should continue until the PK of NME is collected

- It is possible that a single dose of the know inhibitor may be sufficient; in this case, a single-dose study in which the NME is given with and without the known CYP inhibitor with an appropriate washout period may be sufficient.



- Specific safety issues are possible that depend on achieving steady-state exposure of both compounds.
- The interaction is not strictly competitive; for example, mechanism-based or suicidal inhibition occurs or may occur.
- A claim that widens the absolute bioequivalency criteria is desired.
- The time course of induction or inhibition needs to be determined.
- First-dose effects require titration to a standard steady-state dose for either compound.
- One drug shows a significant accumulation ratio, and a single-dose regimen that achieves comparable steady-state concentrations is not feasible.
- One of the drugs at steady-state concentrations forms a metabolite that produces additive induction or inhibition, which cannot be demonstrated through the administration of larger single doses.
- Dose-dependent or time-dependent pharmacokinetics (e.g., phenytoin or omeprazole, respectively), leading to at least a 50% to 100% accumulation of parent.



Population studied

Healthy volunteers

Patients

Advantages

- Controlled environment
- **Short duration to conduct study**
- **Easy to perform (use of placebo, wash-out possible, factorial plan, blood samples)**
- Mechanism of the interaction easy to demonstrate

- **Pragmatic situation**
- **Possibly better sensitivity**
- **may allow to study some pharmacodynamic endpoints not present in healthy subjects**

Disadvantages

- **Situation different from physiopathologic patient condition**
- **Sometimes lower sensitivity**

- **Environment more difficult to manage**
- Concomitant diseases
- Concomitant medications
- **Sometimes placebo treatment and wash-out periods impossible**
- **Difficult to collect many blood samples**
- **Mechanism difficult to assess**
- **Long duration to conduct the study due to patient recruitment**

Subjects

- Most of the time in vivo pharmacokinetic interaction studies could be performed in healthy volunteers, while in vivo pharmacodynamic interaction studies may be performed in patients or healthy volunteers depending on the situation and the pharmacodynamic effect measured. Disease-related interactions should always be considered.
- Subjects participating in metabolic in vivo interaction studies should be appropriately genotyped and/or phenotyped if any of the active enzymes mediating the metabolism are polymorphically distributed in the population. In some cases, clinically relevant interactions may only occur in a subset of the total population, for instance, slow-metabolizers, when an alternative route of metabolism is inhibited.



- Testing should maximize the possibility of finding an interaction
- Choice of the dose:
 - if the question is the effect of a specific drug: approved therapeutic regimen
 - if it is the effect of inhibition/induction: doses higher than approved therapeutic regimen may be necessary to obtain a full inhibitory or inducing effect
- Choice of the respective timing of each of the drugs:
 - concomitant administration
 - staggered to obtain peak concentration/effect at the same time

Treatment: dosage regimen

- Single dose
 - pharmacokinetic interaction at the level of absorption or elimination or competitive inhibition
 - pharmacodynamic interaction with concentration related effects (warfarin, alcohol) or when tolerance develops after repeated dose (benzodiazepine, alcohol)
- Multiple dose to achieve steady state conditions, recommended whenever possible
 - induction need enzyme synthesis : 2 to 3 weeks.
 - better prediction



Treatment: Dosage regimen

- ***What is the question - The effect of inhibition /induction, or, the effect of a specific drug?***
 - If it is the effect of inhibition/induction, then the pharmacokinetic parameters of the inducer or the inhibitor should be carefully considered and steady state conditions be achieved whenever possible. Approved therapeutic dose regimen for the selected inhibitor or inducer may not be optimal to obtain a full inhibitory or inducing effect. The number of daily doses may have to be increased to ensure inhibition/induction over 24 hours. Similarly, the duration of pre-treatment with an inducer should be sufficient to maximize the influence on the metabolic system (1-3 sem).
 - If it concerns the effect of a specific drug, then that drug approved therapeutic regimen should be used.

Assessment criteria

- The aim is to identify clinically significant interactions.
- Thus there is a need to provide clinical (adverse events) and pharmacodynamic parameters when available (CNS drugs: psychomotor and cognitive performance tests ; cardiovascular: BP, HR, ECG intervals ; hemostatis: aPTT, INR, platelet aggregation)
- Always combined with pharmacokinetic profile (AUC, Cmax)
 - ✦ to determine
 - the mechanism of the interaction
 - the clinical relevance of the interaction



■ Pharmacokinetics

It seems reasonable to focus on the exposure of the drug, AUC and the two variables determining this, i.e. extent of absorption, and clearance. Other parameters may also be of importance such as C_{max} and $t_{1/2}$ especially if the safety issue is dependent on the pharmacological action of the product



Pharmacokinetic parameters

- Results should be reported as 90% confidence intervals. CI provides an estimate of the distribution of the observed systemic exposure and convey a probability of the magnitude of the interaction
- When considering potential therapeutic consequences of an interaction (dosage reduction or increase), the acceptance range to conclude lack of interaction may be wider (or narrower) than the interval of 80% to 125% commonly used in establishing bioequivalence
- Always consider the therapeutic index and clinical consequences
 - ✦ weak interaction: 20-50% change
 - ✦ moderate interaction: 50-150% change
 - ✦ large interaction: > 150% change



When performing drug-drug interaction

- In the pre-clinical evaluation:
 - It should be possible to identify, prior to entry-into-man, the major routes of metabolism and excretion, and the effects on cytochrome P450 enzymes (with in vitro human liver cell cultures) and transporters
 - Thus many potential drug-drug interactions should be known prior to entry-into-man



When performing drug-drug interactions ?

- During Phase I, this is an opportunity to :
 - ✦ quantify the human in vivo interactions identified in pre-clinical studies
 - ✦ investigate potentially important interactions with likely co-administered compounds necessary to safely conduct Phase II (e.g. tyramine interaction with MAO-inhibitors)
 - ✦ perform food interaction



When performing drug-drug interactions ?

- During Phase II, this is an opportunity to :
 - ✦ conduct most interaction studies, to ensure that there are no co-medication restrictions in Phase III trials. This will speed-up Phase III by improving knowledge of the safety margin and by facilitating patients recruitment.
 - ✦ keep interaction studies off the critical path
 - ✦ make the drug more attractive to potential licensing/marketing partner



When performing drug-drug interactions ?

- During Phase III, this is an opportunity to :
 - ✦ search for unexpected adverse interactions
 - ✦ use population pharmacokinetics to quantify any interactions with common co-medication
 - ✦ perform clinical pharmacology studies to demonstrate a lack of interactions seen with potential competitors or drugs in the same class using the final formulation and therapeutic dosage regimen



When performing drug-drug interactions ?

- During Phase IV, this is an opportunity to :
 - ✦ conduct studies to remove/reduce the impact of Warning/ Precaution/ Contra-indication statements in the data sheet
 - ✦ allow marketing to sponsor small studies with local opinion leaders
 - ✦ investigate any potential adverse/beneficial interactions with new drugs
 - ✦ quantitatively compare drug with competitors



Conclusion

- More rational characterization of the interaction potential for new drugs
- In vitro data are now essential (part of the submission) but give valuable information mainly for PK/metabolic interactions at CYP level
 - if no interaction in vitro: in vivo human study may not be necessary
 - if interaction present in vitro: need in vivo confirmation, otherwise warning statement
- Pharmacodynamic interactions remain an important area of study in man



Conclusion

- Even very extensive preclinical tests and pharmacological studies in human volunteers and patients cannot exclude with absolute certainty a rare unexpected severe adverse event
- The fact that no severe interaction problems were observed in patients under concomitant drugs in clinical trials does not exclude the possibility of rare serious interactions in some patients and cannot therefore serve as a substitute for careful evaluation of the interaction potential based on the results of the PK studies



Conclusion

- For drugs that are expected to be co-administered with target population and that may represent a particular risk (high first-pass metabolism, narrow therapeutic range, potential for pharmacodynamic interactions), a labeling in the product information indicating the possibility of an interaction should not be acceptable as a substitute for performing the appropriate studies before introduction into clinical practice



Warfarin-drug interaction

- Stereoselective metabolism of Warfarin
- S-warfarin :
 - ✦ CYP2C9 is mainly responsible for the transformation of the active anticoagulant S-warfarin (85%) in its inactive 7-and-6-hydroxy-metabolites
 - ✦ CYP1A2 and CYP3A4 : may contribute
 - ✦ Half-live of 49 hours
- R-warfarin :
 - ✦ CYP1A1 and 1A2 : hydroxylation
 - ✦ CYP3A4 : may contribute
 - ✦ Half-live of 32 hours



Warfarin-drug interaction : study design

- Randomized, double-blind, 2-way crossover, placebo controlled study :
 - ✦ Placebo + Warfarin
 - ✦ Drug + Warfarin
 - Subjects : 12 subjects
 - Drugs :
 - ✦ Warfarin (racemic) : single dose of 25 mg
 - ✦ Study drug : usually multiple doses up to steady-state
 - Assessment criteria :
 - ✦ Pharmacokinetics of both enantiomers of Warfarin up to 168h post-dose
 - ✦ Pharmacodynamics : time course of prothrombin time (or INR) up to 168h post-dose . Calculation of t_{max} , E_{max} , AUCPT
 - Statistical analysis :
 - ✦ ANOVA
 - ✦ 90% confidence interval
- 
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Drug-digoxin interactions

■ Mechanism

❖ Pharmacokinetic interactions :

- inhibition of digoxin absorption (eg: antacids, activated charcoal, metoclopramide, dietary bran fibre, antimicrobials, cancer chemotherapeutic agents, antidiarrhoeals, cholestyramine....)
- inhibition of digoxin renal excretion (active tubular secretion) by inhibiting P-Glycoprotein (PGP)
 - quinidine
 - is a PGP inhibitor
 - inhibition of PGP in the renal tubule decreases digoxin elimination
 - inhibition of PGP in the intestine increases digoxin absorption
 - spironolactone
 - decreases renal clearance by inhibiting renal tubular secretion of digoxin

- Pharmacodynamic interactions :

- ❖ diuretics cause potassium depletion and predisposes to digitalis toxicity
- ❖ beta-blocking drugs potentiate sinus node dysfunction and atrio-ventricular nodal conduction abnormalities induced by digitalis

- Subjects : 12 to 18 healthy subjects
- Study design :
 - Open non-randomized : 3 -way crossover design
 - Drug A alone (single dose or multiple doses until steady-state)
 - Digoxin alone : usually multiple doses (loading dose of 0.5 mg BID on D1, 0.25 mg BID on D2 and then daily doses of 0.25 mg) for 8 to 10 days (until steady-state)
 - Immediately followed by digoxin (same regimen as previous) + drug A (single dose or multiple doses)
 - Assess the interaction of drug A on digoxin and of digoxin on drug A



Drug-digoxin interactions: Assessment criteria

- Randomized, open or double-blind, 2-way crossover design:
 - ❖ Digoxin-multiple doses for 8 to 10 days up to steady state (loading dose: 0.5 mg BID on D1, 0.25 mg BID on D2 and then 0.250 to 0.375 mg QD) [+ placebo (optional)]
 - ❖ Wash-out period of 8 days
 - ❖ Digoxin (same regimen as previous) + drug A (multiple doses) for 8 daysassess the interaction of drug A on digoxin
- Randomized, double-blind, 3 to 4-way crossover design:
 - ❖ Drug A alone (multiple doses)
 - ❖ Digoxin + placebo (multiple doses for 1 week)
 - ❖ Digoxin + drug A (multiple doses for 1 week)
 - ❖ Placebo (multiple doses) (optional)
 - with wash-out periods of 8 daysassess the interaction of drug A on digoxin and digoxin on drug A

Drug-digoxin interactions: Assessment criteria

■ Pharmacokinetics :

- Drug X : blood and urine concentrations
- Digoxin : blood and urine concentrations

■ Safety :

- Adverse events and particularly signs of digoxin toxicity (nausea, vomiting, blurred vision, abnormal color vision)
- ECG (looking for decrease HR, increase PR, AV block, atrial arrhythmia or ventricular ectopy ...)
- On-line digoxin assay
- Routine laboratory test (potassium)



Grapefruit juice - drug interactions

- Grapefruit juice can't markedly augment oral drug bioavailability by reducing presystemic metabolism through selective down regulation of CYP3A4 expression in the intestinal wall (62% after 5 days)
The effect may occur after a single glass and may last 24 hours
- Type and amount of grapefruit juice as well as duration of its use can have significant effect on the magnitude of the interaction
- There is a substantial interindividual variability. Individuals with highest baseline CYP3A4 had the highest proportional increase
- P-glycoprotein is a transmembrane protein involved in drug efflux from the enterocyte back into the intestinal lumen. Grapefruit juice also significantly stimulates P-glycoprotein mediated secretory efflux of drugs that are substrates of both CYP3A4 and P-glycoprotein, thereby partially counteracting the CYP3A4 inhibitory effects. (Soldner et al, CPT, 1999, 65, 205)

Terfenadine-ketoconazole interaction (Honig et al JAMA 1993 269: 1513-18)

- Design: Open, 2-way crossover design; not randomized; not placebo-controlled
- Subjects: 6 healthy subjects of both genders
- Treatment:
 - Terfenadine 60 mg BID from D1 to D14 and QD on D15
 - Ketoconazole 200 mg BID from D9 to D14 and QD on D15
- Assessment criteria:
 - Pharmacokinetics: terfenadine and its active metabolite either at steady state (D8 or D15)
 - Pharmacodynamics: QT/QTc interval
 - ✦ Baseline and trough levels (before dosing) from D8 to D15

