Q-DIPS: COMPUTER-BASED PREDICTION OF KNOWN AND POTENTIAL DRUG METABOLISM INTERACTIONS

P. Bonnabry, J. Sievering, T. Leemann, P. Dayer

Laboratory of Computer Assisted Therapeutics
Clinical Pharmacology and Pharmacy
University Hospital, Geneva, Switzerland
ABSTRACT

Drug metabolism interactions are and will probably remain difficult to predict for clinicians. To help improve their management, we have developed an «expert» computer application: Q-DIPS (Quantitative Drug Interactions Prediction System).

Q-DIPS gives extensive information, in dynamic tables, on which specific isozymes metabolize a given drug, or may be inhibited or induced by it. Quantitative models are being integrated to predict, on the basis of enzymatic, pharmacokinetic and demographic data, the impact of drug treatments on specific isozyme activities and its consequences on concomittently administered drugs. Individual patient situations are easily simulated. Dynamic graphs are used thoughout and references to all information, original and derived, is accessible from any view.

Results from experimental and clinical validation studies involving P450’s are encouraging and Q-DIPS shows promising potential to help improve the management of drug metabolism interactions by the non-specialist.

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Drug interactions are a major source of clinical problems.

Among mechanisms potentially leading to such problems, metabolism by cytochromes P450 is by far the most important.

Owing to the complexity of interactions between drugs and specific isozymes, the occurrence of such interactions is often difficult to predict for clinicians, both qualitatively and quantitatively.
GOAL

To develop an interactive digital workbench, Q-DIPS (Quantitative Drug Interactions Prediction System), supporting:

- the systematic collection of literature data on interactions between drugs and cytochromes P450
- the systematic exploration of predictive models of drug interactions
- the validation of the in vitro / in vivo modelling approach developed in our laboratory
- the operational use of validated models in the clinical context
Q-DIPS: MAJOR FUNCTIONALITIES

- Qualitative and quantitative information on substrates, inhibitors and inducers of specific cytochromes P450 isozymes, in dynamic tables
- Rapid visualization of the risk associated with a given combination of drugs (Clinical case)
- Documentation of each given information and rapid access to the whole library content
- Access by generic names, ATC classification, or commercial names
- Quantitative prediction of in vivo drug interaction from in vitro data
# TABLE OF INTERACTIONS

The image shows a software interface with a table of interactions between various substances and enzymes. The table includes columns for substances such as 'disulfiram', 'erythromycin', 'fluconazole', 'fluoxetine', 'fluvoxamine', 'grapefruit', 'Indinavir', 'itraconazole', 'ketoconazole', 'méthadone', 'nifédipine', 'norfloxacine', 'oméprazole', 'paroxétine', 'phénylbutazone', 'quinidine', 'quinine', 'ritonavir', 'roxithromycine', and 'saquinavir'. The rows represent different enzymes and conditions, with colors indicating the interaction strength or presence. The software window includes options for selecting 'Enzyme(s)' and 'Seuil', which likely control the display of interactions or thresholds for interaction strength.
## Clinical Case

### Substrates

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### Inhibitors

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### Medications

- Ciclosporine
- Imipramine
- Ketoconazole
- Methadone
- Rifampicin

### Tableau Résultant des Choix pour un Cas Clinique

| Enzyme(s) | Annuler |

### Sélection des Substances

- Ciclosporine
- Imipramine
- Ketoconazole
- Methadone
- Rifampicin

### Liste des Choix des Substances

- Imipramine
  - guanfacine
  - haloperidol
  - halothane
  - buprenorphine
  - indinavir
ATC CLASSIFICATION

[Image of a computer screen displaying the ATC classification system with code numbers and substance names.]
Le kétoconazole est un puissant inhibiteur in vitro de l'oxydation de la ciclosporine (Ki=0,022 microM), un marqueur de l'activité du CYP3A4, ce qui confirme les données d'interactions observées in vivo.

L'itraconazole inhibe également fortement le CYP3A4 (Ki=0,7 microM), tandis que le fluconazole est un inhibiteur plus modéré (Ki=40 microM). Pour ces deux dérivés azolés, des interactions avec la ciclosporine ont été décrites in vivo, mais des données contradictoires suggèrent un effet dose-dépendant.

L'itraconazole, finalement, n'inhibe pas significativement l'activité du CYP3A4 in vitro, ce qui confirme l'absence d'interaction avec la ciclosporine rapportée in vivo.
**DOCUMENTATION: DETAILS**

**In vitro**

- **Substance**: kétoconazole
- **Enzyme**: CYP3A4

**Substrat**

- Est inhibé par
- N'est pas inhibé par
- Non documenté

**Substrat test**: ciclosporine
- Ki: 0.022 uM
- IC50: 0.24 uM

**Inhibition par les métabolites**

- Métabolite: [empty]
- Ki: 0 uM

**Type d'inhibition**

- Compétitif
- Non-compétitif
- Mixte
- Non-déterminé
- Irréversible

**Outils d'étude**

- Tranches d'organes
- Hepatocytes
- Fractions subcellulaires
- Systèmes d'expression
- Autre

**Nombre**: 3
Knowledge is required about:

- relevant enzymes (allelic forms) and their demographics
- substrates of specific enzymes
- inhibitors (isomers, metabolites) of specific enzymes
- inhibitor / substrate concentrations at enzyme site
- inhibition mechanism
- role of specific enzymes in substrate's pharmacokinetics
- substrate's pharmacokinetics-pharmacodynamics relationship
SIMPLEST CASE ASSUMPTIONS

- **free concentrations** drive metabolism and inhibition
- free drug concentrations in **liver and blood** are identical
- inhibition is **reversible**
- inhibitor's **metabolites** are not themselves inhibitors
- substrate has a **low extraction ratio**
- substrate elimination kinetics are **linear**
- substrate elimination is controlled by a **single enzyme**

These assumptions can be relaxed for specific cases, but the prediction model must be modified.
**IN VIVO EFFECT OF INHIBITOR**

This *Inhibition Index* ($I_I$) presents interesting features:

- it is characteristic of a given enzyme/inhibitor pair
  - it is independant from substrate
  - it is identical for all substrates of a given enzyme
- the kinetics of a drug's Inhibition Index can be simulated

\[ I_I = 1 + \frac{f_u \cdot I_{pl}}{K_i} \]

\[ I_I = 1 + \frac{\alpha \cdot f_u \cdot I_{pl}}{K_i} \]

$I_{pl}$: inhibitor total concentration in plasma

$\alpha$: intrahepatocyte/plasma free concentration

$f_u$: fraction unbound in plasma

**Simplest case model**

**Accumulation model**
The impact of an inhibitor on a substrate's pharmacokinetics can be estimated as:

\[
CL_{[I]} = \frac{CL}{I_I}
\]

\[
t_{1/2[I]} = t_{1/2} \cdot I_I
\]

\[
C_{ss[I]} = C_{ss} \cdot I_I
\]
Validation of predictions is actually necessary to progressively improve their reliability.

Major sources of uncertainty are the following:

- Concentrations of drugs at enzyme site are difficult to evaluate; they could significantly differ from free plasma concentrations (Von Moltke LL, Biochem Pharmacol 1998; 55:113-22)
- Main parameters ($K_i$, $f_u$) are often poorly characterized for metabolites
- Quality of published inhibition constant ($K_i$) and pharmacokinetic data ($f_u$ e.g.) is sometimes doubtful
EXEMPLE: ANTIFUNGALS / CYP3A4
CONCLUSIONS AND PERSPECTIVES

• Q-DIPS shows promising potential to help improve the management of drug metabolism interactions by the non-specialist

• Results from experimental and clinical validation studies of in vitro-in vivo predictions are encouraging

• Future developments will incorporate "intelligent" mechanisms (expert system) allowing questioning, automated deduction and individualized adaptive problem resolution