AFPC Conference 2009

InterMed-Rx : Harmony and optimal therapy in the use of medication

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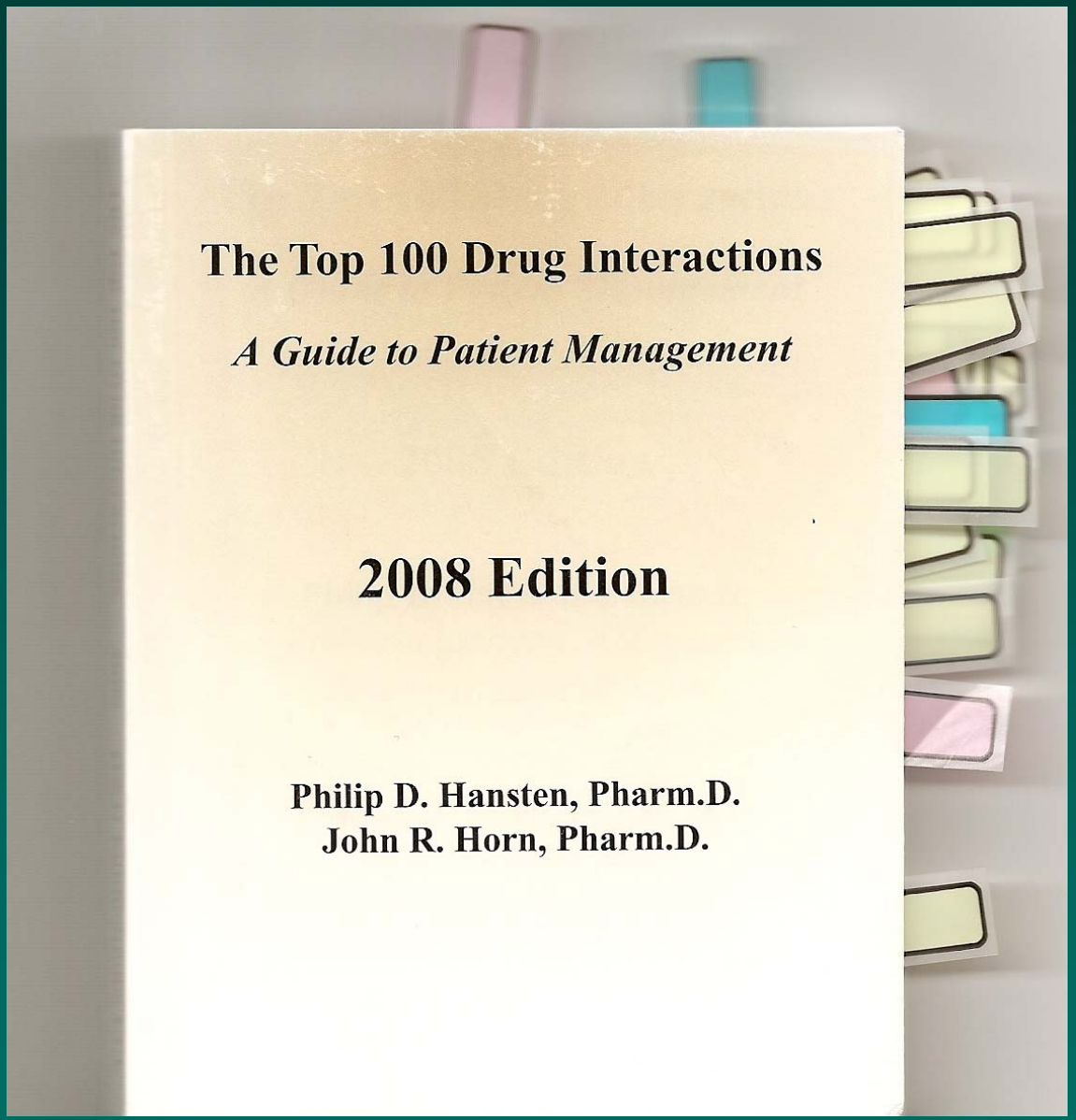
Conflict of interests

- Expert consultant:
  - Solvay
  - Abbott
  - Janssen Ortho
  - PharmaSciences
  - Bayer
- President et stock holder:
  - Intermed-Rx

Objectives

- To understand basic principles of drug-drug interactions in order to avoid misuse of drugs in multiple drug prescriptions especially, with regards to CYP450 substrates.
- To explain and predict the clinical relevance and consequences of drug-drug interactions.
- To present clinical tools that allow identification of relevant drug-drug interactions.

Most frequent drug-drug interactions



Most frequent drug-drug interactions

- Warfarin – aspirin – acetaminophen
- Resins and acidic products
  - NSAIDs, diuretics, warfarin, hypoglycemic agents
- Antiacids and antibiotics
- MAO inhibitors and SSRI
- Nitrates and .....afil (Viagra®, Levitra®, Cialis®)
- Thyroxin and antiacids and resins
- Potassium and ACE inhibitors
- Calcium et tetracyclines/quinolones
- β-blockers and hypoglycemic agents
- β-blockers and stimulants (ephedrine)
- Digoxin and Ca channel blockers and β-blockers
- Cytochromes P450

Three concepts to master

- Isoenzyme concepts
- Affinity concepts
- Oral clearance concepts

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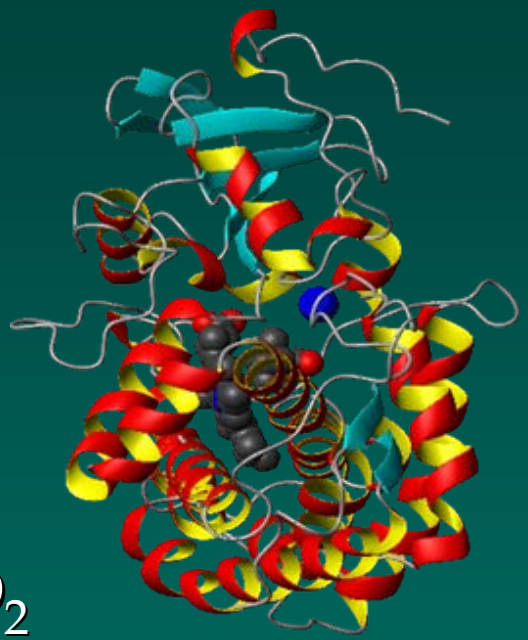
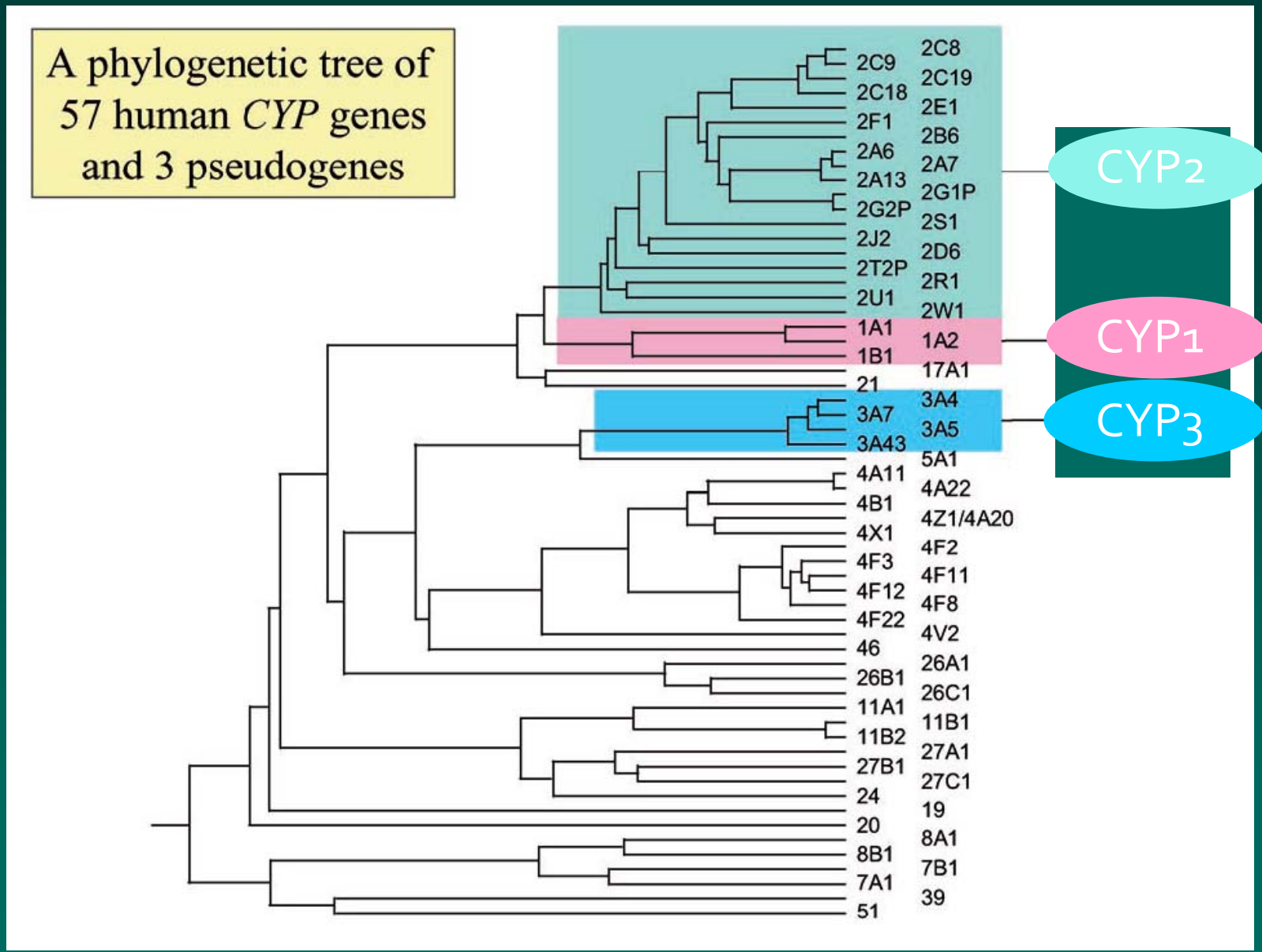
Cytochromes P450



Intersubject variability in drug response



Basic concepts in drug-drug interactions

CYP	Substrates	Inhibitors	Inducers
1A2	Theophylline, caffein, imipramine, mexiletine	Quinolones	Cigarette smoking
2A6	Coumarin, nicotine	Diethyldithiocar-bamate	
2C9	NSAID, losartan, irbesartan, S-warfarin, celecoxib	Sulfaphenazole	Rifampin
2C19	Omeprazole, R-warfarin		
2D6	Codein, antiarrhythmics, β-blockers, anti-H1, SSRI	Quinidine	
2E1	Alcohol, chlorzoxazone		Alcohol
3A4	CCB, anti-H1 2nd, BZD, cyclosporin, HMG CoA	Macrolides, imidazoles	Rifampin, phenytoin

Three concepts to master

- Isoenzyme concepts
- Affinity concepts
- Oral clearance concepts

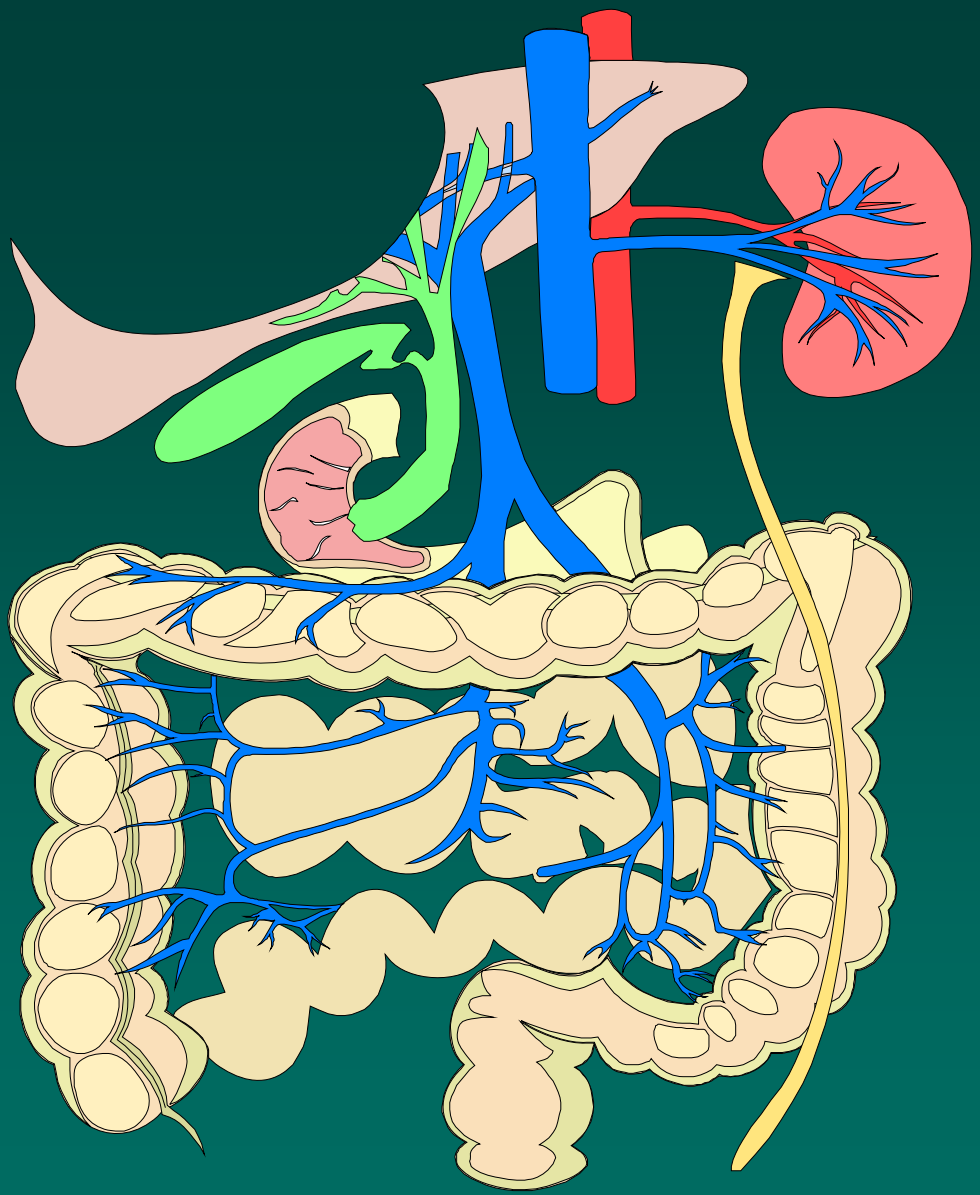
CYP2C9

Inhibitors	Substrates			Inducers
Fluconazole	Fluvastatin	Ibuprofene	Glyburide	Rifampin
Sulfaphenazole	S-warfarin	Diclofenac	Irbesartan	
Sulfinpyrazone	Celecoxib	Flurbiprofene	Losartan	
		Naproxene	Candesartan	
		Phenytoin		
		Tolbutamide		

Three concepts to master

- Isozenzyme concepts
- Affinity concepts
- Oral clearance concepts

Intersubject variability in drug response



Simvastatin has an oral bioavailability of 5%. By how much would its plasma concentrations raise during the co-administration of clarithromycine?

20 fois

Interactions between inhibitors and substrates of CYP3A4

- The coadministration of erythromycin, clarithromycin, ketoconazole, itraconazole
  - Simvastatine/lovastatine :
    - Cmax increases 5- à 20-fold
    - Rhabdomyolysis
  - Pravastatin, Cerivastatin, Fluvastatin, Atorvastatin
    - < 2-change increase in PK parameters
    - Rhabdomyolysis

Clin Pharmacol Ther 1998;64:177-182
Clin Pharmacol Ther 1996;60:54-61
Eur J Clin Pharmacol 1999;54:851-855
J Clin Pharmacol 1999;39:501-504
Transplantation 1996;15:1559-1564

Drug-drug interactions

Case #1

A 56 years old man has symptoms of depression and fatigue. He has known hypertension treated with hydrochlorothiazide 12,5 mg ID and metoprolol 100 mg BID. He has been started 5 days ago on paroxetine (Paxil®) 10 mg ID to improve its depression related symptoms. The patient complains that he is really tired, with no energy. His pulse rate is at 44 beats/min.

Drug-drug interaction softwares

1) Based on data bank and case reports
   a) Epocrates
   b) First Data Bank
   c) Vigilance Santé
   d) www.accp.com/p450.html
   e) www.tthhivclinic.com/interactions.htm
   f) www.fda.gov/oashi/aids/pitabv.html
   g) www.HIV.medscape.com/Medscape/HIVdDrugInteractions/index.html
   h) www.hopkins-aids.edu/geneva/hilites_flex_drug.html

2) Based on pharmacokinetics and drug metabolism algorithms
   a) Intermed-Rx.ca (www.Intermed-rx.ca)
   b) GeneMedRx (www.mhc.com/cytochromes/)
   c) www.dml.georgetown.edu/depts/pharmacology/clinlist.html

www.InterMed-Rx.ca

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InterMED-Rx

Harmony and Optimal Therapy in the use of Medication

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- P-450 Table

:: Forgotten password :: E-mail : Password : ENTER

WELCOME

The use of therapeutic regimes that rely on polypharmacy entail higher risks of drug interactions. Consequently, these interactions must be monitored more closely by health professionals.

The **InterMED-Rx.ca** Website provides health professionals with a user-friendly tool at the cutting edge of scientific knowledge. This site provides a better grasp of drug interactions related to the cytochrome P450 superfamily.

Jacques Turgeon, B.Pharm., Ph.D.

CYTOCHROME P-450 THEORETICAL NOTIONS

The cytochrome P450 is a superfamily of enzymes whose main role is to transform liposoluble substances into more hydrosoluble

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Isoenzymes	Inhibiteurs	Substrats			Inducteurs
CYP1A2	Anastrozole Ciprofloxacin Fluvoxamine Interferon alfa-2b Isoniazid Methoxsalen	Aromatic Amines Warfarin	Cinacalcet Clozapine Duloxetine Flutamide Mexiletine Olanzapine Rasagiline Tacrine Trifluoperazine	Acetaminophen Aminophylline Caffeine Clomipramine Dacarbazine Frovatriptan Imipramine Oxtriphylline Pentazocine Primaquine Ropinirole Theophylline Tizanidine Zolmitriptan	Charcoal cooking Cigarette smoking Mebendazole
CYP2B6	Delavirdine Orphenadrine Ticlopidine	Efavirenz Nelfinavir Ritonavir	Cyclophosphamide Ifosfamide Methadone Nevirapine	Bupropion Flunarizine Procarbazine Propofol	Dexamethasone Doxylamine Nevirapine Pentobarbital Phenobarbital Phenytoin Primidone Rifampicin Ritonavir
CYP2C8	Phenelzine Trimethoprime	Gemfibrozil	Loperamide Paclitaxel	Cerivastatin Chloroquine	Pentobarbital Phenobarbital


CYP2D6
Amiodarone
Chloroquine
Cinacalcet
Imatinib Mesylate
Methotrimeprazine
Orphenadrine
Propoxyphene
Quinidine
Terbinafine
Flecainide
Fluoxetine
Paroxetine
Propafenone
Thioridazine
Carvedilol
Chlorpromazine
Clemastine
Diphenhydramine
Doxepin
Duloxetine
Fluphenazine
Haloperidol
Maprotiline
Methadone
Metoclopramide
Metoprolol
Mexiletine
Propranolol
Risperidone
Tamoxifen
Amitriptyline
Amphetamine
Atomoxetine
Citalopram
Clomipramine
Codeine
Desipramine
Dextroamphetamine
Dextromethorphan
Dimenhydrinate
Dolasetron
Donepezil
Escitalopram
Flunarizine
Galantamine
Hydrocodone
Idarubicin
Imipramine
Mirtazapine
Nortriptyline
Ondansetron
Oxycodone
Procainamide
Pyrantel
Timolol
Tolterodine
Tramadol
Trimipramine
Venlafaxine
Zuclopenthixol

X	MÉDICAMENTS	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4
☑	Metoprolol						✓	
☑	Hydrochlorothiazide	NON P450*						

438 msec

-------- Medications ---------

Next Medication

In this section, the healthcare provider may enter the medications that make up the patients posological regime, one by one.

Medications available for interaction analysis can be found in the pulldown menu.

Inhibitor
Strong Sub.
Medium Sub.
Weak Sub.
Inducer

By clicking the «Next Medication» button, you may choose the next medication.

To delete a medication form the interactions table, un-check the checkbox to the left of the medication and click the «Next Medication» button.

When all medications are entered, you may click the «Interaction Analysis» button to launch the process that will identify possible interactions.

X	MÉDICAMENTS	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4
☑	Metoprolol						✓	
☑	Hydrochlorothiazide	NON P450*						
☑	Paxil						✓	

2734 msec

-------- Medications ---------

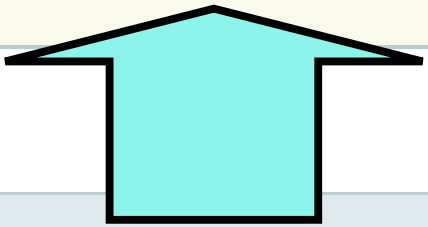
Next Medication

2-2 INTERACTIONS

Medication 1 : Metoprolol Dose : 100.00 mg 2 times daily

Medication 2 : Paxil Dose : 10.00 mg 1 time daily

Submit for analysis



ANALYSIS #1	P450
RESULT: These two substrates are metabolized by the same cytochrome P450 isoenzyme, namely : CYP2D6	
OPINION: Since Paxil demonstrates a greater affinity for CYP2D6, we should expect greater concentrations of Metoprolol . It would therefore be prudent to lower the dosage of Metoprolol .	

ARTICLES RETAINED FOR CYP2D6 AND METOPROLOL AND PAXIL
In vitro-in vivo extrapolation of CYP2D6 inactivation by paroxetine: prediction of nonstationary pharmacokinetics and drug interaction magnitude.
metabolism of metoprolol in human liver microsomes: inhibition by the selective uptake inhibitors.
Co-prescription of cytochrome P450 2D6/3A4 inhibitor-substrate pairs in clinical practice. A retrospective analysis of data from Norwegian primary pharmacies.
CYP2D6 genotype and phenotyping by determination of dextromethorphan and metabolites in serum of healthy controls and of patients under psychotropic medication.
Relationship of paroxetine disposition to metoprolol metabolic ratio and CYP2D6*10 genotype of Korean subjects.
Selecting an appropriate medication for treating neuropathic pain in patients with diabetes: a study using the U.K. and Germany mediplus databases.
Inhibition of metoprolol metabolism and potentiation of its effects by paroxetine in routinely treated patients with acute myocardial infarction (AMI).
Complete atrioventricular block associated with concomitant use of metoprolol and paroxetine.

1: Eur J Clin Pharmacol. 1998 May;54(3):261-4. Related Articles, Links

The oxidative metabolism of metoprolol in human liver microsomes: inhibition by the selective serotonin reuptake inhibitors.

Belpaire FM, Wijnant P, Temmerman A, Rasmussen BB, Brosen K.

Heymans Institute of Pharmacology, University of Gent Medical School, Belgium.
frans.belpaire@rug.ac.be

OBJECTIVE: Biotransformation of metoprolol to alpha-hydroxymetoprolol (HM) and O-demethylmetoprolol (ODM) is mediated by CYP2D6. The selective serotonin reuptake inhibitors (SSRIs) are known to inhibit CYP2D6. The aim was to study in vitro the potential inhibitory effect of SSRIs on metoprolol biotransformation. METHODS: Using microsomes from two human livers, biotransformation of metoprolol to alpha-hydroxymetoprolol (HM) and O-demethylmetoprolol (ODM) as a function of the concentrations of the SSRIs and of some of their metabolites was studied. RESULTS: The kinetics of the formation of both metabolites are best described by a biphasic enzyme model. The estimated values of Vmax and kM for the high affinity site are for the alpha-hydroxylation in human liver HL-1 32 pmol mg(-1) min(-1) and 75 micromol x l(-1) respectively, and in human liver HL-9 39 pmol mg(-1) x min(-1) and

Clinical Case #2

A patient complains of arthritis pain and her doctor prescribes celecoxib/Celebrex® 200 mg die.

Her pharmacological fil shows :
Metformine/Glucophage® 500 mg tid
Glyburide/Diabeta® 2.5 mg bid
Omeprazole/Losec® 20 mg die
Amitriptyline/Elavil 10 mg HS
Conjugated oestrogens/Premarin® 0.625 mg die
Calcium 500 mg bid

Upon her next visit to your pharmacy, the patient complains about flushing, weaknesses and drowsiness since few days. She is convinced that her hormonal drug has to be reviewed but she also mentioned that on occasion, her glycemia seems lower than previously. What pertinent drug-drug interaction can be unmasked?

Interactions médicamenteuses

X	MÉDICAMENTS	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4
☐	Metformine	NON P450						
☐	Diabeta				✓			
☐	Oméprazole					✓		
☐	Amitriptyline						✓	
☐	Premarin							✓

-------- Selectionner ---------

Autre médicament

Analyse des interactions

Interactions médicamenteuses

X	MÉDICAMENTS	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4
☐	Metformine	NON P450						
☐	Diabeta				✓			
☐	Oméprazole					✓		
☐	Amitriptyline						✓	
☐	Premarin							✓
☐	Celebrex				✓			

-------- Selectionner ---------

Autre médicament

Analyse des interactions

Interactions médicamenteuses

Clinical Case #3

A patient aged 41 years old a chronic pain since several years. She is followed by a chronic pain clinic and in psychiatry.

For her pain control, she receives :
Baclofen/Lioresal® 10 mg 4 co/day
Gabapentin/Neurontin® 300mg 15 caps/day
Mexiletine 100 mg 6 caps/day
Methadone 17.5 mg bid

For her mood, she receives :
Bupropion/Wellbutrin SR® 100 mg 3 co/day
Carbamazepine/Tegretol® 200 mg 3 co HS
Paroxetine/Paxil® 20 mg 2 co die
Clonazepam/Rivotril® 2 mg tid prn

What can be sais about drug-drug interactions in this patient?

Interactions médicamenteuses

X	MÉDICAMENTS	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4
☐	Tegretol							✓
☐	Rivotril							✓
☐	Méthadone		✓				✓	✓
☐	Mexilétine	✓					✓	
☐	Paxil						✓	
☐	Baclofène	NON P450						
☐	Neurontin	NON P450						
☐	Wellbutrin SR		✓					

-------- Selectionner ---------

Autre médicament

Analyse des interactions

Conclusions

- Clinical consensus and the availability of new classes of drugs are factors that contribute to the emergence of polypharmacy.

- Drug-drug interactions are no longer of the academic world. They can be understood, they can be predicted and they can be managed with tools that can support clinicians by providing new information.

References

- Hansten PD et Horn JR. The top 100 Drug interactions. 2008 edition. H&H Publications.
- www.intermed-rx.ca
- www.medicine.iupui.edu/flockhart/
- Drug interaction facts
- PubMed