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Taking drug–drug interactions into account: a monitoring platform

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Notes are linked to the references page.

According to the American Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER), the inappropriate use of drugs is, depending on the study, the fourth to sixth leading cause of death and is responsible for numerous hospitalisations and emergency department consultations[1]. Clinical decision support tools may be an effective way to personalise a treatment regimen and manage drug–drug interactions.

A BRIEF HISTORY OF DRUG USE

Until the 1980s, medicine was 'preferential', i.e. the prescriber preferentially prescribed drugs to his/her patients that they had experience with. Subsequently 'evidence-based medicine' demonstrated that patients had their own specific characteristics and that a tailored approach was required. Prescriptions were then based on the results of large clinical studies and on population algorithms. We are now in the era of 'precision' medicine in which patients are characterised particularly on a genetic basis in order to better select their treatment and the dose to be administered to them.

This era may already have passed and we now are entering the era of 'predictive' medicine. This uses clinical decision support tools and is based on large amounts of data from multiple sources, including electronic medical files, databases, pharmacometrics and system pharmacology and artificial intelligence.

ADVANCES IN OUR UNDERSTANDING OF THE MECHANISMS OF DRUG–DRUG INTERACTIONS

Studies have shown that 50% of patients who take five to nine drugs daily have major interactions and serious adverse events. This rises to 100% with three to four major adverse events if the treatment regimen includes 20 or more drugs[2,3].

Prevention of drug–drug interactions is, therefore, a major public health challenge. Our better understanding of the mechanisms involved now allows us to predict the number of drug–drug interactions and to adapt and personalise treatments.

The majority of drug–drug interactions involve cytochrome P450

Some drug–drug interactions are caused by physicochemical incompatibilities or synergistic or antagonistic effects. However, the majority (probably over 80%), involve the enzyme system responsible for their metabolism, cytochrome P450 (CYP450).

Cytochrome P450 is an enzyme superfamily

Fifty-seven CYP450 isoenzymes have been identified to date in humans. These contribute to both the biotransformation of endogenous and exogenous substances and to the production of endogenous compounds. The different isoenzymes are designated as follows: CYP3A4, CYP2D6, CYP1A2, etc.

Before we go in to further detail, the following definitions are pertinent:

- **A substrate** is a molecule with a degree of affinity for a protein, which results in its chemical transformation. A drug is a substrate of a CYP450 isoenzyme if the isoenzyme can convert this medicine into one of its metabolites.

- **An inducer** is a substance able to increase the activity of a CYP450. Typically, inducers increase the production of these enzymes and thereby increase their activity.

- **An inhibitor** is a substance able to reduce the activity of a CYP450 isoenzyme as a result of competitive (by binding to the enzyme, a substance prevents another substrate binding to it) or non-competitive inhibition (not preventing binding of the substrate to the enzyme; the inhibitor changes the conformation of the enzyme and therefore makes it non-functional).

Some CYP450 are genetically determined and may be absent in a proportion of the population. For example, the genetic polymorphism is observed for CYP2D6.

It should be emphasised that the bio-transformations catalysed by each of these isoenzymes only involve a limited number of substrates. General information such as the fact that drug X is a CYP450 inducer or inhibitor, or a CYP450 substrate is too vague; it is now more appropriate to refer to a compound as a CYP3A4 substrate, CYP1A12 inducer or a CYP2D6 inhibitor, for example.

Concepts with major therapeutic implications

Taking account of the concepts of substrate, inhibitor, inducer, affinity, metabolic pathways and bioavailability has important therapeutic consequences, which enable us to predict some drug–drug interactions.

• *Substrates, inhibitors, inducers*
Most substrates, inhibitors or inducers have preferential affinity for specific isoenzymes. This means that a substrate which inhibits CYP2D6 does not change the metabolism of the substrates for CYP3A4, CYP1A2 or CYP2C9.

• *Affinity for isoenzymes*
Substrates exhibit different degrees of affinity for CYP450 system isoenzymes. When two substrates for the same isoenzyme are administered simultaneously, competition for binding to the isoenzyme occurs in the substrate with the greatest affinity acting as a competitive inhibitor of the second substrate. When both substrates have the same affinity for the same isoenzyme and are administered simultaneously, the substrate that is administered at the highest dose is generally metabolised first and the plasma levels of the other substrate increase as its biotransformation falls. The concept of competitive inhibition between two drugs has major consequences in terms of drug–drug interactions.

• *Metabolic pathways*
A drug may be the substrate for one or more CYP450 isoenzymes. The likelihood of drug–drug interactions is reduced if the drugs are metabolised by a single isoenzyme, although the magnitude of the interaction when it occurs may be far greater. When several metabolic pathways exist, the risks of drug–drug interactions are greater, although their clinical importance may be lower.

However, the clearance of a drug that is 50% metabolised by CYP3A4 is reduced by half in the event of inhibition due to the concomitant receipt of a substrate or inhibitor for this isoenzyme.
The mean plasma concentrations of the drug are also increased by a factor of two. It is generally considered that a 30% reduction in overall metabolic capacity for a drug, which reflects in a 30% increase in its plasma concentration, is clinically significant but is not significant below this level.

• *Bioavailability*
The oral bioavailability of a drug is defined as the amount of this drug that reaches the systemic circulation in unchanged form after being administered orally. If a drug has low bioavailability, a large proportion of the drug is lost during the 'first pass' effect. If a drug has high bioavailability then the majority of the drug is absorbed and reaches the systemic circulation.

CONSTRUCTION OF CLINICAL DECISION SUPPORT TOOLS

Drug–drug interactions and the adverse events attributable to them can be avoided if the pairs of drugs that interact can be identified. However, the amount of information that needs to be generated rapidly becomes insurmountable when the treatment regimen of a patient contains ten or even 20 or more drugs as, is seen commonly in an ageing population.

Design of a first mapping of substrates, inhibitors and inducers of CYP450s

Starting from the principle that biotransformations catalysed by each of the CYP450 system isoenzymes only involve a limited number of substrates, mapping of several classes of drugs by their CYP450 isoenzyme was conducted in 1995. We were then in a position to predict certain drug–drug interactions and as a result to adjust and personalise treatments (see Table 1).

Table 1. Initial mapping (1995) of CYP450s substrates, inhibitors and inducers

CYP	Substrates	Inhibitors	Inducers
1A2	Theophylline, caffeine, imipramine, mexiletine	Quinolones	Cigarette smoke
2A6	Coumarin, nicotine	Diethyldithiocarbamate	
2C9	Non-steroidal anti-inflammatory drugs, losartan, irbesartan, S-warfarin, celecoxib	Sulphaphenazole	Rifampicin
2C19	Omeprazole, R-warfarin		
2D6	Codeine, beta-blockers, Anti-arrhythmics, H1 antagonists, specific serotonin reuptake inhibitors	Quinidine	
2E1	Alcohol, chlorzoxazone		Alcohol
3A4	Calcium antagonists, 2nd generation H1 histamine antagonists, benzodiazepines, cyclosporine, statins	Macrolides, imidazoles	Rifampicin, phenytoin

Each CYP450 isoenzyme exhibits selectivity for substrates, inhibitors or inducers of its activity.

Table 1 highlights that:

1. CYP1A2 metabolises theophylline, caffeine, imipramine and mexiletine; as cigarette smoke is a CYP1A2 inducer, smokers would metabolise theophylline more actively and should receive higher doses of this agent than a non-smoking patient.

2. If a patient is taking mexiletine and a concomitant quinolone, a CYP1A2 inhibitor, the metabolism of mexiletine is inhibited and its plasma levels rise; this patient should receive a lower dose of the anti-arrhythmic.

3. The macrolides inhibit the metabolism of calcium antagonists, statins and benzodiazepines by CYP3A4; this effect may explain why patients complain that this antibiotic puts them to sleep. Concomitant administration of a macrolide and a benzodiazepine results in reduced metabolism of the benzodiazepine and an increase in its plasma concentrations resulting in increased drowsiness (see Table 1).

Construction of an extending map to understand the effects of competitive inhibition

We have seen that when two substrates for the same isoenzyme are administered simultaneously competition occurs for binding to the isoenzyme, and it is the affinity of each of the substrates that determines which substrate is subject to inhibition of its metabolism.

Over the years, we have mapped all of the drugs marketed for the substrate inducer criterion and added to this the concept of substrate affinity for the different isoenzymes (see. Table 2). The level of affinity for the isoenzyme is shown in a colour: orange for high affinity, dark yellow for intermediate affinity and light yellow for low affinity.

This mapping reveals for example that concomitant receipt of verapamil and alprazolam, both substrates for CYP3A4, causes competitive inhibition. Verapamil, which has higher affinity for the isoenzyme (orange colour) , inhibits the metabolism of alprazolam (light yellow colour) and the plasma levels of alprazolam increase.

Table 2. Each isoenzyme CYP450 and its inhibitors, its substrates and its specific inducers[3].

CYP3As

Inhibitors	Substrates			Inducers
Chloramphenicol	Amiodarone	Almotriptan	Alfentanil	Bosentan
Cimetidine	Amprenavir	Amlopidine	Alfuzosin	Butalbital
Clarithromycin	Atazanavir	Aprepitant	Alprazolam	Carbamazepine
Erythromycin	Dasatinib	Atorvastatin	Astemizole	Efavirenz
Fluconazole	Delavirdine	Bicalutamide	Bromocriptine	Modafinil
Grapefruit juice	Dihydroergotamine	Bosentan	Budesonide	Nevirapine
Isoniazide	Diltiazem	Buspirone	Cabergoline	Pentobarbital
Itraconazole	Fosamprenavir	Chlorpromazine	Carbamazepine	Phenobarbital
Ketoconazole	Imatinib Mesylate	Cinacalcet	Cerivastatin	Phenytoin
Miconazole	Indinavir	Cyclophosphamide	Chlordiazepoxide	Primidone
Orphenadrine	Methysergide	Cyclosporine	Chloroquine	Rifabutin
Oxiconazole	Nelfinavir	Dapsone	Cisapride	Rifampicin
Phenelzine	Ritonavir	Doxycydine	Clindamycin	St. John's Wort
Telithromycin	Saquinavir	Eletriptan	Clobazam	Topiramate
Troleandomycin	Verapamil	Eplerenone	Clonazepam	Troglitazone
	Voriconazole	Erlotinib	Clopidogrel	
	Warfarin	Etoposide	Codeine	
		Felodipine	Clochicine	
		Isradipine	Conjugated Estrogens	
		Loperamide	Cyclobenzaprine	
		Loratadine	Cytarabine	
		Lovastatin	Danazol	

Some of these substrates have high affinity (orange), others have intermediate affinity (dark yellow) or low affinity (light yellow). Drugs with high affinity for an isoenzyme are liable to cause interactions whereas those with lower affinities are more likely to reduce them.

Identification and quantification of competitive inhibition effects

Taking account of the affinity of drugs for the isoenzymes

In the following example (see Table 3), a patient is receiving five different drugs. Two of these agents are metabolised by CYP2C9 and the other two agents by CYP3A4. Therefore, competition may occur for these isoenzymes. Celecoxib has higher affinity (orange colour) than glyburide (light yellow colour) for the isoenzyme CYP2C9. As a result, concomitant receipt of celecoxib and glyburides by this patient will result in a rise in the sulphonylurea concentration, with a risk of hypoglycaemia. This parameter will need to be monitored.

Table 3. Analysis of the phenomenon of competitive inhibition.

SUBSTANCES	F%	AE %	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4	NON-CYP
Omeprazole (oral)	35	0.1					65		35	-
Metoprolol (oral)	50	5						80		-
Glyburide (oral)	80	15				65				-
Conjugated oestrogens (oral)	-	-							-	-
Celecoxib (oral)	15	3				80				-

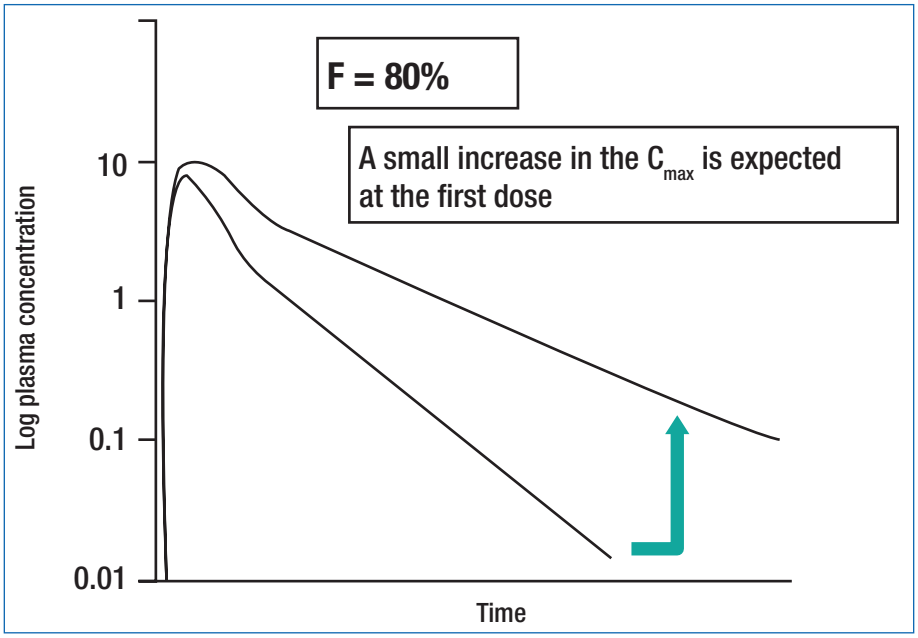
AE: amount removed unchanged in urine; F: oral bioavailability.

Taking account of the bioavailability of drugs

Bioavailability provides information about the magnitude and type of drug–drug interactions expected.

The oral bioavailability of glyburide involved in example drug-drug interaction above is 80% (see Table 3). This means that the first pass intestinal and hepatic effect will only have a minimal impact on the C_{max}. Similarly, its concomitant administration with celecoxib which is another CYP2C9 substrate will have limited effect on the C_{max} observed on first dose. The half-life of glyburide will, however, increase and plasma glyburide concentrations will rise gradually, resulting in a risk of hypoglycaemia after 5–6 days (see Figure 1). It can be seen that inhibition of the metabolism of drugs with a bioavailability in the region of 5% (such as the statins and macrolides) will result in a 20-fold increase in its plasma concentrations.

Figure 1. Change in plasma concentrations of a drug with high bioavailability in the event of inhibition of its metabolism.



A drug with a high oral bioavailability (80%) will have a minimal increase in its C_{max} after the first dose. Its mean plasma concentrations, however, will increase gradually with repeated doses as the half-life of the drug is prolonged because of inhibition of its metabolism.

Taking account of the metabolic pathway

The number 65 shown in the box for glyburide in Table 3 indicates that two-thirds of its clearance occurred through CYP2C9. As a result, the co-administration of glyburide and celecoxib results in an increase in glyburide concentrations by a factor of 3 as its clearance falls from 100% to 35%.

Practical consequences of analysing competitive inhibition effects

In practice, the treatment strategy involves avoiding the concomitant administration of two substrates for the same isoenzyme. When possible, the lowest affinity substrate is administered first whereas the substrate with higher affinity is administered after a period equal to or greater than the T_{max} of the lower affinity substrate. We use this strategy on a daily basis to optimise the treatment regimen in poly-medicated patients.

CONCLUSION

The presence of drug–drug interactions in polymedicated patients requires the greatest of care. Clinical decision-making support tools help to provide access to a large amount of information enabling health professionals to take informed clinical decisions.

Taking account of competitive inhibition, affinity, metabolic pathways and environmental and genetic factors are all issues to be considered in determining the ideal therapeutic regimen alongside treatment guidelines for specific diseases, economic factors, access to care and risk stratification.

REFERENCES (Underlined references are linked to PubMed abstracts)

1. Turgeon J, Michaud V. Clinical decision support systems: great promises for better management of patients' drug therapy. Expert Opin Drug Metab Toxicol 2016;12:993-5.
2. Doan J, Zakrzewski-Jakubiak H, Roy J, Turgeon J, Tannenbaum C. Prevalence and risk of potential cytochrome P450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. Ann Pharmacother 2013;47:324-32.
3. Zakrzewski-Jakubiak H, Doan J, Lamoureux P, Singh D, Turgeon J, Tannenbaum C. Detection and prevention of drug-drug interactions in the hospitalized elderly: utility of new cytochrome p450-based software. Am J Geriatr Pharmacother 2011;9:461-70.