

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Unmet Needs in Preventing Adverse Drug-Drug Interactions



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H&O What has been the main focus of drug-drug interaction research over the last few decades?

MR Drug-drug interactions (DDIs) have been a long-standing issue, not just in oncology. It is sometimes said that the probability of an adverse drug reaction is proportional to the square of the number of drugs a patient is receiving. DDIs were initially characterized in the 1960s. The focus of DDI research over the last few decades has primarily been on the cytochrome P450 (CYP) family of enzymes. Although the P450 system is only one of many sites of potential DDIs, the overall importance of drug interactions in health care became clearer as additional DDI studies were conducted. This led to several drugs being removed from the market. For example, increased plasma concentrations of the CYP3A4 substrate terfenadine occurred when coadministered ketoconazole (a CYP3A4 inhibitor). This increase led to life-threatening and fatal cardiac arrhythmias. The US Food and Drug Administration (FDA) recalled terfenadine after 13 years on the market.

H&O How has technology played a role in assisting professionals when prescribing multiple medications? Despite regular use of these programs, what evidence is lacking (eg, do they actually help prevent DDI-associated morbidity)?

MR Drug interaction software programs can be troublesome in that they may fail to detect important interactions

that can harm patients, and they can generate nuisance alerts that are of little value. In most programs, a large number of alerts must be reviewed before encountering one that can be harmful. Intrusive and time-consuming nuisance alerts generated by some programs may lead frustrated users to ignore both important and unimportant warnings. Although these software programs and databases are routinely adopted by pharmacies, it is unclear whether they are truly effective in preventing downstream DDI-associated morbidity and mortality.

H&O What are some recent findings regarding imatinib DDI studies?

MR Imatinib has been utilized with great results in a variety of diseases, including chronic myelogenous leukemia, advanced gastrointestinal stromal tumors, and a number of hematologic and oncologic malignancies. Imatinib is expected to come off patent in 2015. If this happens, the drug will likely be considerably less expensive, which may result in an increase of generic imatinib prescriptions. As such, understanding the pharmacokinetics of the drug—and thereby determining potential DDIs—is of significant importance.

MS In the September 2013 issue of *Clinical Pharmacology & Therapeutics*, Filppula and associates will present data from their recent study, which evaluated the effects of the strong CYP2C8 inhibitor gemfibrozil on the pharmacokinetics of single-dose imatinib among healthy vol-

unteers. Gemfibrozil was found to reduce the formation of the main imatinib metabolite, *N*-desmethylinatinib, resulting in impaired absorption and diminished plasma concentration fluctuations of imatinib. This study, which validates previous *in vitro* findings, emphasizes the significant participation of CYP2C8 in the metabolism of imatinib in humans, and supports involvement of an intestinal influx transporter in imatinib absorption.

H&O What are the main issues with drug labels/updates to remove risks? How might this affect patient care?

MR Drug labels are infrequently updated by the FDA. For example, despite available evidence that supports a less significant role for CYP3A4 and a larger contribution by CYP2C8, there remains a strong warning on the imatinib label regarding potential interactions with CYP3A4 inhibitors. However, the imatinib label does not mention any risk involved when the drug is administered with a CYP2C8 inhibitor. Following FDA approval, the inserts of drug labels are seldom updated and may therefore pose substantial threats to patients.

H&O What are some expectations and challenges associated with genomic-based prescribing?

MS Pharmacogenomics is an area of research made possible over the past decade by a better understanding of the human genome. However, translating that knowledge from research labs to the clinic has been a challenge. At the University of Chicago Medicine's Center for Personalized Therapeutics, we are conducting an ongoing clinical study, known as The 1200 Patients Project,

which creates a database of how patients with particular genetic profiles react to specific drugs, and then puts that information online for physicians in the clinic to use and compare against. Determining how the genomic prescribing system could be integrated into routine care is one of the most exciting aspects of the study.

H&O What does the future hold?

MR We are working on developing better systems that would be useful in the prevention of DDIs and for personalized therapeutics. As genomic-based prescribing becomes more prevalent in practice, a greater understanding of interindividual variability in drug response is inevitable. However, obtaining a greater understanding of intraindividual variability is also crucial, and DDIs are a major contributor to such variability. DDI software and databases need to be updated to ensure greater accuracy, and should also provide useful information to the prescriber that will hopefully improve patient care. We must move beyond the simple cataloging of potential DDIs and expand the focus of such systems to clinically important interactions, ideally supported by validated data.

Suggested Readings

Seminario MJ, Ratain MJ. Preventing adverse drug-drug interactions: a need for improved data and logistics. *Mayo Clin Proc.* 2013;88(2):126-128.

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O'Donnell PH, Bush A, Spitz J, et al. The 1200 patients project: creating a new medical model system for clinical implementation of pharmacogenomics. *Clin Pharmacol Ther.* 2012;92(4):446-449.

Filppula AM, Tornio A, Niemi M, Neuvonen PJ, Backman JT. Gemfibrozil impairs imatinib absorption and inhibits the CYP2C8-mediated formation of its main metabolite. *Clin Pharmacol Ther.* 2013 May 8. doi: 10.1038/clpt.2013.92. [Epub ahead of print]