Drug–drug interactions: How scared should we be?

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There are 2 concerns in drug safety: adverse reactions and adverse interactions. When multiple drug therapies are prescribed, drug–drug interactions (more correctly, drug–protein–drug interactions) become an important consideration for patients and physicians. Because specific diagnostic codes for drug interactions are lacking,[1] it is difficult to obtain precise rates of incidence and prevalence. However, we do know that drug interactions cause up to 2.8% of hospital admissions.[2,3,4] Although it is impossible to remember all potential drug interactions, knowledge of the interactive properties of drugs can help reduce the risk of serious adverse outcomes. Moreover, it is the responsibility of physicians to counsel patients regarding drug interactions.[5]

An increased understanding of drug metabolism is solving much of the mystery behind interactions. Over 90% of drug oxidation can be attributed to 6 main P450 cytochromes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. These are affected by genetics (polymorphic genes cause particular enzymes, such as CYP2D6, to be inactive in some people), drugs (a drug may inhibit or catalyse a cytochrome, or interfere in the chemical pathway of another drug, as in the inhibition of cyclosporine metabolism by ketoconazole), chemicals (e.g., dioxin induces P450 and grapefruit juice inhibits CYP3A4) and the environment (cigarette smoke induces CYP1A2 metabolism). Deciding which among such interactions is clinically relevant is a challenging and relatively new field of investigation.

The metabolism of a drug can be investigated before the drug is tested in humans. In the case of recombinant human P450 cytochromes, it is possible to determine metabolic pathways, potential genetic polymorphisms, the ability to induce or inhibit drug metabolism, and possible drug interactions. This in vitro information can be used to guide expensive in vivo studies. That being said, using in vitro tests that focus on cytochrome enzymes alone to predict clinical interactions may not always be reliable. First, it is not always possible to know the therapeutic concentration of a new drug and of its primary metabolites in specific tissues.[6] Second, it is impossible to test all of the many possible pathways and interactions. Third, even the demonstration of an in vitro effect does not tell physicians whether the effect is likely to occur in clinical practice; that is, the clinical significance of an in vitro interaction is unknown. Until clinical data demonstrate the presence or absence of a clinically significant interaction, dosage adjustments are premature.[7] Multiple clinical reports of interactions are the best evidence that the concurrent use of 2 drugs may have an adverse outcome. The issue of levels of evidence can be illustrated by the recent examples of terfenadine and terbinafine.

Terfenadine was removed from the North American market because of cardiotoxic interactions. In 1990 a case report alerted us to prolongation of the QT interval and torsades de pointes arrhythmias when terfenadine was given concomitantly with ketoconazole.[8] Excessive serum concentrations of terfenadine and low concentrations of its main metabolite suggested that the metabolism of the parent drug was inhibited. Subsequently, 6 healthy volunteers who were given ketoconazole after a steady-state concentration of terfenadine was achieved demonstrated excessive serum levels of terfenadine with concomitant prolongation of the QT interval. This interaction was neither clearly defined nor appreciated until 11 years after the drug was first marketed.

Terbinafine is an orally active allylamine antifungal agent used in the treatment of dermatophytoses in Canada since 1993. Other oral antifungals, namely ketoconazole, itraconazole and fluconazole, are inhibitors of CYP3A4. Terbinafine was not known to impair drug metabolism, but recent investigations led to the discovery that terbinafine strongly inhibits CYP2D6,[9] an enzyme that metabolizes more than 35 drugs, including potentially arrythmogenic agents such as some β-blockers, tricyclic antidepressants and donepezil. The clinical implications of this finding are still unknown, but there should at least be a change in the information that patients are given when this drug is prescribed. Although terbinafine has been on the market for 6 years, we are still gaining fundamental information about its metabolism.

Another important concept to grasp is that not all drugs within a given class are equally susceptible to drug interactions. As Dr. Robert J. Herman describes in this issue,[10] (page 1281), the "statin" family is a prime example. Only some statins are cleared by the enzyme CYP3A4. Understanding the differences in the potential of the various statins for drug interactions has clinical relevance. To date, all reports of significantly increased rates of myalgia in patients receiving combination therapy with a statin and cer-

tain other agents involve simvastatin or lovastatin, the statins with the highest known metabolic dependency on the CYP3A4 pathway for elimination.[11,12] Fluvastatin is metabolized by CYP2C9 and therefore is not expected to interact with CYP3A4 inhibitors, but it may interact with CYP2C9 inhibitors. Pravastatin is not metabolized by CYP3A4 to a clinically significant extent.[13]

Why does it take so long to learn about drug–drug interactions? Drugs are prescribed on the basis of indications that may have their own adverse effects on patient outcome. Studies involving healthy volunteers cannot determine the contribution of underlying diseases to the development of interactions. Moreover, drug interactions are affected by genetics, drugs, chemicals and the environment. This variability causes confusion; for example, Herman says that ketoconazole is a CYP2D6 inhibitor, while others say it is not.[10,14] Regulatory agencies should work with manufacturers to encourage comprehensive and relevant studies.

What can a clinician do? Since no one can be expected to know all drug interactions, good resources such as the *Medical Letter*'s *Handbook of Adverse Drug Interactions* become invaluable. However, most desk references are limited by generalizations based on drug class. For example, the differentiation among statins is not noted in the *Handbook*. More research at the early stages of drug development is needed to identify new interactions, define mechanisms of older interactions and examine the safety of new drugs from classes that are known to cause interactions. Physicians need better tools, but, in the meantime, understanding the nuances of the P450 cytochromes will help take the fright out of prescribing.

Because the best evidence for clinically relevant drug interactions comes from case reports, prescribing physicians can have an important impact. Observations of drug interactions should be confirmed, if possible, by determining serum drug concentrations. They should then be reported to regulatory bodies and in medical journals. By understanding the mechanisms behind drug interactions and staying alert for adverse reactions, we can help make drug therapy safer and reduce the fear of drug interactions.

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References

1. Weideman RA, McKinney WP, Bernstein IH. Predictors of potential drug interactions. *Hosp Pharm* 1998;33:835-40.
2. Jankel CA, Gitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. *Drug Saf* 1993;9:51-9.
3. Schneitman-McIntire O, Farnen TA, Gordon N, Chan J, Toy WA. Medication misadventures resulting in emergency department visits at an HMO medical centre. *Am J Health Syst Pharm* 1996;53:1416-22.
4. Hamilton RA, Briceland LL, Andritz MH. Frequency of hospitalization after exposure to known drug-drug interactions in a Medicaid population. *Pharmacoepidemiology* 1998;18:1112-20.
5. Hoey J. Drug interactions: Who warns the patient? [editorial]. *CMAJ* 1999;161:117.
6. Drug interactions. *Med Lett Drugs Ther* 1999:41:61-2.
7. Ford N, Sonnichsen D. Clinically significant cytochrome P-450 drug interactions — a comment. *Pharmacotherapy* 1998;18:890-1.
8. Monahan BP, Ferguson CL, Kelleavy ES, et al. Torsades do pointes occurring in association with terfenadine use. *JAMA* 1990;264:2788-90.
9. Agdel-Rahman SM, Gotschall RR, Kauffman RE, Leeder JS, Kearns GL. Investigation of terbinafine as a CYP2D6 inhibitor in vivo. *Clin Pharmacol Ther* 1999;65:465-72.
10. Herman RJ. Drug interactions and the statins. *CMAJ* 1999:161(10):1281-6.
11. Bottorf MB. Distinct drug-interaction profiles for statins. *Am J Health Syst Pharm* 1999;56:1019-20.
12. Iliadis EA, Rosenson RS. Long-term safety of pravastatin-gemfibrozil therapy in mixed hyperlipidemia. *Clin Cardiol* 1999;22:25-8.
13. Ford NE, Sonnichsen DS. Clinically significant cytochrome P450 drug interactions: a comment. *Pharmacotherapy* 1998;18:890-1.
14. Michalets EL. Update: Clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy* 1998;18:84-112.

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