STRATEGIC PROPOSALS TO AVOID DRUG INTERACTIONS DURING DRUG DEVELOPMENT: A LESSON FROM A TERFENADINE-RELATED DRUG INTERACTION

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Introduction

Antihistamines are among the most frequently prescribed drugs in the world. Because the clinical use of older antihistamines (e.g., diphenhydramine, hydroxyzine) was limited by their anticholinergic and sedative properties, the pharmaceutical industry successfully developed a new generation of antihistamines that are essentially free of sedative and anticholinergic side-effects. Terfenadine (marketed as Triludan in Japan and Seldane in the USA) was the first of these new drugs¹⁾.

Perhaps because the older antihistamines were generally free of serious life-threatening side-effects and because the newer drugs had even fewer side-effects, the later antihistamines were readily accepted by clinicians and assumed to be safer. However, in 1986, several reports appeared suggesting that patients who took intentional overdoses of terfenadine or astemizole (another new non-sedating antihistamine) could develop a malignant ventricular arrhythmia, i.e., torsades de pointes²⁻⁵⁾. It is now accepted that some antihistamines, under certain clinical circumstances, can exhibit major cardiac toxicity, leading to life-threatening arrhythmias⁶⁾. Clinical and basic research has been carried out to assess the mechanism and predisposing factors for these reactions since the first report on torsades de pointes occurring in association with terfenadine use was made by Monahan *et al.*⁷⁾ in 1990.

Drug interactions and the historical perspective

Terfenadine was approved and introduced into clinical practice in the USA in 1986 as the first non-sedating antihistamine for the treatment of allergic rhinitis. Recognition that terfenadine could cause arrhythmias occurred about 5 years later: the occurrence of a rare, life-threatening ventricular arrhythmia in an otherwise healthy young woman⁷⁾ led alert clinicians to consider the possibility that the patient's near-fatal arrhythmias were triggered by a drug-drug interaction involving her antihistamine (terfenadine) and antifungal (ketoconazole) medications. A pharmacokinetic and electrocardiographic study of the terfenadine-ketoconazole interaction by Honig *et al.*⁸⁾ suggested that ketoconazole inhibited the oxidative metabolism of terfenadine and their analysis of blood samples revealed that subjects who were taking both drugs had high levels of unmetabolized terfenadine, a compound not usually detectable in blood. Honig *et al.*⁸⁾ have also shown that concentration of terfenadine, but not its main metabolite (terfenadine carboxylate), correlated significantly with corrected QT interval (QT_c) prolongation, suggesting that the parent drug is arrhythmogenic. This possibility has been confirmed by Woosley *et al.*⁹⁾ in 1993.

Data have been analyzed from more than 25 reported cases of torsades de pointes in patients receiving terfenadine therapy in an attempt to better define the population at risk⁹⁾. As a result, clinicians were warned of the risk of giving terfenadine to patients re-

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ceiving concomitant drugs (e.g., ketoconazole, itraconazole, erythromycin) that are known to be the inhibitors/substrates for CYP3A4 or to patients with underlying liver disease (e.g., cirrhosis)^{9,10}. Thus, the two reports describing the terfenadine-ketoconazole interaction^{8,9} as well as the terfenadine-erythromycin interaction mechanism¹¹ show clearly that increased levels of the parent drug (prodrug as an antihistamine), terfenadine, provoked by inhibitors of CYP3A4, inhibit the cardiac potassium slow channel, leading to prolongation of the QT-interval and torsades de pointes. Indeed, Yun *et al.*¹² have demonstrated using CYP3A4 from human liver microsomes that terfenadine is extensively metabolized to the main metabolite, terfenadine carboxylate (active as an antihistamine, but not arrhythmogenic).

What we learn from the terfenadine-ketoconazole interaction

In retrospect, one may argue that the cardiac drug-interaction effects of anti-histamines could have been predicted from earlier pharmacological (preclinical and/or clinical) studies undertaken during the development of a new drug. However, in this author's opinion, this has not been the case for many drugs (e.g., the digoxin-quinidine interaction was reported in 1978, 55 years after quinidine was introduced for clinical use in 1923)¹³. There appears to be several reasons why many drug interactions were not detected during earlier pharmacological studies. The author wishes to discuss some important aspects involved in the detection of drug interactions during the development of a new drug, based upon what we have learned from the history of the terfenadine-ketoconazole interaction described above.

The entire terfenadine drug interaction episode is a good illustration of how a drug-drug interaction mediated via hepatic metabolism can be an important source of adverse drug reactions. CYP3A4 is an important cytochrome P450 enzyme known to metabolize

many drugs^{14,15}, including terfenadine, cyclosporin, dihydropyridine calcium channel blockers, some benzodiazepines and macrolide antibiotics. Thus, if the metabolic pathway of terfenadine and CYP isoform(s) involved had been studied in detail and identified during its development, it is possible that some interactions between terfenadine and other drugs whose metabolism is mediated via the same CYP isoform (i.e., CYP3A4)¹² could have been predicted before marketing. Clearly, during the drug development stage, researchers have the task of studying and identifying CYP isoform(s) involved in the metabolic pathway(s) of a drug, looking at concomitant drug(s) that might be coadministered and interact on a metabolic basis, and assessing the pharmacological properties of the parent drug as well as its major metabolite(s). At present, fortunately, there are several *in vitro* and *in vivo* approaches for studying drug metabolism and assessing the CYP isoform(s) involved, as exemplified by the terfenadine-ketoconazole story^{8,9,12}.

Human liver microsomes and recombinant human CYP isoforms are increasingly available for drug metabolism and interaction studies *in vitro* and provide screening tools to determine the CYP isoforms that might be involved in the metabolic pathway(s) of a new drug. Indeed, as indicated by Peck *et al.*¹⁰, some major pharmaceutical companies have already used these *in vitro* techniques to study drug metabolism and potential drug interactions of new chemical entities very early in their development programs, sometimes prior to the initiation of dosing in humans (i.e., early clinical pharmacology trials or phase I). It is emphasized that the dominant metabolic pathway(s) of a drug such as terfenadine is (are) microsomal in origin^{10,12} which simplifies the research strategy, because microsomes are freely available and easily stored. A growing number of specific recombinant human CYP isoforms are also available. In addition, inhibitors (specific antibodies and

pharmacological agents) can also be used to identify the role of specific CYP isoform(s) involved in the metabolic pathway of a new drug.

Lastly, it must be emphasized that drug interaction information and its detection can be helped by feedback from clinical case reports. Indeed, this has been the case for the terfenadine-ketoconazole interaction that was never detected before terfenadine became widely used in clinical practice: once the drug-drug interaction was the subject of a single case report⁷⁾, a rigorous clinical study of the suspected drug interaction was undertaken⁸⁾. The clinical study included both pharmacokinetic and pharmacodynamic assessments⁸⁾, an ideal approach which seems to be essential for a definitive evaluation of the clinical significance of any drug-drug interaction. A lesson from the terfenadine-ketoconazole (or other drugs or substrates involved with CYP3A4) interaction appears to indicate that drug-drug interactions can be detected prior to the marketing of new pharmaceutical products if appropriate strategic tools to identify the corresponding CYP isoform(s) involved in their major metabolic pathway(s) are used during the development stage.

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