EDITORIAL

Cardiovascular Therapeutics

Drug–Drug Noninteractions

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Understanding and documentation of drug–drug interactions (DDIs) are an important component of drug development, and of clinical therapeutics. Because clinical DDI studies are costly, time-consuming, and involve some risk, not all clinical DDI questions can be realistically addressed through human DDI trials. *In vitro* models have been used to identify and predict drug combinations that might interact, and combinations that are unlikely to interact. This screening or "filtration" information allows clinical resources to be targeted in a more informed way. Still, many DDI studies will end up with a negative result. Negative DDI results constitute important and clinically relevant information, and scientific reports of such studies are candidates for publication.

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The topic of drug–drug interactions (DDIs) has received a great deal of recent attention from the regulatory, scientific, and health care communities [1–3]. Ironically, this is a by-product of unprecedented success in therapeutic innovation. Drug discovery and development activities within the pharmaceutical industry over the last 25 years have led to numerous breakthrough pharmacologic treatments of human disease. Examples include HMG-CoA reductase inhibitors, antiretroviral drugs, azole antifungal agents, proton pump inhibitors, nonsedating antihistamines, serotonin reuptake-inhibitor antidepressants and "atypical" antipsychotic drugs. These newer drug therapies have prolonged survival and improved quality of life for large numbers of patients. Nonetheless, many of the medications have the additional property of inducing or inhibiting the activity of drug-metabolizing enzymes [4], raising the possibility or actuality of pharmacokinetic DDIs, in which one drug (the "perpetrator") changes the metabolic clearance and plasma levels of another (the "victim" or "substrate") [2].

The phenomenon of pharmacokinetic DDIs has long been recognized, but general awareness was raised to a higher level some 20 years ago via the terfenadine incident. The nonsedating antihistamine terfenadine (Seldane) itself was a prodrug or drug precursor of fexofenadine. Under usual circumstances, terfenadine was essentially completely converted to fexofenadine by Cytochrome P450-3A (CYP3A) enzymes in the liver and gastrointestinal tract mucosa [5]. Fexofenadine—not the precursor terfenadine—accounted for clinical antihistamine activity. However, in those few patients happening to take terfenadine along with strong CYP3A inhibitors (such as ketoconazole, itraconazole, or erythromycin), significant amounts of intact terfenadine reached the systemic circulation [5,6]. Since terfenadine itself has the property of prolonging the cardiac QT interval [7–9], the result was several cases of serious and even fatal ventricular arrhythmias [7,9–11]. Terfenadine was eventually withdrawn from the market, but the fallout from the incident included increased regulatory requirements for DDI evaluation during drug development and postmarketing surveillance—namely, requirements to conduct well-controlled clinical pharmacokinetic DDI studies.

Easily said, but not so easily done. For any given marketed drug or drug candidate, the number of

potential DDIs is very large because polypharmacy is so common in clinical practice. It is unrealistic to expect that a clinical study can be conducted to evaluate each of these possibilities. Clinical DDI studies that meet regulatory standards are expensive, time-consuming, and—most importantly—involve some risk to volunteer subjects that participate in the studies. Institutional Review Boards serve to assure that the risk is low and acceptable, but the risk is non-zero nonetheless. Given the time, cost, and risk of clinical DDI studies, a "filtering" mechanism is needed to identify those drug combinations having highest priority for a DDI study to either confirm or exclude a clinically important DDI.

A filtering process that is generally accepted by the scientific community and the FDA is the *in vitro* metabolic model based on human liver microsomes [3,12–18]. The model establishes the transformation of a specific substrate to its principal metabolites by the liver microsomal enzyme preparation. The effect of a specific candidate inhibitor on that transformation process can be quantitatively characterized by either an *in vitro* inhibition constant (K_i) or a 50% inhibitory concentration (IC_{50}). If C_{max} represents the maximum plasma concentration of the inhibitor attained *in vivo* with the highest recommended therapeutic doses, a ratio of C_{max} divided by K_i or IC_{50} can be used to roughly forecast the possibility of a clinical DDI. The available predictive models are far from perfect [19–26], and regulatory guidelines accordingly are very conservative. Current guidelines state that a C_{max}/K_i or C_{max}/IC_{50} ratio less than 0.1 indicates that a DDI is "unlikely," while greater than 10.0 indicates "probable." For the in-between range (0.1 to 10.0), a DDI is deemed "possible." The boundaries are arbitrary and the range broad, but the guidelines do allow targeting of clinical resources to the "possible" range. When ratios are less than 0.1, studies are generally not needed. Ratios greater than 10.0 indicate a high enough probability of a DDI that the drug combination may actually be prohibited through labeling restrictions.

In this issue, Schwartz and associates [27] report a clinical DDI study in which laropiprant—the candidate drug under development by the sponsor (Merck)—was evaluated as an inhibitory "perpetrator," and rosiglitazone served as the substrate "victim." The study serves to define the DDI interaction potential between these specific drug pairs, but the outcome can be logically extended to other substrate victims that, like rosiglitazone, are metabolized mainly by the specific Cytochrome P450-2C8 (CYP2C8) isoform. As such, rosiglilazone is termed an "index" or "probe" substrate for CYP2C8.

The study outcome demonstrated no interaction between laropiprant and rosiglitazone—a drug–drug noninteraction. This is the hoped-for result, and good news for the sponsor. The product label for laropiprant can explicitly cite the pharmacokinetic noninteraction between the two drugs, and further assure that laropiprant is unlikely to inhibit the clearance of other drugs that are substrates for CYP2C8.

Reassuring as a definitive noninteraction study may be, there is residual discomfort about whether the study really needed to be done in the first place. Was the possibility of a clinically important DDI real enough to warrant the dollar cost, and the low and acceptable—but still non-zero—human subjects risk of a clinical DDI study? Invoking the *in vitro* filter criteria, Schwartz et al. [27] state that laropiprant is a moderate *in vitro* inhibitor of CYP2C8, with an IC_{50} in the range of approximately 6.5 micromolar. No reference is cited to support this critical piece of information, and readers have no way to evaluate the validity of the stated IC_{50} value. In any case, if the stated IC_{50} is accepted as valid, their reference 15 reports a mean laropiprant steady-state C_{max} of 2.1 micromolar at a dose of 30 mg per day, and 3.9 micromolar at 60 mg per day [28]. The corresponding C_{max}/IC_{50} ratios are 0.32 and 0.60. At 40 mg, the ratio per day is likely to fall between 0.32 and 0.60, indicating—by FDA criteria—that a DDI is "possible." This is reasonable rationale and justification for moving forward with a clinical DDI study. It is also very likely that the sponsor considered consequences of *not* conducting the clinical study. With a DDI deemed "possible" based on *in vitro* data and not definitively ruled out in a clinical trial, the FDA could impose labeling to the effect that DDIs are possible, have not been evaluated in clinical studies, and that coadministration of laropiprant and CYP2C8 substrate drugs is either prohibited—or undertaken only with special caution and monitoring—until clinical data became available. Such labeling would constitute a restriction of clinical use, and might put the sponsor at a competitive disadvantage in the marketplace. All things considered, the sponsor elected to proceed with the clinical DDI study, as reported by Schwartz et al. [27].

A word about biostatistical analysis: For the Schwartz et al. [27] study, statistics are not really needed. No sane person looking at their Figure 2 could possibly argue that there is remotest evidence of a DDI. The statisticians can sit this one out. But when a study does show a change in plasma levels of the substrate victim due to coadministration of the precursor, the scientific and health care communities need answers to the following questions: How big is the DDI? Could it have happened by chance? Is the DDI of possible or actual clinical importance? We turn to biostatisticians to *help* us come up with the answers (though *not* to answer the questions for us).

Unfortunately, FDA guidelines for statistical analysis of DDI studies obfuscate and confuse—rather than clarify and illuminate—the biomedical phenomenon that we are hoping to understand through the study outcome [29]. The FDA demands that DDI studies be treated as bioequivalence studies—which they most certainly are not. Data manipulations, such as logarithmic transformation and calculations of geometric or harmonic means, distort the real central tendencies expressed as arithmetic means of untransformed values. If manuscripts on DDI studies submitted to scientific or medical journals simply transplant the FDA-mandated statistical analysis from the regulatory report, the community of scientists and clinicians reading the journal may end up confused rather than enlightened about the DDI. As for statistical significance of an apparent DDI, the straightforward, transparent, and unarguable answer comes from a nonparametric equivalent of Student's *t*-test, yielding the probability that the observed difference could have happened by chance. Finally we have the clinical importance of a DDI—an issue that no statistical method can resolve out of context. Is the change in plasma levels of the victim substrate drug caused by the DDI sufficiently large to make a clinical difference, and require some sort of corrective action? Examples would be: a need for increased monitoring or reduced dosage of the substrate, or a drug toxicity hazard warranting prohibition of the drug combination. This is not a matter of statistics—a small but statistically significant DDI may be of no therapeutic importance and pose no hazard of drug toxicity. What is needed is an understanding of the concentration–response or dose-response relationship of the victim drug. With that knowledge, a *clinical judgment* can be made as to whether the effect of the DDI is large enough to change the response to the victim drug.

With passing years we have learned that DDIs in general have received too much "hype." In an era of polypharmacy, the number of concurrently-administered drug pairs that *might* interact is huge, yet the actual prevalence of significance DDIs is very small [30–32]. Nonetheless DDI evaluation is now a permanent piece of the drug development process. Drug–drug noninteraction studies provide biomedical and public health information as important as the studies with positive results. Among the "population" of all DDI studies, too few negative results means that our filter is too stringent, and we probably are failing to conduct some studies that would be positive. On the other hand, an excessive number of noninteraction results imply that our filter is identifying drug combinations that are not realistic candidates for a clinical DDI. Filtering mechanisms to predict clinical DDIs are imperfect [19–26], and require ongoing refinement to improve accuracy.

Conflict of Interest

The authors declare no conflict of interests.

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