VIEWPOINT

ORCA: OpeRational ClassificAtion of Drug Interactions

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Over the past 30 years, more than 15,000 journal articles on drug–drug interactions have been published. This information—especially the recent data on cytochrome P450 isozymes and ATP-binding cassette (ABC) transport proteins—has advanced our understanding of drug interaction mechanisms and has dramatically improved our ability to predict which drug pairs are likely to interact clinically.

But this flood of information has also overwhelmed even the most dedicated and compulsive of health care providers. It has become unrealistic to expect individual practitioners to read all of the relevant data and determine on their own which drug interactions are the most important clinically. Accordingly, most books and computer systems evaluating drug interactions use classification systems to help the clinician with this process.

While there is general agreement that dividing drug interactions into categories is desirable, several barriers continue to impede the successful implementation of such systems. The inadequacies of the available drug interaction data constitute a major impediment; these inadequacies are deeply rooted and will not be easily resolved. Other problems, however, are attributable to inadequacies in the classification systems themselves, and these are much more easily corrected. As we describe in the article on pages 200–4 of the Research section of this issue of *JAPhA*, these problems have led to deficiencies in currently available pharmacy drug interaction software.

Here we review the specific problems with drug interaction data, demonstrate the resulting problems in drug interaction software, and propose a scheme for optimizing clinicians' ability to use and interpret drug interaction information quickly and easily at the point of patient care.

Inadequacies of Drug Interaction Data

Lack of Data on Clinical Importance

The problems with drug interaction information begin in the clinical literature. The published data, coming primarily from studies of healthy volunteers and case reports of individual patients, often lack adequate information for assessing clinical importance. This omission leads directly to a lack of information about what patient-specific factors make the occurrence of drug–drug interactions likely.

Most classification systems currently in use are designed to give the user an estimate of the "clinical significance" of the interaction in question. But, with few exceptions, such classifications presuppose a level of knowledge about the relative importance of drug interactions that extends far beyond that which even practitioners well versed in the available data could justifiably be expected to have. The overwhelming majority of published papers in the clinical literature on drug interactions fall into two categories: pharmacokinetic studies in healthy subjects and case reports. Very few epidemiologic studies on the adverse outcomes of drug interactions have been performed. Hence, neither researchers nor clinicians can estimate how often a particular drug–drug interaction causes unwanted effects in patients, even when it is clear that some patients are adversely affected.

Moreover, some drug interactions are innocuous to most people, but potentially life-threatening under certain conditions. For example, the concomitant use of warfarin and thyroid replacement therapy rarely causes difficulties if warfarin therapy is begun in the presence of long-term, stable thyroid-replacement therapy. Conversely, initiating thyroid replacement therapy in the presence of stabilized warfarin therapy is likely to increase the hypoprothrombinemic response, and serious bleeding has occurred when the patient was not carefully monitored.[1,2]

Lack of Information on Risk Factors

How clinically important a drug interaction will be to a given patient depends on both the inherent danger of the drug combination and the extent to which the presence of risk factors predisposes the patient to the interaction. Such risk factors include: dose and duration of therapy; route of administration; sequence of administration; timing of doses; monitoring planned for the patient; therapeutic window of object drug; other drugs the patient is receiving; genetics; presence of predisposing diseases; presence of smoking, alcohol, and drugs of abuse; diet; and reasons for use of the drugs.

Because each patient has a unique set of risk factors, the clinical outcome of most interactions is highly variable. Thus, placing such interactions in categories of clinical relevance is almost always an oversimplification.

For example, while it is true that combining angiotensin-converting enzyme inhibitors (ACEIs) with potassium-sparing diuretics can result in symptomatic or even life-threatening hyperkalemia,[3] such combinations are used routinely in clinical practice without observable adverse consequences. A predisposed patient (e.g., an elderly person with diabetes and renal impairment who consumes a high-potassium diet) has a much higher chance for an ACEI–potassium-sparing diuretic interaction than a person lacking such risk factors. Nonetheless, drug interaction classifi-

cases of the adverse drug interaction and the likely frequency of concurrent use of the two drugs in the general patient population? In other words, can we estimate the number of patients exposed (denominator) to place the case reports (numerator) in better perspective? For example, isolated case reports have described possible serotonin syndrome after the use of dextromethorphan in the presence of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and paroxetine.[8,9] Serotonin syndrome is a potentially life-threatening adverse event with characteristic symptoms such as tremors, rigidity, myoclonus, hyperreflexia, sweating, and confusion. It does not occur naturally in the absence of drug therapy, and it usually results from the combined effects of two or more drugs. Theoretically, combined use of dextromethorphan and an SSRI could increase the risk of serotonin syndrome, because both have serotonergic effects. Nonetheless, given the widespread use in the general population of both SSRIs and dextromethorphan (found in numerous cough-and-cold products), hundreds of thousands—perhaps millions—of patients have likely been exposed to these drugs concomitantly. Although we do not have definitive epidemiologic data on this interaction, we can presume that, if the interaction does occur, it does not frequently cause clinically important cases of serotonin syndrome.

Are there warnings in drug labeling regarding the interaction? This issue is particularly important when the drug labeling states that a particular combination of drugs is contraindicated or when the potential adverse outcome could result in litigation. For example, although the purported ability of certain antibiotics to reduce the efficacy of oral contraceptives is scientifically unproven,[10,11] warnings about this interaction appear in the product information and have appeared in many lay publications. Moreover, the clinical evidence does not disprove the interaction. Hence, an argument could be made that women taking oral contraceptives should be warned of the possibility of interaction with oral antibiotics until more definitive data are available.

Development of a New Classification Scheme

The drawbacks of drug interaction classification systems notwithstanding, most health professionals clearly desire some form of categorization of drug interactions. The gap is simply too wide between drug interactions that have produced life-threatening reactions and drug interactions that have resulted in minor, clinically unimportant changes in the serum concentrations of a relatively innocuous drug. To not differentiate between such extremes is to burden the health care provider with unnecessary warnings about trivial drug interactions. Therefore, it seems necessary to improve, rather than abandon, the classification schemes for drug interactions.

An initiative to improve drug interaction classification was begun several years ago in the Netherlands. It led to the development of the OpeRational ClassificAtion for drug interactions (ORCA). ORCA was developed by the Drug Interaction Foundation (DIF), with input from an international group of physicians, pharmacists, and researchers. Unlike other classification systems, it is oriented toward the clinical management of drug interactions—hence the term "operational." The classification system is in the public domain, and it may be used by anyone who wishes to do so. To see how ORCA has been implemented in practice, the reader may consult References 12 and 13.

In developing the ORCA system, the DIF committee members looked first at the perceived deficiencies of the current drug interaction classification systems used in the United States and Europe. Most of these deficiencies are described above. The following changes were made in an effort to correct those problems that were amenable to correction.

Use of Operational Categories

Because the health care provider will ultimately need to decide on a course of action (or inaction) for each potential drug interaction, the categories are oriented toward management rather than an elusive assessment of "clinical significance." Because it is seldom possible to determine a priori which patient will have a clinically important adverse outcome from a drug interaction, classification of interactions is more helpful when it provides the user with management options that can reduce patient risk. Focusing on the clinical management of drug interactions will make it possible—theoretically, at least—to prevent virtually all adverse drug interactions.

Substitution of a Noninteracting Drug

Frequently, optimal management of a drug interaction involves selection of a noninteracting alternative for one of the interacting drugs. But this requires careful attention to potential differences in the interactive properties of members of drug classes. Some current resources, including computer-based drug interaction screening programs, use drug classes to group interacting drugs. The developers of these resources assume, usually incorrectly, that all members of a class of drugs with similar pharmacologic action will interact in a similar manner. In fact, the opposite is true. One need only look at the class interactions incorrectly ascribed to the H_2-receptor antagonists, β-adrenergic blockers, calcium channel blockers, or macrolide antibiotics to appreciate the perils of assuming all drugs in a class will interact in a like manner.

Choosing to avoid concurrent use of two drugs that are suspected to interact is a benefit–risk assessment. This process must include an evaluation of the potential risk of the interaction to the specific patient, the ability to manage the risk via patient monitoring and/or drug or dosage adjustment, and the availability of acceptable noninteracting drugs. The ORCA system guides the practitioner in estimating the risk of an adverse

cation systems based on assessing "clinical importance" must assign this interaction to a category, even though the clinical outcome ranges from harmless to fatal, depending on the presence of risk factors.

Given that the combination of ACEIs and potassium-sparing diuretics can be fatal, albeit rarely, one could argue that this interaction should be given the highest clinical importance rating. But making this assignment tends to have a numbing effect on pharmacists, who, day after day, are alerted to an interaction that is obviously safe in the vast majority of patients. Thus, pharmacists—inured by repetition and familiarity—will tend to discount the interaction for all patients, including the elderly person with diabetes and renal impairment who may, in fact, be at substantial risk.

Inadequacies of Drug Interaction Classification Systems

Despite the problems inherent in assigning drug–drug interactions to classification schemes, many have attempted to do so, given the complexity of the information and the clinician's need for guidance. The available drug interaction classification systems suffer from numerous inadequacies, including lack of consistency and classifications based on too few criteria.

Lack of Consistency Among Systems

The various groups involved in classifying drug interactions use different classification systems, and different individuals within the groups are responsible for evaluating available data. It is not surprising, therefore, that disagreements occur over the ratings of specific drug–drug interactions.[4]

These differences can create confusion among users, who often have access to more than one drug–drug interaction resource. These discrepancies also raise questions about the validity of the various rating systems. If a particular drug interaction is given three different ratings by three different systems, the user will reasonably assume that at least two of them must be incorrect.

Inadequate Criteria for Classification

Historically, most classification systems for drug interactions have been based on two primary criteria: (1) potential severity of the adverse outcome and (2) adequacy of documentation in the literature.

The potential severity of an adverse drug interaction is particularly difficult to assess because of the many possible outcomes. For example, the interaction between a nonsteroidal anti-inflammatory drug (NSAID) and a diuretic is of minimal clinical importance in most patients who are taking the diuretic for hypertension and the NSAID on a short-term basis for acute pain.[5] The combination in a patient with congestive heart failure, however, can produce serious adverse outcomes, including acute cardiac decompensation. Similarly, the potential outcome of the combination is likely to be very different in patients with normal renal function versus those with chronic renal failure.

The second criterion, the adequacy of documentation, was a more important consideration when little was known regarding the mechanisms of drug interactions. Historically, individuals involved in classifying drug interactions assessed the adequacy of the documentation based on the number of case reports or prospective pharmacokinetic studies. However, they sometimes directed too little attention toward the quality of these articles; the report was simply accepted as correct and added to an ever-increasing list of interactions. Today, armed with knowledge on which drugs are substrates, inhibitors, or inducers for the various cytochrome P450 enzymes and ABC transporters, experts in drug interactions can predict the occurrence of many drug interactions that have never been studied clinically.

Other Potential Criteria

Given the limitations in applying the two primary criteria listed above, could other criteria be added to improve the classification systems? Indeed, restricting consideration to just those two criteria can result in misleading classifications, which can, in turn, result in less-than-optimal clinical decisions. For example, in the mid-1990s the potentially fatal interaction between dextromethorphan and monoamine oxidase inhibitors was not well documented, and it was relegated to lower levels of importance by some drug interaction sources. Despite the existence of published case reports of serious adverse effects in patients who received the combination, as well as the presence of a plausible mechanism by which the two drugs could interact (i.e., additive serotonergic effects), the interaction was largely ignored, and the result was harm to the patient.[6]

Hence, it would appear that the use of additional criteria might lead to a more robust and clinically useful classification. Insight into the importance of drug interactions can be achieved by, for example, considering several additional criteria.

What is the degree of congruity of the purported interaction with the proven interactive properties of the two drugs? This is an important consideration, particularly when the available clinical data are meager. For example, the calcium-channel blocker verapamil is known to be highly sensitive to interactions with drugs that induce CYP3A4.[7] Suppose a new rifampin analogue is proven to be a potent CYP3A4 inducer, and a case report is published describing a marked reduction in verapamil effect when the two drugs were coadministered. Even though the interaction is "poorly documented," with only the one report, the report is very likely an accurate account of a clinically important interaction. The fact that it is completely consistent with the well-established interactive properties of the two drugs lends strong support to the existence of the interaction.

What is the relationship between the number of reported

Table 1. OpeRational ClassificAtion (ORCA) System for Classifying Drug Interactions

Class	Description	Examples
1: Contraindicated	No situations have been identified where the benefit of the combination outweighs the risk.	*Monoamine oxidase inhibitor + pseudoephedrine:* The risk (a life-threatening hypertensive reaction) is unacceptable given the potential benefit (possible improvement in cold symptoms).
2: Provisionally Contraindicated	The combination increases the risk of adverse effects. Avoid concurrent use unless interaction is desired or no alternative is available. If the combination is used, increased monitoring may be necessary.	*Warfarin + aspirin:* Acceptable if aspirin is used intentionally as an anticoagulant after evaluation of benefits and risks; not acceptable if aspirin is used for another purpose, such as for pain or fever. *Clarithromycin + carbamazepine:* The risk of carbamazepine toxicity is substantial; if possible, use an alternative macrolide, such as azithromycin or dirithromycin.
3: Conditional	Risk may be increased, depending on the clinical situation. Assess risk and take action as needed.	*Ciprofloxacin + antacids:* Binding in the gastrointestinal tract can be minimized by giving ciprofloxacin 2 hours before or 6 hours after antacid. *Warfarin + thyroid:* Risk is minimal if warfarin started in patients stabilized on thyroid. Monitor clotting status any time a change in clinical thyroid status occurs.
4: Minimal Risk	Risk of adverse outcome appears small. No special precautions appear necessary.	*Caffeine + oral contraceptives:* Serum caffeine concentrations may increase somewhat, but adverse effects are unlikely.
5: No Interaction	Evidence suggests that drugs do not interact.	*Cyclosporine + ofloxacin:* Ofloxacin does not appear to affect cyclosporine pharmacokinetics.

drug interaction and then provides potential alternatives to reduce the risk. The five classes of the ORCA system are shown in Table 1.

Additional Classification Criteria

In addition to the traditional criteria of adequacy of documentation and potential severity of the adverse outcome, ORCA uses other criteria. These include consistency of the reported effect with the known interactive properties of the two drugs, estimated frequency of use of the two drugs, and medico-legal considerations. These additional criteria can provide a more robust underpinning by which drug interactions can be assigned to the appropriate categories.

Conclusion

Although drug interaction classification systems are clearly needed to focus pharmacists' attention on the more important drug interactions, such systems have generally not lived up to expectations. Because some of the limitations of such classification systems are amenable to improvement, it should be possible to create a system that provides prescribers and pharmacists with useful information without overwhelming them with unnecessary alerts. The ORCA system considers the potential severity of the adverse outcome of the interaction, the factors known to increase or decrease the risk of the adverse outcome, and the management alternatives available to avoid the interaction or reduce the risk. We would certainly welcome any input readers may have regarding the ORCA system.

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See related articles on pages 159 and 200.

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