CURRENT OPINION

Drug Safety 2001; 24 (9): 637-643
0114-5916/01/0009-0637/$22.00/0

Manufacturer's Drug Interaction and Postmarketing Adverse Event Data

What Are Appropriate Uses?

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Abstract

Governmental agencies overseeing pharmaceutical products use a risk/benefit approach to analyse data and make regulatory decisions. Comprehensive public dissemination of the safety profile of pharmaceutical products is part of an overall strategy for reducing risk associated with the use of any medical product. In the US, reports of postmarketing surveillance of approved drugs are in the public domain. Some, but not all, of the information in drug interaction studies is available to the public through the Freedom of Information Act (FOIA). However, there are concerns over the misuse of these data for commercial or other gain. The need to protect intellectual property and foster innovation in drug development, and concerns of legal liability are often cited as reasons to limit full public access to data from drug development studies. In contrast, intellectual freedom, public safety, and a mandate for transparent decision-making processes by regulatory agencies are issues that support open access to these data. Ultimately, concern for the public safety justifies open access to postmarketing surveillance data, and to a lesser degree, data regarding drug interactions in marketed products, and should outweigh the potential loss of competitive advantage by pharmaceutical companies.

Postmarketing reporting systems serve to identify rare and unexpected adverse drug events. Many adverse drug reactions are related to the metabolism of a medication, or interactions with metabolic pathways when different medications are administered concomitantly. Examination of adverse drug reactions in marketed products often has resulted in the elucidation of metabolic systems in humans. The molecular characterisation of metabolic pathways has directly contributed to successful predictions of the basis of drug metabolism, and to prevention of significant interactions in patients. This knowledge has been applied to the drug development process, in which *in vitro* studies, in some cases, can predict interactions for new drug entities. Thus, the identification of adverse events often has occurred by examination of postmarketing surveillance data.

1. Studies of Drug Interactions

Recent efforts to predict drug interactions have centred on the hepatic mono-oxygenase enzyme system and the clinical relevance of individual isoenzymes in drug metabolism. In the early 1990s, case reports of fatal torsade des pointes were induced by accumulation of terfenadine, whose metabolism was inhibited by coadministration of ketoconazole or erythromycin.[1,2] These case reports

focused attention on the enormous clinical implications of the cytochrome P450 (CYP450) system in mediating adverse drug reactions and drug interactions. Subsequently, cisapride, astemizole, and mibefradil, all Food and Drug Administration (FDA)-approved drugs, were discontinued from the market in the US due to adverse, and potentially fatal, CYP450 metabolic profiles.

These experiences during postmarketing surveillance contributed to the reorganisation of the drug development process, emphasising the need to search for predictable adverse reactions in the pre-approval stage of drug development. More recently, multidrug resistance transporter P-glycoproteins have been increasingly recognised as sources of drug interactions.[3] These advances permit promising compounds in the drug development pipeline to be screened for adverse reactions in a 2-stage process. First, drugs are examined for the their ability to inhibit metabolic enzymes *in vitro* using hepatic microsomes, recombinant CYP450, and human hepatocytes in culture. Results from these *in vitro* screens guide the design of clinical drug interaction studies.

Previously, the interaction of a new agent with existing medications was examined empirically, based on the likelihood of its coadministration with a standard battery of drugs with low therapeutic indices (e.g. digoxin, warfarin).[4] More recently, a more rational approach to the choice of agents to be evaluated in drug interaction studies has become prominent. This approach is codified by a recent FDA guideline, which specifies a framework within which to identify drugs that require evaluation in clinical drug interaction studies.[5] It is recognised that studies *in vitro* do not always predict interactions *in vivo*. For example, drugs that induce CYP450, undergo significant transport by P-glycoproteins, or are significantly protein bound may have pharmacokinetic profiles that are substantially different from those predicted,[6] highlighting the need for human clinical studies.

While there is no mandated number of drug interaction studies that must be performed prior to approval of a new compound, regulatory agencies such as the FDA or European Agency for the Evaluation of Medicinal Products (EMEA) require an investigation of possible serious interactions. Although pharmaceutical sponsors have some discretion concerning which studies are performed, ultimately, the number and type of studies required for approval is determined in collaboration with national or international regulatory agencies.

2. Postmarketing Surveillance of Adverse Drug Events

Evaluation of safety and adverse events continues after a medication has received market approval by regulatory agencies for therapeutic use. The importance of postmarketing surveillance is highlighted by the estimate that studies conducted in phases I to III (pre-market) of drug development may miss delayed-type toxic reactions with a frequency of 1 in 1000.[7] However, many are challenges associated with the collection of spontaneous adverse drug reactions, including low capture rate relative to incidence, preponderance of reports on newly-released medications, heterogeneity and quality of physician[8] and patient-assessed[9] causality for events, and poor follow-up of reports. In the US, spontaneous adverse drug event data is collected by the MedWatch system. The Adverse Events Reporting System (AERS) is a database of these reports used by the Office of Postmarketing Drug Risk Assessment (OPDRA) to identify serious adverse drug reactions. In Europe, national agencies conduct pharmacovigilance, in co-operation with the EMEA. Standardised reports from Europe,[10] the US and other part of the world are forwarded to the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring in Uppsala, Sweden [now known as the Uppsala Monitoring Centre (UMC)].[11]

These systems are not designed to be repositories for all drug reactions but rather, a place to report unexpected and serious reactions.[12] There is consensus that these reporting systems are effective in identifying rare and serious adverse events not identified in pre-marketing studies, and thus can serve as an early warning system for further inves-

tigation. However, there have been calls for focussed surveillance when there is a physiological basis to suspect a specific adverse event or there is inconclusive evidence of a drug-associated adverse event from pre-marketing evaluation.[13]

3. Freedom of Information Act and Public Access

In the US, the results of all drug interaction studies are provided to the FDA in the New Drug Application (NDA). This document is required for approval of new pharmaceuticals in the US and must support the language on the product label as proposed by the manufacturer. The product label plays a critical role in communicating the risk/benefit ratio of a pharmaceutical product to the public. Consequently, the FDA invests substantial effort in approving the specific wording of product labels.

Public access to parts of the NDA is mandated by the Freedom of Information Act (FOIA). Analyses of NDA data and reports by FDA reviewers are posted on the FDA website. Confidential and proprietary information is removed from the NDA review prior to placement in the public domain. However, the lag between filing, approval, and posting on the FDA website can be significant. Once the contents of NDA reviews are made public, they can be obtained from the FDA by visiting their reading room in Rockville, Maryland, from postings on the FDA website or in electronic format on CD ROM.

In the case of the US, the limiting factor in electronic retrieval is the format in which information is offered to the requester. Data are not linked to a search engine and access requires more than casual expertise in computer information technology. However, costs are not onerous and the availability of information to those willing to invest the effort to retrieve it fulfils the requirements of the FOIA. Similarly, unprocessed AERS postmarketing surveillance data are available in an electronic format at a nominal cost. The challenges of searching the available information in this format are akin to those associated with retrieving electronic information from NDAs. While data sets obtained through FOIA requests for data compiled through MedWatch reports are perhaps more complete compared to NDA filing reviews, there are no associated analyses or interpretations such as those available when perusing comments of the reviewers of the application.

In several European countries, drug regulation is excluded from freedom of information legislation.[14] In 1998, the Cochrane Injury Group requested safety data associated with albumin use from the UK Medicines Control Agency. The reluctance of the Agency to provide the information caused a call for increased freedom of information in Europe.[15,16] The level of public and professional access to pharmacovigilance data in Europe is heterogenous on a country-to-country basis. However, this has been mitigated in part by the compilation of Europe-wide surveillance data for all centrally authorised products at a single site,[17] the use of standardised dictionaries such as the Medical Dictionary for Drug Regulatory Activities (MedDRA), strict attention to privacy concerns of member states, and use of unified electronic reporting.[18] Moreover, the UMC will make available requests for numerical data to third parties. With full access, this worldwide database has the potential to be a powerful resource in pharmacovigilance and signal detection.

4. Risk Management

What are the goals of extensive pre-marketing drug interaction studies and postmarketing surveillance? It is clear the complete elimination of risk is untenable. The goal of regulatory agencies worldwide is congruent with that outlined by the FDA, which is not the elimination of risk of a given medical product, but rather the management of risk associated with use.[19] This process involves elements in both pre- (drug interaction studies) and postmarketing (pharmacovigilance) processes.

The first step in the management of risk in the life cycle of a pharmaceutical product is interaction between a regulatory agency and a pharmaceutical sponsor regarding requisite pre-clinical testing of a compound. The previously mentioned emphasis

on *in vitro* models of metabolism is an example of such risk management. In the US, the next step is Investigational New Drug (IND) approval. When this has been granted and the drug moves into clinical development, the next level of risk management revolves around FDA guidance concerning appropriate *in vivo* studies required to gain approval. Approval of a compound for marketing based upon the NDA is the ultimate in risk management: does the anticipated benefit of the new compound outweigh the actual or theoretical risks associated with its use?

The product label is the primary mechanism by which agencies regulate information disseminated to medical practitioners and consumers. All known drug interactions and data from postmarketing surveillance are compiled in this document. Finally, as mentioned previously, there is an ongoing assessment of risk in the monitoring of postmarketing events.

5. Dissemination of Information and the Management of Risk

It is clear that drug interactions considered to be significant are included on the product label. However, although all studies performed prior to drug approval are available to the FDA as part of the NDA filing, details of specific studies performed in support of approval of a product may not be listed on the product label and may not be available to the general public. The significant results of drug-drug interaction studies are generally clearly reported on the product label. This may not be the case with specific details of pre-clinical and clinical trials, such as sample sizes and statistical variances, which can be valuable to competitors developing new drugs in the same class.[20]

The amount of information released to the public from pre-approval drug studies is a balance between the public's right to know and the manufacturer's intellectual property interests. Consumer advocacy groups have argued that dissemination of safety information should always take precedence over propriety interests.[21] Industry supporters have argued that the cost of developing a successful drug is approximately $US500 000 000, and continued innovation is dependent upon perceived return on investment of research capital.[22] Industry will not deny the importance of disseminating information that has an impact on public safety. In contrast to manufacturing and chemistry information for new drugs, which are clearly protected as intellectual property, the quantity of information from drug interaction studies appropriate for release to the public remains open to debate.

Clearly, the recent explosion of pharmaceutical innovation was facilitated, in part, by patent protection of intellectual property. However, while a reasonable case can be made to protect details of drug formulation and chemistry for marketed drugs, it is less clear that information concerning safety in general, and drug interactions specifically, should be protected similarly.

6. Drug Interaction Studies and Public Access

What case can be made for withholding details of drug interaction studies? The reluctance on the part of the pharmaceutical industry to release such results appears to be based on concerns regarding competitive advantage and litigation. There is evidence that studies performed during drug development that demonstrate an adverse effect profile for a compound are less likely to be published in the scientific literature than those which demonstrate a favourable profile.[23] Practitioners of medicine are denied critically important clinical information for guidance in utilisation of a marketed drug when unpublished data are not included on the product label or the NDA review. On the other hand, a competitor may focus their marketing effort on data that reveal significant drug interactions and which are obtained from the public domain; a manufacturer's own data might be used in a negative manner by the competition.

In the US, the FDA is not in the business of promoting products of one manufacturer over those of another. Rather, the FDA has a mandate to promote the proper use of medications. Dissemination of information concerning drug interactions is

a critical part of mitigating risk, not only for the healthcare provider and consumer, but also for the pharmaceutical scientist screening new products.

From a safety perspective, it is difficult to justify anything short of full public access to relevant studies of drug interactions for marketed products. Recent advances in the pharmacology and biochemistry of CYP450 systems have rationalised the evaluation of drug interactions. FDA guidelines specifically delineate those potential interactions that require further investigation from those that do not. Furthermore, these guidelines define criteria that demonstrate the lack of drug interactions, such as no-effect boundaries, and the method by which such interactions should be reported on the product label.[5]

It may be argued that 'misuse' of unpublished drug interaction data for the purpose of competitive marketing by rival pharmaceutical companies may represent a benefit to healthcare practitioners and patients. The promulgation of factual information contained in publicly accessible documents by pharmaceutical rivals may reduce drug interactions. In a therapeutic armamentarium with multiple agents within a particular class (lipid lowering, antidiabetic and antihypertensive agents to name but a few), it is logical to avoid drugs with metabolic properties known to be associated with adverse drug interactions. Some of these unfavourable characteristics include: inhibition of multiple CYP450 isoenzymes; extensive metabolism by a single cytochrome with wide pharmacogenetic heterogeneity; single isoenzyme substrate specificity; and induction of metabolism of a drug.

Avoiding drugs with these characteristics is especially important if there are other therapeutically efficacious agents without these properties available for an indication. While the size of marketing budgets between large and small pharmaceutical companies differ by orders of magnitude, all must abide by the same regulations for dissemination of marketing materials to practitioners and the mass market.[24] The mandate of regulatory agencies to disseminate safety information extends to the policing of advertisement and product detailing.

7. Postmarketing Surveillance and Public Access

Data regarding postmarketing events are commonly misunderstood and can be easily misrepresented. As noted previously, the power of pharmacovigilance will likely improve with increased automation in case collection and data analysis. However, surveillance for postmarketing events works best as a system for the detection of rare, serious events. Other conclusions cannot be reliably generated based solely on these data, though such observations can be used as a basis for further investigation under more controlled circumstances. Under-reporting of events and failure to normalise the number of cases (e.g. events per units sold) make estimation of true annual incidence tenuous at best.[25]

In addition, the difficulty of assessing causality confuses these issues further. For example, reported events in critically ill patients may represent the underlying condition, the effect of the drug in question, another drug administered to the patient, or a combination of any of these variables. There are limited methods to control for these factors or to assess the quality of individual reports when examining surveillance data. Despite these difficulties, authors and groups have inappropriately cited surveillance data to support their claim of associations with adverse events, or claims of comparative safety between drugs.[26] Even drugs in the same therapeutic class cannot be reliably compared using surveillance data, due to their use for different indications and in patients with varying disease severity.

One specific concern regarding postmarketing surveillance data is a lack of sensitivity, or 'power', to detect moderate increases in common conditions or events separated in time from administration of the drug.[27] Another is the false attribution of an adverse effect to a drug. There is neither standardisation of epidemiological methods to analyse spontaneous reporting nor an understanding by the scientific community of the limitations of spontaneous reporting.[28]

A problem with any postmarketing surveillance system is the misrepresentation of data to support marketing or nonscientific issues. Restriction of access to this information will not decrease its misuse. In fact, it can be argued that free dissemination of data levels the competitive playing field in the pharmaceutical market. Furthermore, adverse event reports are generated from the populace and practitioners, and can be argued to be property in the public domain. A system that is open and transparent engenders the most popular support and compliance. Japanese public pressure at perceived failures in pharmacovigilance have pressed the Japanese health ministry to mandate increased reporting of adverse events for new products.[29] In addition to their analysis of spontaneous adverse event reports, regulatory agencies share a critical role in ensuring that data are not grossly misrepresented in advertisements to those without the time (practitioners) or expertise (the mass market) to critically assess claims based on postmarketing surveillance data.

Misrepresentation of adverse event and drug-drug interaction study data in legal proceedings can be compared to the misuse of those data for marketing purposes. Thus, whereas data themselves are neutral, their interpretation and presentation are subject to abuse. The recent experience with silicon breast implants demonstrated that the US judicial system has not uniformly acknowledged the general scientific consensus regarding the safety of medical products and issues of causality of adverse events.[30,31] However, this should not serve as an excuse to suppress important information that has potential to improve public health. A more rational approach would be to amend the American tort process. A less ambitious, but more practical, approach is to improve the process by which scientific evidence is evaluated in the courtroom. Efforts toward this goal, such as court-mandated independent experts, have been implemented.[32]

Finally, while pharmaceutical manufacturers under FDA mandate provide the majority of events reported to the MedWatch system, the most valuable reports are those submitted by physicians. However, there is general acknowledgement of significant under-reporting of events by physicians, a critique levelled at the FDA in a recent report by the Office of Inspector General of the US Department of Health and Human Services.[33] In addition, the relevance of MedWatch data derived from a population of adults to the paediatric population has been questioned.[34] It is vital to ensure that physicians and patients realise they are important participants in the postmarketing surveillance process. Integral to this is open access to the data generated by their experiences with pharmaceutical products.

8. Conclusions

Dissemination of information about pharmaceutical products is one of the ways in which regulatory agencies manage risks associated with the use of drugs. A number of approved products have been withdrawn from the market due to adverse events observed during postmarketing surveillance. Many of these withdrawals have been based on the observation of significant drug interactions. Though innovation depends, in part, on the protection of intellectual property, these issues do not justify confidentiality of data regarding the safety of a marketed drug. It is clear that data concerning the safety of a drug can be misrepresented, especially in the case of postmarketing surveillance. However, the solution to this issue is the continued maintenance of marketing standards by the appropriate regulatory agency. This creates a more level playing field for manufactures of all sizes. The solution to the legal misuse of such information in the US lies more in a re-examination of the tort system rather than limiting the access of the public to information on the safety of drugs.

Acknowledgements

The authors would like to thank Drs Howard Greenberg, Roger Williams and Kenneth Chepenik for their assistance in the preparation of this manuscript. This work was supported by NIH Grant 1K30 HL04522. Walter Kraft was supported by NIH Training Grant 5T32 GM08562. Scott A.

Waldman is the Samuel M.V. Hamilton Professor of Medicine, Thomas Jefferson University.

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