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Accurate prediction of human drug toxicity: a major challenge in drug development

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Abstract

Over the past decades, a number of drugs have been withdrawn or have required special labeling due to adverse effects observed post-marketing. Species differences in drug toxicity in preclinical safety tests and the lack of sensitive biomarkers and nonrepresentative patient population in clinical trials are probable reasons for the failures in predicting human drug toxicity. It is proposed that toxicology should evolve from an empirical practice to an investigative discipline. Accurate prediction of human drug toxicity requires resources and time to be spent in clearly defining key toxic pathways and corresponding risk factors, which hopefully, will be compensated by the benefits of a lower percentage of clinical failure due to toxicity and a decreased frequency of market withdrawal due to unacceptable adverse drug effects.

Keywords: Human drug toxicity; Patient; Trials

1. Drugs with adverse effects routinely escape preclinical and clinical trials

One of the major challenges in drug development is the accurate assessment of human drug toxicity. A review by Lasser et al. [1] found that in the last four decades, 2.9% of the marketed drugs were withdrawn from the market due to severe adverse drug effects, with seven drugs approved and marketed since 1993 and subsequently withdrawn to be associated with over 1000 deaths. Lasser et al. [1] also estimated that from 1975 to 1999, 10.2% of approved drugs required black box warnings to be added post-marketing. Examples of the recently withdrawn drugs and drugs that required box warnings are shown in Tables 1 and 2, respectively.

The occurrence of unexpected adverse drug effects after a drug is approved and marketed illustrates that the current practice in safety evaluation (Table 3), although effective in most cases, allows a number of drugs with unacceptable safety profiles to be marketed. The cost of withdrawal of a drug from the market is astronomical, including losses in resources and time spent in drug development (the cost to develop a successful drug has been estimated to be $800 million, with an average development time of 12–15 years [2]), loss in potential revenues, a compromised public image. There is also an ethical issue of causing harm to the patient population.

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Table 1
Examples of drugs that were withdrawn from the market due to unexpected adverse drug effects

Drug (chemical)	Indication	Adverse effects	Year approved	Year withdrawn
Propulsid (cisapride)	Gastric reflux	Cardiotoxicity	1993	2000
Rezulin (troglitazone)	Type II diabetes	Hepatotoxicity	1997	2000
Duract (bromfenac)	Analgesic	Hepatotoxicity	1997	1998
Posicor (mibefradil)	Calcium channel blocker	Drug–drug interactions	1997	1998
Raxar (grepafloxacin)	Antibiotic	Cardiac arrhythmia	1996	1997
Redux (dexfenfluramine)	Obesity	Heart valve damage	1996	1997
Lotronex (alosetron)	Irritable bowel syndrome	Ischimic colitis	2000	2000
Raplon (rapacuronium bromide)	Surgery relaxant	Bronchospasm	1997	2001
Baycol (cerivastatin)	Cholesterol lowering	Rhabdomyolysis	1997	2001

Information obtained from the U.S. Food and Drug Administration webpage: http://www.fda.gov/medwatch.

Table 2
Examples of drugs recently required to add safety alerts (box warning)

Drug (chemical)	Indication	Adverse effects	Year approved	Year safety warning added
Arava (leflunomide)	Rheumatoid arthritis	Hepatotoxicity	1998	2003
Viramune (nevirapine)	HIV	Hepatotoxicity	1996	2004
Prandin (repaglinide)	Type II diabetes	Drug–drug interactions	1997	2003
Risperdal consta (risperidone)	Schizophrenia	Stroke	2003	2003
ORLAAM (levoacetyl methadol)	Opiate dependency	Arrythmia	1993	2001
Accutane (isotretinoin)	Severe nodular acne	Pregnancy (interaction with birth control pills); deformity	1982	2003

Information obtained from the U.S. Food and Drug Administration webpage: http://www.fda.gov/medwatch/.

There is therefore an urgent need to develop approaches to enhance the accuracy of the prediction of human drug safety to avoid the marketing of drugs with serious adverse effects. The ability to accurately predict human adverse effects in practical terms means a higher percentage of clinical trial successes and a lower frequency of withdrawal of marketed drugs due to unexpected adverse effects, thereby enhancing the overall efficiency of drug development. A recent study estimated that a drug manufacturer can reduce the cost of drug development by approximately $350 million via an increased clinical success rate from one-in-five to one-in-three (saving $221 million), and by reducing the total development and regulatory review time by 25% (saving $129 million) [3].

2. Reasons for failures in the prediction of human drug toxicity

A clear understanding of reasons for the failure to predict human drug toxicity is the first step to the devel-

Table 3
An example of a common approach to drug safety evaluation

1.	Selection of drug candidates based on efficacy (e.g. potency)
2.	Pharmacokinetics, pharmacodynamics and toxicokinetics studies in laboratory animals for dose selection
3.	Preclinical safety studies: acute, subchronic, chronic in three animal species
4.	Application to FDA for Investigative New Drug (IND) status for human trials
5.	Phases I, II, III clinical trials for safety and efficacy evaluations
6.	New Drug Application (NDA) to FDA for marketing approval
7.	Post-marketing survey
8.	If unexpected adverse effect, report to FDA and send Dear Health Professional letter; FDA will also send warning letters
9.	Probable change in labeling, “boxed warning”, or market withdrawal, depending on circumstances

opment of a better approach. A review of the standard approach to drug development yields clues on why human drug toxicity is not always accurately predicted (Table 3). Drug safety is initially evaluated preclinically in laboratory animals, generally in three animal species such as mouse, rat and dog. Preclinical safety study results are submitted to the U.S. Food and Drug Administration (FDA) for the approval of Investigative New Drug (IND) status for subsequent clinical trials in human subjects.

This standard approach appears to be adequate—toxicity is first defined in three species of animals followed by human trials. Drug candidates with unacceptable toxicity toward both laboratory animals and humans should be detected by the preclinical safety trials. Drugs with toxicity only in humans and not in nonhuman animals should be detected in the clinical trials. However, this approach has several pitfalls:

1. Studies in laboratory animals do not always reflect human drug toxicity because of species–species differences:
   a. Toxic and detoxifying mechanisms may be different between laboratory animals and humans. A drug may be nontoxic to laboratory animals and toxic to humans if, for instance, the toxicity is due to a human-specific metabolite, or if the detoxifying mechanism in the rat is absent in humans. That animals and humans have different drug metabolizing enzymes is a well-established phenomenon. A dramatic difference between rat and man in drug metabolism is demonstrated by the metabolism of coumarin, an anticoagulant. The human metabolite, 7-hydroxycoumarin, is not made by the rat [4].
   b. Sensitivity to toxic effects is different between laboratory animals and humans. Species differences in toxicity may not be due to differences in metabolism, but due to the inherent sensitivity of the affected cell populations to the toxicant. An example is observed with bizelesin, a potent synthetic derivative of the anticancer agent CC-1065 that preferentially alkylates and binds the minor groove of DNA. Results with myelopoietic cells in vitro, in the absence of liver metabolism, reproduced species differences in myelosuppression as observed in vivo, showing that murine cells are 1000-fold more sensitive than human and canine cells [5]. The results of this in vitro study suggest that in addition to species differences in drug metabolism, target cell sensitivity differences between species may also account for species differences in toxicity.
2. The assumption that all drugs that are toxic to humans would be detected in clinical trials may not be true for the following reasons:
   a. Limitations with toxicity endpoints. Unlike in laboratory animals where one can sacrifice the animals and examine the tissues, for ethical reasons, only relatively noninvasive endpoints for toxicity evaluation can be used in human clinical trials. Such endpoints include overt signs of toxicity and clinical chemistry of body fluids which only yield information that reflects serious, acute toxicity.
   b. Limitation of the number of individuals in a study. The number of patients involved in clinical trials is significantly smaller than the millions of patients that may be administered a new drug. Events that occur in rare frequencies (e.g. idiosyncratic drug toxicity that occurs in less than 1 in 5000 patients [6]) would not be detected in Phases I, II and III clinical trials, but would show up after the marketed drug is administered to a large patient population.
   c. Lack of representation of the true patient population. The patient population administered the drug post-marketing may contain individuals which may not be represented in the clinical trials. Some environmental conditions (e.g. co-administered drugs and foods) are extremely difficult to model in the clinical trials. Rare genetic variations, especially genetic factors which are not yet discovered but may enhance drug toxicity, are not likely to be represented in the clinical trials.
   d. Alterations of formulation after approval. New formulations manufactured and marketed after the initial approval may have a different dosage form or higher bioavailability, thereby may lead to unexpected adverse drug reactions. This, however, is one factor that can be corrected via vigilance in drug labeling and usage.

3. A need for toxicology to be an investigative discipline

Toxicity is a complex biological property that cannot be accurately estimated purely based on dose–response relationships without a sound scientific understanding of the effects. Classical toxicologists rely on Paracelsus' Principle [7]:

"All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison."

This principle of toxicology derived in the 15th century is the cornerstone of today's traditional practice of toxicology. Dose–response relationship is the most important data set from which safety is determined. For drugs, safety is estimated based on therapeutic index, a ratio of the toxic dose to the dose required for efficacy. It is because of Paracelsus' Principle that toxicologists in general believe that safety can be estimated based on dose–response relationships without a need for mechanistic definition [7].

This empirical approach to safety evaluation is apparently not adequate, judging from the number of drugs with serious, sometimes fatal adverse effects which have been erroneously concluded to have an acceptable toxicity profile in preclinical and clinical safety studies. It is proposed here that drug toxicity should be defined based not only on dose–response relationship, but also as a function of all relevant scientific disciplines including pharmacology, chemistry, metabolism and environmental and genetic risk factors. In other words, toxicology should be changed from an empirical practice to an investigative discipline.

A clear mechanistic understanding of drug toxicity and the corresponding risk factors should improve the accuracy of the prediction of drug toxicity in the human population from experimental findings. Accurate prediction of human drug toxicity therefore requires additional resources and time to be spent in clearly defining key toxic pathways and the evaluation of risk factors. It is argued here that the additional resources spent will be more than compensated by the benefits of a lower percentage of clinical failure due to toxicity and a decreased frequency of market withdrawal due to unacceptable adverse drug effects.

4. Conclusion

Over the past decades, a number of drugs have been withdrawn or have required special labeling due to adverse effects observed post-marketing. Species differences in drug toxicity in preclinical safety tests and the lack of sensitive biomarkers and nonrepresentative patient population in clinical trials are probable reasons for the failures in predicting human drug toxicity. It is proposed that toxicology should evolve from an empirical practice to an investigative discipline. Accurate prediction of human drug toxicity requires resources and time to be spent in clearly defining key toxic pathways and corresponding risk factors, which hopefully, will be compensated by the benefits of a lower percentage of clinical failure due to toxicity and a decreased frequency of market withdrawal due to unacceptable adverse drug effects.

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