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

Albert P. Li

Advanced Pharmaceutical Sciences, Inc., PMB#146, 6400 Baltimore National Pike, Baltimore, MD 21228, USA

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Over the past decades, a number of drugs have been withdrawn or have required special labeling due to adverse effects observed post-marketing.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 [1] found that in the last four decades, 2.9% of the marketed drugs were withdrawn from the market due to severe adverse drug effects, with seven drugs approved and marketed since 1993 and subsequently withdrawn to be associated with over 1000 deaths.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 Examples of the recently withdrawn drugs and drugs that required box warnings are shown in Tables 1 and 2, respectively.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.
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 develop-

<table>
<thead>
<tr>
<th>Drug (chemical)</th>
<th>Indication</th>
<th>Adverse effects</th>
<th>Year approved</th>
<th>Year safety warning added</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azaia (leflunomide)</td>
<td>Rheumatoid arthritis</td>
<td>Hepatotoxicity</td>
<td>1998</td>
<td>2003</td>
</tr>
<tr>
<td>Viramune (nevirapine)</td>
<td>HIV</td>
<td>Hepatotoxicity</td>
<td>1996</td>
<td>2004</td>
</tr>
<tr>
<td>Pravusil (repaglinide)</td>
<td>Type II diabetes</td>
<td>Drug-drug interactions</td>
<td>1997</td>
<td>2003</td>
</tr>
<tr>
<td>Riopental (isoprenaline)</td>
<td>Schizophrenia</td>
<td>Stroke</td>
<td>2003</td>
<td>2003</td>
</tr>
<tr>
<td>ORLAAM (levosulfa)</td>
<td>Opiate dependency</td>
<td>Agranulocytosis</td>
<td>2003</td>
<td>2003</td>
</tr>
<tr>
<td>Accutane (isotretinoin)</td>
<td>Severe nodular acne</td>
<td>Pregnancy (interaction with birth control pills); deformity</td>
<td>1982</td>
<td>2003</td>
</tr>
</tbody>
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Information obtained from the U.S. Food and Drug Administration webpage: http://www.fda.gov/medwatch/.

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 Investigational New Drug (IND) status for human trials
5. Phase 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 in nonhuman animals should be detected by the preclinical and humans should be detected in the toxicity evaluation can be used in human clinical studies. 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) 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 toxicity 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.

References