Chemico-Biological Interactions 192 (2011) 65–71

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

Risk assessment and mitigation strategies for reactive metabolites in drug discovery and development

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ARTICLE INFO

Article history:
Available online 11 November 2010

Keywords:
Reactive metabolite
Adverse drug reaction
Hepatotoxicity

ABSTRACT

Drug toxicity is a leading cause of attrition of candidate drugs during drug development as well as of withdrawal of drugs post-licensing due to adverse drug reactions in man. These adverse drug reactions cause a broad range of clinically severe conditions including both highly reproducible and dose dependent toxicities as well as relatively infrequent and idiosyncratic adverse events. The underlying risk factors can be split into two groups: (1) drug-related and (2) patient-related. The drug-related risk factors include metabolic factors that determine the propensity of a molecule to form toxic reactive metabolites (RMs), and the RM and non-RM mediated mechanisms which cause cell and tissue injury. Patient related risk factors may vary markedly between individuals, and encompass genetic and non-genetic processes, *e.g.* environmental, that influence the disposition of drugs and their metabolites, the nature of the adverse responses elicited and the resulting biological consequences.

We describe a new strategy, which builds upon the strategies used currently within numerous pharmaceutical companies to avoid and minimize RM formation during drug discovery, and that is intended to reduce the likelihood that candidate drugs will cause toxicity in the human population. The new strategy addresses drug-related safety hazards, but not patient-related risk factors. A common target organ of toxicity is the liver and to decrease the likelihood that candidate drugs will cause liver toxicity (both non-idiosyncratic and idiosyncratic), we propose use of an *in vitro* Hepatic Liability Panel alongside *in vitro* methods for the detection of RMs. This will enable design and selection of compounds in discovery that have reduced propensity to cause liver toxicity. *In vitro* Hepatic Liability is assessed using toxicity assays that quantify: CYP 450 dependent and CYP 450 independent cell toxicity; mitochondrial impairment; and inhibition of the Bile Salt Export Pump. Prior to progression into development, a Hepatotoxicity Hazard Matrix combines data from the Hepatic Liability Panel with the Estimated RM Body Burden. The latter is defined as the level of covalent binding of radiolabelled drug to human hepatocyte proteins *in vitro* adjusted for the predicted human dose. We exemplify the potential value of this approach by consideration of the thiazolidinedione class of drugs.

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1. Introduction

Discovery and development of innovative new medicines is essential to address unmet medical need, yet is a high risk activity. The costs of drug discovery and development are substantial and increasing due to the great expense incurred in running large clinical trials to prove efficacy and safety. However, the likelihood of success is low because of the high rate of attrition of candidate drugs throughout all stages of preclinical and clinical development. One of the most important causes of attrition is toxicity [1]. For many compounds, toxicity is evident during preclinical Safety Testing in Preclinical Species and results in compound termination prior to clinical progression, or restricted levels of exposure in humans which reduces the likelihood that clinical efficacy can be achieved [2]. However, numerous candidate drugs do not cause toxicity in preclinical species, even though they cause adverse effects in man.

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0009-2797/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.cbi.2010.11.002

Typically, such adverse events occur relatively infrequently, typically 1 in 10,000 to 1 in 100,000 patients [3]. Further they do not exhibit overt dose dependency, *i.e.* patients who develop these do not receive higher doses of drug than non-susceptible individuals. Collectively, these toxicities are termed "idiosyncratic" adverse drug reactions (IADRs) [2,4,5].

Since they are not detected in non-clinical drug safety studies and occur rarely in man, IADRs are a major cause of drug attrition in late phases of clinical development, failed drug licensing, drug withdrawal post-licensing and restrictive monitoring and/or labeling. The clinical consequences encompass a broad range of clinically severe and potentially life threatening conditions which include injury to the liver (the most frequent IADR) and/or other target organs, cutaneous reactions, aplastic anemia, blood dyscrasias and immune hypersensitivity reactions [2,4]. Although the incidence of IADRs caused by individual drugs is typically low, many hundreds of different drugs can cause such reactions. Consequently, they represent a leading cause of serious ill health in the human population, when considered collectively.

A reduction in the likelihood that a drug candidate will cause toxicity detected in preclinical species, and/or IADRs detected in man, has therefore the potential to markedly improve both the health of the patient population by minimizing human exposure to drugs that may cause adverse effects and the success rate in drug discovery and development within the pharmaceutical industry. A major challenge confronting the industry currently is to establish how this can be achieved.

It is widely recognized that some drugs have markedly higher potential to cause either dose dependent toxicity or IADRs than other drugs, and that overall this is unrelated to overt pharmacological activity or clinical efficacy. Numerous examples have been described, which include neuroleptics (rank order of IADR risk clozapine > olanzapine, quetiapine); anxiolytics (IADR risk alpidem > zolpidem), antidiabetics (IADR risk carutamide > tolbutamide) and volatile anesthetics (rank order halothane > enflurane > isoflurane > desflurane) and many other drug classes [6]. Furthermore, the incidence, severity and pattern of IADRs vary markedly between drugs. This implies that the risk factors relevant to drug safety can be broadly split into two groups: drug-related and patient-related (Fig. 1) [7]. The drug-related factors define the chemical insult to the relevant target organ, and will include the Absorption, Distribution, Metabolism and Excretion (ADME) properties of the drug, target organ exposure to the drug and its metabolites which in turn will be influenced by dose and disposition. Further the drug-related factors also include the molecular and cellular events by which toxicity may arise (which are discussed below). The patient-related factors define the nature of the biological response to chemical insult within the individual patient. These can be expected to encompass a broad range of properties, *e.g.* underlying disease, age, gender, co-medications, nutritional status, activation of the innate immune system, physical activity and genetic predisposition.

One important mechanism by which toxicity may arise (and hence a key drug-related risk factor) is *via* formation of chemically reactive metabolites (RM). The relationship between RM formation and drug toxicity is complex. An essential first step is RM formation within the relevant target cell, which can involve many different drug metabolizing enzymes but is commonly mediated by Cytochrome P450 (CYPs). The RM represents a "chemical insult", which interacts with cellular macromolecules and cell signaling systems and elicits a complex cascade of biological responses that are not well characterized, even for toxic compounds that have been investigated extensively. A relatively small number of drugs cause dose dependent toxicity, and the role played by RMs in toxicities caused by some of these is well established. A classic example is the liver toxicity caused by acetaminophen, which is oxidized within hepatocytes by the cytochrome P450s (CYPs) to a quinone imine reactive metabolite that can be detoxified by conjugation to glutathione. When acetaminophen is administered in overdose high levels of the RM are formed which result in glutathione depletion, oxidative stress, covalent binding to hepatic proteins, activation of the innate immune system and ultimately hepatocellular necrosis [8].

Formal proof that RM formation is directly responsible for IADRs in man has yet to be obtained. This is due to their relative infrequency, the paucity of relevant animal models and the complex processes involved. Nonetheless, a substantial weight of evidence has been accumulated which implicates RM formation in numerous IADRs, and has been reviewed extensively by previous authors. In particular, compelling evidence has been obtained linking RM mediated protein haptenation to induction of drug-specific adaptive immune responses, which cause a broad range of immune mediated IADRs [9,10]. It is important to be aware that RM formation is one of several processes which have the potential to initiate both dose dependent toxicity and IADRs. Among other important initiating mechanisms are mitochondrial toxicity; lysosomal

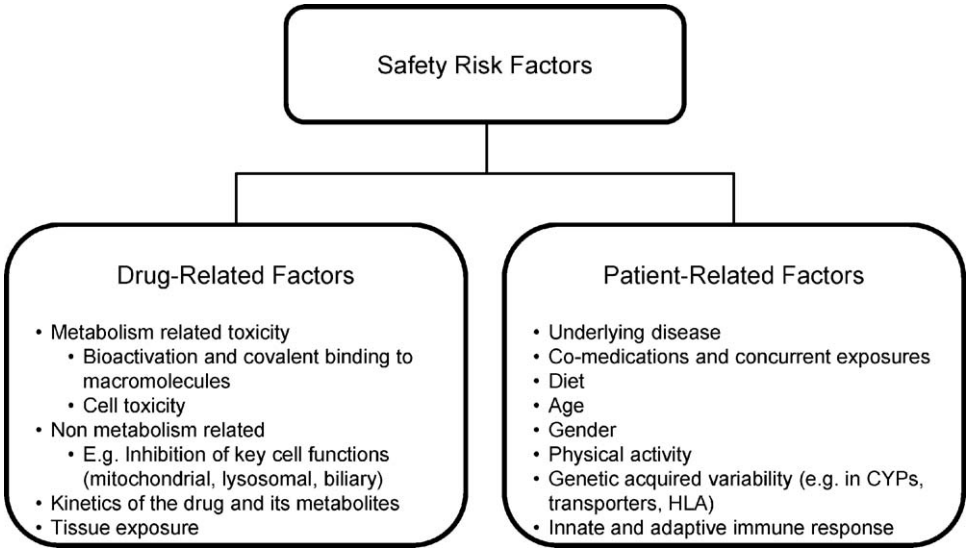

Fig. 1. Safety risk factors [7].

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