Idiosyncratic Drug Reactions
Metabolic Bioactivation as a Pathogenic Mechanism

Munir Pirmohamed, Stephen Madden and B. Kevin Park
Department of Pharmacology and Therapeutics, The University of Liverpool, Liverpool, England

Contents

Summary .................................................. 215
1. The Role of Drug Metabolism in Idiosyncratic Toxicity ........................................ 217
2. Drug Metabolising Enzymes Involved in Bioactivation ........................................ 218
3. Cytochrome P450 (CYP) Enzymes ................................................................. 218
   3.1 CYP1A Subfamily .................................................. 219
   3.2 CYP2 Family .................................................... 220
   3.3 CYP3A Subfamily .................................................. 222
   3.4 Multiple CYP Isoforms .................................................. 223
4. Phase II Enzymes .................................................. 224
   4.1 Glucuronyl Transferase .................................................. 225
   4.2 Glutathione-Transferase .................................................. 225
   4.3 Microsomal Epoxide Hydrolase .................................................. 225
   4.4 Myeloperoxidase .................................................. 225
   4.5 Prostaglandin H Synthetase .................................................. 226
5. Conclusion .................................................. 226

Summary

The metabolism of drugs to chemically reactive metabolites may play a pivotal role in the pathogenesis of idiosyncratic drug toxicity. A large number of in vitro studies and a limited number of in vivo studies have demonstrated that many drugs are not toxic per se, but produce toxicity after undergoing enzyme-mediated bioactivation to chemically reactive species. Such reactive species may inflict a toxic insult on the cell either directly or indirectly by acting as a hapten and initiating an immune-mediated reaction.

The enzymes responsible for bioactivation have been widely studied, both quantitatively and qualitatively, the most important being the enzymes of the cytochrome P450 (CYP) mixed function oxidase system. CYP enzymes are the most predominant drug metabolising enzymes in the liver and are also present in most other tissues of the body. The diversity of this enzyme system means that a wide range of xenobiotic substrates can be bioactivated by either a single CYP isoform or multiple isoforms of this enzyme superfamily. Other enzymes do, however, play an important role in drug bioactivation. In white blood cells, for example, myeloperoxidase has been shown to bioactivate a wide range of drugs.

In other tissues low in CYP activity, prostaglandin H synthase may also be responsible for bioactivation; e.g. in the kidney paracetamol (acetaminophen) toxicity is thought to result from activation via this enzyme. The phase II or conjugation enzymes may also be important in the ultimate bioactivation of drug
molecules. Whilst activation by these enzymes is, to date, apparently confined to chemicals, most drugs are also substrates for these enzymes and bioactivation by them must remain a possibility.

Toxic reactions to drugs can take many forms, can simulate any disease, affect any organ and vary in severity. Although many different classifications of drug toxicity have been described, perhaps the simplest and clinically most useful classification is where adverse reactions are divided into 2 types: [1]

- Dose-dependent reactions (also called type A reactions), which can be predicted from the known pharmacology of the drug, and can be alleviated by dose reduction.
- Apparently dose-independent reactions, also termed idiosyncratic reactions (type B reactions), which are not predictable from the known pharmacology of the drug, and which usually require drug discontinuation rather than dose reduction to alleviate the reaction.

Idiosyncratic drug reactions are usually thought to be dependent on the host, predisposition being due to either the environment or genetic constitution of the host, or a combination of both. As such, idiosyncratic drug reactions are much less common than dose-dependent reactions, and tend to be more severe; they cannot usually be reproduced in animal models. [2]

It is important to note that there are many mechanisms for idiosyncratic drug reactions and not all are due to drug bioactivation; these have been covered elsewhere. [3] In this review, we focus on those idiosyncratic reactions in which drug metabolism, and in particular drug bioactivation to toxic chemically reactive metabolites, plays an important part. [3]

It is also important to note that the term idiosyncratic does not imply whether such reactions are because of direct toxicity of a chemically reactive

Fig. 1. The role of drug metabolising enzymes in the bioactivation and bioinactivation of drugs. The formation of a chemically reactive metabolite, if inadequately detoxified, may lead to covalent binding to cellular macromolecules, resulting in various forms of toxicity including necrosis, teratogenicity and hypersensitivity.

© Adis International Limited. All rights reserved.