The Role of Drug Metabolism in Toxicity

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1 INTRODUCTION

The term "toxicity" in general denotes any adverse event that results from exposure to an agent, which includes a wide variety of substances: natural or man-made, physical, chemical, biological or radiological, and endogenous or exogenous. Toxicity can result from exaggerated on-target pharmacology, unrelated off-target activity, or biotransformation to a metabolite that is reactive and/or more potent in its on- or off-target activity. Evolutionary pressures have equipped species, from bacteria to humans, with a complement of enzymes that help to regulate and limit the exposure and/or accumulation of xenobiotic agents, such as those encountered in the diet, the environment, accidental or deliberate exposure to poisons, or from administration of therapeutic agents. Usually these drug-metabolizing enzymes (DMEs) facilitate the elimination of xenobiotics from the body and serve principally as a detoxification process. However, in some cases, the same enzymes can be involved in the bioactivation of a xenobiotic and/or its metabolite(s) to facilitate adverse reactions and toxicity. In addition to the toxic agent itself, several important factors also contribute to or even determine the interspecies and interindividual variability and susceptibility to toxicity. These include differences in the expression of metabolizing enzymes, population differences or polymorphisms in the enzymes expressed, physiological state, underlying disease, age, and interactions associated with concurrently administered drugs.

There are many textbooks and reviews on both toxicity and the role of biotransformation; however, very few articles have reviewed the specific role of DMEs and susceptibility to toxicity. This chapter is intended for the practicing pharmaceutical scientist and provides real-world examples potentially encountered when evaluating and developing drug candidates. We describe the drug toxicity that is mediated predominantly through the formation of reactive metabolites. To extend the scope beyond the specific case to the general, we also summarize some key characteristics of the common enzymes encountered in metabolic clearance of drugs and highlight elements to consider, such as differences in tissue expression between species and/or gender. Examples are offered

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