Evaluating and Predicting Human Cytochrome P450 Enzyme Induction

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1 INTRODUCTION

Cytochrome P450 (CYP) isoforms are the predominate enzymes involved in the biotransformation and elimination of xenobiotics. Since their identification and characterization in 1962, they have become one of the most published enzyme systems in pharmaceutical research (Omura and Sato, 1962). Given their prevalence for metabolizing and eliminating drugs, interactions or events that manipulate the concentration or function of CYP enzymes have great impact on drug disposition, toxicity, and pharmacology. The most common alterations to drug-metabolizing enzyme function are due to (i) genetic polymorphisms, (ii) enzyme inhibition, and (iii) enzyme induction. The focus of this chapter will be on CYP enzyme induction, including methods to evaluate, predict, and quantitate drug interactions due to enzyme induction. Enzyme induction is the action of creating more enzymes than is normally present in a biological system and can be manifested by increased gene transcription or decreased protein or mRNA degradation. As early as 1954, the first report of enzyme induction appeared in a manuscript by Brown *et al.*, who described the enzyme-inducing effects of various food diets when given to rodents and the resulting increased enzymatic effects of *N*-demethylation in liver homogenates (Brown, Miller and Miller, 1954). This was followed some time later by the first review on microsomal enzyme induction in 1967 (Conney, 1967). Interestingly, some of the original nomenclature used to describe CYP enzymes was based on enzyme-inducing agents employed to increase CYP-isoform levels making them easier to characterize. For example, BNF-B was used to identify a CYP1A enzyme and PB-4/5 for a CYP2B enzyme, after treatment with the inducing agents β-naphthoflavone and phenobarbital (PB), respectively.

The increase in enzyme activity caused by a drug is reflected in an increased hepatic clearance of drugs metabolized by the induced enzyme. Various terms are used to describe the drug that causes enzyme induction (perpetrator or inducer) and the drug

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