Enzyme Inhibition

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1 INTRODUCTION

Inhibition of the catalytic activities of the drug-metabolizing enzymes has received considerable attention from clinical pharmacologists and pharmaceutical companies in the past 20 years, because of the fact that several widely used drugs or drugs in the late stages of development were shown to cause life-threatening adverse affects when given to patients taking other drugs due to their ability to inhibit the metabolism of those drugs. The inhibition of the metabolism of one drug by another drug taken concurrently by the patient has now been shown to be a very important cause of adverse drug reactions (ADRs). The potential for drugs to interact with one another by competing for metabolism by the same drug-metabolizing enzyme continues to be a significant health concern and, if anything, will probably become of greater concern in the coming years. ADRs are suggested to be responsible for up to 10% of all hospital admissions (Kohler *et al.*, 2000). In addition, drug–drug interactions are estimated to be implicated in up to 20% of all ADRs (Levy *et al.*, 1980). The probability that ADRs associated with drug–drug interaction increase as the number of drugs administered concomitantly increases is generally accepted as true, and the occurrence of ADRs is believed to increase very rapidly as the number of drugs given simultaneously to a patient increases. When the activity of a given drug-metabolizing enzyme is modified by inhibition, this modification may not only change the pharmacokinetics of the drug whose metabolism is inhibited by leading to an increase in the levels of the parent drug in the patient but, where more than one enzyme may be responsible for the metabolism of a drug and the different enzymes may result in the formation of different products, it may result in a significant change in the profile of the metabolites formed. If any of the different products formed have significantly enhanced or decreased biological and/or toxicological properties, this may lead to significantly altered biological or toxicological activity. Since many of the drug-metabolizing enzymes may be viewed as being relatively nonspecific (i.e. very promiscuous) in their substrate specificity, it is not surprising that two or more drugs can compete for metabolism by the same enzyme resulting in inhibition of the metabolism of one or both of the drugs. This can lead to enhanced metabolism

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