Clinical Drug–Drug Interactions

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1 INTRODUCTION

In the current health-care system, patients are typically on multiple medications for the treatment of one or more medical conditions. It is thus plausible that drugs may interact with each other in the human body. When these *in vivo* interactions result in a significant change in the pharmacokinetic or pharmacodynamic properties of at least one of the drugs, it is considered a clinical drug–drug interaction (DDI). Pharmacokinetic interactions are often multifactoral; these involve alteration of drug metabolism, drug transporter functions, percent of drug bound to plasma proteins, and drug excretion. Pharmacokinetic interactions that lead to adverse reaction or lack of efficacy are extremely detrimental to the patients and constitute as a major concern to the health-care providers. Pharmacodynamic interactions are those where the drug levels at the site of action are unaffected but its effects are altered; these may be synergistic, additive, or antagonistic in nature. Given the scope of this book, the following chapter will focus on the pharmacokinetic-based DDIs.

Recognizing and remembering pharmacokinetic-based DDIs are a daily challenge for many clinicians. It is thus important that drugmakers identify potential interactions that may occur when a drug is coadministered to humans with other medications. Several *in vitro* studies conducted at the drug discovery/development stages can alert against the possible risk for drug interaction and can help designing appropriate clinical studies to fully address the potentials of pharmacokinetic-based DDI. Early clinical studies directed toward studying potential DDIs are an integral and critical component of the drug discovery/development processes. Although the occurrence of a DDI does not preclude the use of a drug, it alerts the medical practitioner against the potential for DDI when used in combination with other drugs.

The factors that influence DDIs can be categorized as patient-related and drug-related. The patient-related factors are age, sex, disease condition, diet/nutrition, genetics, and environment. The drug-related factors include dose, dosing frequency, pharmacokinetic parameters like half-life, volume of distribution, oral availability, route of elimination, and interaction mechanism (Herman, 1999) (Fig. 1).

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