Handbook of Drug Interactions

FORENSIC SCIENCE AND MEDICINE

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HANDBOOK OF DRUG INTERACTIONS

A CLINICAL AND FORENSIC GUIDE

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Cover illustration: Two complementary views of drug interactions. The mathematical modeling of the drug is shown as a classic first order kinetic elimination curve and alteration in pharmacokinetics is amongst the best understood potential for undesired effects from combinations of two or more pharmaceuticals. But harder to grasp are the dynamic effects of drugs. The results of binding to target proteins, such as ion channels, can change the overall activity of cells, such as neurons, which in turn impinge on other target tissues. These pharmacodynamic interactions are complex and culminate in the symptomatology observed in the patient. Any combination of chemicals in the body, endogenous or not, is a fluid game of competitions, synergies, or antagonisms at the metabolic and functional level. The results may go unseen, may be beneficial, may be harmful or, in some cases, lethal to the subject.

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Preface

Drug interactions and adverse drug effects have received much attention since studies published in daily newspapers have shown that they result in upwards of 100,000 Americans each year being hospitalized or remaining hospitalized longer than necessary, as well as leading to the death of a number of patients. Use of multiple drugs (8–12 on average in hospitalized patients) is common in a number of therapeutic regimens. In addition to multiple drug therapy, a patient may have access to several prescribers, and may have predisposing illnesses or age as risk factors for interactions. Drug interactions may occur between prescription drugs, but also between food and drug, and chemical and drug. Whereas some may be adverse, interactions may also be sought to decrease side effects or to improve therapeutic efficacy.

Combining drugs may cause pharmacokinetic and/or pharmacodynamic interactions. Pharmacokinetic mechanisms of interaction include alterations of absorption, distribution, biotransformation, or elimination. Absorption can be altered when drugs that alter pH or motility are co-administered, as seen with certain antiulcer or antidiarrheal medications, or when drugs are chelators or adsorbents (tetracyclines and divalent cations, cholestyramine, and anionic drugs). Distribution variations can result from competition for protein binding (sulfa drugs and bilirubin binding to albumin) or displacement from tissue-binding sites (digitalis and calcium channel blockers or quinidine). Induction of gene expression (slow), activation or inhibition (much quicker) of liver and extrahepatic enzymes such as P450, and conjugating enzymes have long found a place of choice in the literature describing the potential for adverse drug interactions resulting from altered metabolism. For example, induction is well described with the major anticonvulsant medications phenytoin, carbamazepine, and barbiturates, whereas inhibition can occur with antimicrobials from the quinolone, the macrolide, and the azole families. Finally, excretion can also be modified by drugs that change urinary pH, as carbonic anhydrase inhibitors do, or change secretion and reabsorption pathways, as probenecid does. Pharmacokinetic interactions in general result in an altered concentration of active drug or metabolite in the body, modifying the expected therapeutic response.

A second form of interaction has received little attention because of its modeling complexity and perhaps the poor understanding of basic physiological, biochemical, and anatomical substrates for drug action. Pharmacodynamic interactions involve additive ($1 + 1 = 2$), potentiating ($0 + 1 = 2$), synergistic ($1 + 1 = 3$), or antagonistic ($1 + 1 = 0$)

effects at the level of receptors. Receptors are mainly proteins, such as enzymes (acetylcholinesterase, angiotensin-converting enzyme, for example), transport proteins (digitalis and Na^+/K^+ ATPase), structural proteins (colchicine and tubulin), or ion channels (Class I antiarrhythmics and voltage-dependent sodium channels). Large families of receptors to drugs involve signal transduction pathways and changes in intracellular second messenger concentrations (autonomic nervous system drugs and α , β , muscarinic receptors, for example). Finally, even less understood are interactions at the level of nucleic acids such as DNA and RNA, which can change the levels of expression of key proteins in target tissues (tolerance, tachyphylaxis of numerous central nervous system drugs).

Handbook of Drug Interactions: A Clinical and Forensic Guide addresses both types of drug interactions, emphasizing explanations when possible, and careful review of the general pharmacology. The result, we hope, will prove useful to health and forensic professionals as well as medical, pharmacy, nursing and graduate students alike.

Ashraf Mozayani
Lionel P. Raymon

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