

Drug Interactions

Interaction is a familiar term to most biostatisticians. When the effect of one factor differs across levels of a second factor, interaction between the factors is present. Drug disposition refers to the processes of how a drug is absorbed, distributed, metabolized (broken down), and excreted [6]. Variations in drug disposition and/or effect may result from interactions with, for example, diseases or genetic make-up. *Drug interactions* refers to the alteration of the disposition and/or effect of one drug, owing to the presence of a second drug.

What Causes Drug Interactions and Why are They Important?

Drug interactions arise from a myriad of complex physiologic conditions [5]. **Pharmacokinetics** refers to what the body does to the drug (processes of drug disposition), while pharmacodynamics refers to what the drug does to the body (the drug effect). Changes in the processes of drug disposition, known as the pharmacokinetic interaction, may take place when one drug's rate of elimination from the kidneys or liver is altered by a second drug. In such circumstances a drug can improperly accumulate in the body or be excreted too quickly. Another type of pharmacokinetic interaction can occur when specific enzymes that metabolize a drug become inhibited or induced by the presence of a second drug. A pharmacodynamic interaction refers to the alteration of the effects of one drug when given concurrently with another drug. The net result of a pharmacodynamic interaction may be an enhanced or diminished effect or the appearance of a new side-effect that was not seen with either drug alone.

Drug interactions may pose a dangerous threat to public health, especially when two commonly prescribed (and co-administered) drugs interact. A notable example is the gravely serious drug interaction between terfenadine (Seldane), a commonly prescribed anti-histamine, and ketoconazole, a popular anti-fungal drug [2, 4] When these drugs were taken simultaneously, unexpected life-threatening

EKG changes (a syndrome known as Torsades de Pointes) and deaths occurred that were later attributed to an interference to the same key metabolizing enzymes shared by both drugs.

How Does Inter-Subject Variability Play a Role?

Studies that measure drug pharmacokinetics and/or pharmacodynamics are often challenged by substantial and unpredictable *inter-subject variability*. How the body processes a drug can differ greatly among subjects. This inherent variability in drug disposition is known as inter-subject pharmacokinetic variation. For a group of subjects given a fixed dose of a single drug, a large variation in serum drug levels (i.e. a coefficient of variation of 60% or greater) is commonly noted. Hence, for a two drug interaction study it is extremely difficult to partition the observed pharmacologic variation of one drug into underlying inter-subject pharmacokinetic variation vs. the variation due to the presence of a second drug. Moreover, identifying the sources of observed variability in drug effect, termed inter-subject pharmacodynamic variation, poses even greater difficulties. Suppose a target serum drug level can be achieved and maintained in a group of subjects. Even though the body's exposure to the drug is the same in all subjects, the variation in effect (e.g. lowered blood pressure) among subjects may be substantial. Introducing an additional source of variability, such as a second drug, further complicates the interpretation of inter-subject differences.

Which Study Design Addresses Inter-Subject Variability?

One design appropriate for testing drug interaction is a repeated measure design (*see Longitudinal Data Analysis, Overview*) [1]. This design, commonly called a crossover or **randomized complete blocks designs**, allocates all treatments to each subject, with an adequate "washout" period between treatments. Repeated measures denotes the serial measurements of drug disposition and/or effect after each treatment is administered. As each subject serves as his/her own control, all sources of variability among subjects are controlled. Only variation within subjects (the treatment effect) enters into the analysis. Typically,

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crossover studies designed to test for pharmacokinetic interaction enroll 10–25 subjects.

For a two-drug interaction study of drugs A and B, each subject receives drug A, drug B, and a combination of drugs A and B. The order of the three treatments is often randomly assigned and balanced so that the measurements are not **confounded** by treatment order. The model for a repeated measures design for a two-drug interaction study is

$$Y_{ij} = \mu_{..} + \rho_i + \tau_j + \varepsilon_{ij}, \\ i = 1, \dots, n, j = 1, 2, 3,$$

where i denotes the subjects and j denotes the treatments (let $j = 1$ for drug A, $j = 2$ for drug B, and $j = 3$ for a combination of A and B). Y_{ij} denotes the measure of drug disposition or effect when the i th patient is given the j th treatment, $\mu_{..}$ denotes the overall outcome mean, ρ_i denotes the subject effect, τ_j denotes the treatment effect, and ε_{ij} denotes the error term. Individual subject effects are not of interest and only serve to reduce experimental error due to inherent inter-subject variability. Interaction is tested by a comparison between treatment means (analogous to a **paired t test**) and is performed by planned **contrasts**. For example, to test whether the effect of drug A is altered by drug B, the **null hypothesis** of no interaction is tested by

$$H_0 : \mu_{.j} - \mu_{.j'} = 0,$$

where, as noted above $j = 1$ and $j' = 3$. Similarly, to test whether the effect of drug B is altered by drug A, the null hypothesis of no interaction is tested by:

$$H_0 : \mu_{.j} - \mu_{.j'} = 0,$$

where $j = 2$ and $j' = 3$.

A recently published crossover study designed to test for the pharmacokinetic interaction between two agents, atovaquone and zidovudine, serves as an example [3]. Patients with human immunodeficiency virus (HIV) are at risk from adverse drug interactions because of the many drugs commonly prescribed to treat their disease and symptoms, such as pneumocystis carinii pneumonia (PCP). Atovaquone is an agent shown to be effective against PCP. Zidovudine is an anti-retroviral agent used as primary treatment for acquired immunodeficiency syndrome (AIDS). A high percentage of patients who receive treatment for PCP are also treated with anti-retroviral agents, so it is likely that these agents may be co-administered.

A study was conducted to test whether the drugs could be co-administered without significant pharmacokinetic interaction. The treatment consisted of 26 consecutive days of therapy, defined by three dosing periods. Zidovudine was administered in the first dosing period (on days 1 and 2). Periods 2 and 3 consisted of 12-day intervals in which either atovaquone alone or atovaquone plus zidovudine was administered. The order of periods 2 and 3 was randomly assigned (*see Randomization*). Fourteen men with HIV enrolled on the study. Repeated measures analysis revealed that zidovudine and atovaquone could be co-administered without clinically significant pharmacokinetic interaction. Zidovudine had no effect on the disposition of atovaquone, while the systemic exposure of zidovudine was found to be increased by 33% after atovaquone administration.

References

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(*See also Dose–Response in Pharmacoepidemiology; Drug Approval and Regulation; Drug Utilization Patterns; Effect Modification; Interaction Model; Pharmacoepidemiology, Overview; Pharmacoepidemiology, Study Designs; Postmarketing Surveillance of New Drugs and Assessment of Risk-10*).

ROSEMARIE MICK