

Interactions between Drugs Based on Pharmacokinetics

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Introduction

When a patient receives two medications, the pharmacokinetic and pharmacodynamic characteristics of the drugs may change. Drug interactions primarily occur at the drug metabolism level, but they can also happen at the drug absorption level (e.g., inhibition of intestinal CYP3A4 activity by grapefruit juice or St. John's wort and subsequent reduction in presystemic clearance of CYP3A4 substrates), distribution level (e.g., displacement of warfarin plasma protein binding by ibuprofen with a resulting increase in hemorrhagic risk), or elimination level (e.g., Additionally, drug-drug interactions may happen at the receptor level (via competitive antagonism); many of these are deliberate and help paediatric patients therapeutically (e.g., antihistamine reversal of histamine effects, naloxone reversal of opiate adverse effects) [1].

Drug interactions can also happen at the pharmaceutical level when two drugs are mixed because of physicochemical incompatibility. Such interactions typically change one or both constituents' chemical structures, rendering them inactive and potentially hazardous (e.g., IV infusion of crystalline precipitate or unstable suspension). Due to instances of newborn mortality brought on by crystalline deposits in the lungs and kidneys, ceftriaxone should be avoided in infants younger than 28 days old if they are getting or anticipated to receive IV calcium-containing drugs. Alternatively, a complex that is created when two medications are taken orally at the same time may prevent drug absorption (eg., co-administration of doxycycline with a food or drug containing divalent cations) [2,3].

Description

Based on a priori knowledge of a particular drug's biotransformation profile, drug-drug interactions at the level of drug metabolism can be partially predicted. These limitations with *in vitro* to *in vivo* extrapolation include

- (1) Using animal models for describing metabolism;
- (2) Extrapolating enzyme kinetics from pooled human liver microsomes or recombinant human drug-metabolizing enzymes to estimates of *in vivo* drug clearance; and
- (3) Extrapolating *in vitro* data to estimates of *in vivo* drug clearance. Although such information can be derived from the primary literature, it may not be immediately translated into a useful clinical context.
- (4) The potential role of enzyme induction or inhibition *in vivo* that is not reflected by conditions used for *in vitro* metabolism studies;
- (5) Inaccurate accounting for pharmacogenetic variation in drug-

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metabolizing activity (i.e., constitutive activity); and the contribution of multiple different drug-metabolizing enzymes in overall drug biotransformation.

Despite these drawbacks, knowledge of a drug's effects on drug-metabolizing enzymes (such as substrate, inducer, or inhibitor) can help determine whether the drug has the potential to compete with, induce, or inhibit the metabolism of another drug (e.g., enzyme inhibition enhanced effect vs. enzyme induction diminished effect) of a drug-drug interaction.

PD and PK interactions are the two types of drug-drug interactions. The exposure-response consequences of a PK interaction that result in a stronger pharmacologic impact are sometimes mistaken for interactions that are classified as PD. Antiinfective medication frequently takes advantage of these PD interactions, and it is through this mechanism that combination therapy can have a synergistic impact. PD interaction quantification is, at best, challenging. Although slightly more "predictable," PK interactions still exhibit significant population variability.

Reduction of drug absorption by concurrent drugs

Drug interactions that reduce drug absorption include the chelation of an antibiotic with a cation like calcium, magnesium, or iron. This is the most typical type of absorption interaction. Unless a study has amply established a lack of significant interaction with their coadministration, oral antiinfectives should not be taken within 1 hour before or 2 hours after the administration of oral divalent or trivalent cations.

Displacement from protein-binding sites

Although this interaction theoretically could improve the distribution and effectiveness of antiinfective drugs in tissues, homeostatic mechanisms work to make unbound drugs more difficult to get rid of, leaving little to no change in the amount of drugs that are generally exposed to the body.

Activation of DMEs or transporters

Drug interactions that inhibit, induce, or activate DMEs or transporters are by far the most significant ones observed in clinical practise. The majority of data on drug-drug interactions are gathered from a very small group of people, frequently healthy volunteers, and may not be applicable to the broader populace. It's crucial to keep in mind a few fundamental principles about these drug interactions.

- The baseline activity of DMEs and transporters can be influenced by genetic and environmental variables in addition to the microbiome composition, which will impact the likelihood of drug-drug interactions.
- Despite the fact that drug interactions have been documented in the literature, not all patients actually experience them. Both genetic and environmental factors influence this.
- Drug-drug interactions are less likely to occur in patients with low or null DMEs or transporter activity; but, if this low baseline activity is brought on by a reversible pathologic disease, the risk of drug-drug interactions will rise when the pathologic process is well treated [4,5].

Conclusion

At the level of drug CL, numerous drug interactions take place, especially for medications that are subject to metabolism. Antibiotics are among the many medications whose metabolism is carried out by the CYP450 enzyme system.

Substrate can inhibit, stimulate, or saturate these enzymes. Given that CL is either increased or lowered as a result of changes in enzyme activity, there is the possibility for considerable variations in blood concentration for antibiotics that are primarily metabolised by one CYP450 isoform. Although the intestinal mucosa also includes CYP450 enzymes and is the site of numerous drug-drug interactions that alter bioavailability, the liver contains the largest concentration of these enzymes.

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Conflict of Interest

The author shows no conflict of interest towards this manuscript.

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