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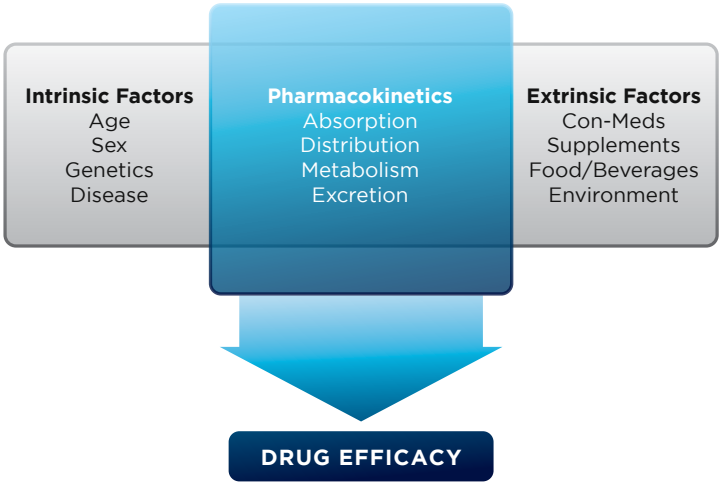
EFFECTIVE PHARMACEUTICAL THERAPIES – UNDERSTANDING THE INTRINSIC AND EXTRINSIC FACTORS THAT ALTER EXPOSURE TO LIMIT ADVERSE EFFECTS AND MAXIMIZE TREATMENT RESPONSE

Drugs play a critical role in the prevention and treatment of diseases. Though they are necessary to sustain and enhance the quality of patients' lives, the increasing number of available drugs on the market leads to a greater potential for drug-drug interactions (DDIs). More complex drug regimens with multiple compounds administered to treat one condition, or different compounds given to treat comorbidities, are contributing factors. DDIs as well as drug-alcohol or food effects are examples of how extrinsic factors can alter the exposure of drugs and cause serious adverse effects or a reduction in efficacy. Furthermore, intrinsic factors such as age, gender, comorbidities or genetics can also potentially alter drug exposure.

Clinical studies can be used to determine the effects these intrinsic and extrinsic factors can have on systemic exposure, and investigate possible interactions. *In vitro* studies can be conducted to determine whether a drug is a substrate, inhibitor, or inducer of certain metabolizing enzymes and/or intracellular transporters. These are followed by *in vivo* drug interaction studies to validate whether the nature of these interactions are clinically relevant. Furthermore, orally administered drugs are often studied to explore food interactions (typically with a high fat meal). Depending on the indication, the effects of age, gender, or other intrinsic factors may also need to be examined. Drug and food interaction studies are an integral part of any new drug application and need to be summarized on the drug label.

FACTORS CONTRIBUTING TO VARIABILITY IN DRUG RESPONSE



KEY FACTORS TO CONSIDER IN THE COURSE OF DRUG DEVELOPMENT

Age

As people age, physiological changes in renal and/or hepatic function, and nutritional deficiencies, may result in pharmacokinetic alterations that alter the bioavailability of drugs. Therefore, it is of interest to evaluate the impact of age on drug exposure. As per the FDA's recommendation, drugs should be studied in all age groups, including the elderly.

Gender

Gender can affect how a drug is metabolized and accordingly, how well the patient responds to it. Differences in gender such as lipid distribution, renal blood flow, and metabolic efficiency can alter the rate of drug absorption, distribution, metabolism, and elimination. Identifying these differences is crucial in correctly treating both sexes effectively.

A great example is Zolpidem (brand name Ambien), a drug prescribed as a sleeping aid. Over a period of time, research data showed that men metabolized the drug much faster than women and that blood levels in some patients could be high enough the morning after use to impair activities that require alertness, including driving. A release issued by the FDA stated that "women appear to be more susceptible to this risk [of next day impairment] because they eliminate zolpidem from their bodies more slowly than men." After receiving close to 700 reports of zolpidem and "impaired driving ability and/or road traffic accidents", reviewing pharmacokinetic differences between the two genders and examining driving simulation data, the FDA recommended that manufacturers lower the recommended bedtime doses by half for women — from 10 mg to 5 mg for immediate-release formulas (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release formulas (Ambien CR). The lower doses would help decrease the level of the drug that remained in the bloodstream in the morning, reducing the risk of impaired driving.

Due to the concern of the FDA for next day driving impairment, Altasciences has been designing and conducting driving simulation studies to establish the extent and duration of drug-related impairment. Such studies can allow drug manufacturers to identify drug-related cognitive impairment early in their drug development, related to gender or other intrinsic and extrinsic factors, and prevent cases such as with Ambien.

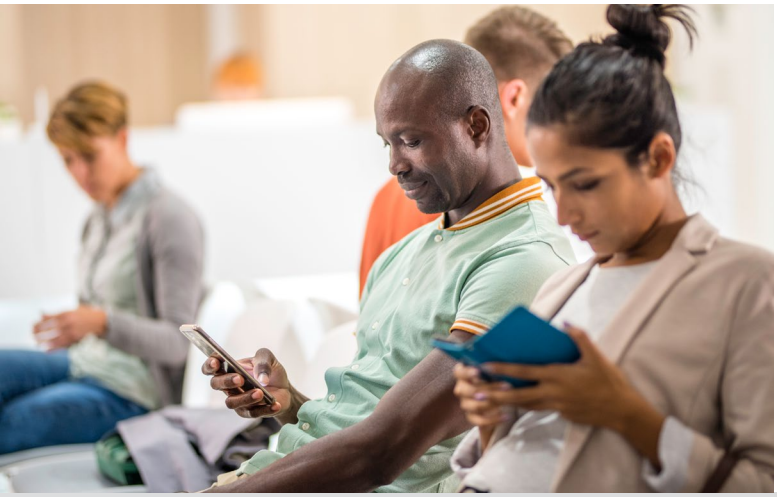
Over the years, several FDA regulations and guidances have been put in place to ensure that both sexes are represented in all phases of clinical trials and that gender-related differences be assessed in the clinical evaluation of drugs. This allows medical products to be labeled appropriately and indicates any differences in the way male and female patients respond to a specific medication.

Genetic Variations

Genetic variations in drug exposure come from different alleles of enzymes that metabolize or transport drugs. These genetic variations can be observed on individual levels or by focusing on racial background. The main enzymes involved in drug metabolism belong to the cytochrome P450 (CYP) group, and are a major source of variability in drug pharmacokinetics and response. Although the CYP450 group has more than 50 enzymes, six of them metabolize 90 percent of drugs, with the two most significant enzymes being CYP3A4 and CYP2D6. Genetic variability (polymorphism) in these enzymes may affect a patient's response to commonly prescribed medications and are responsible for observed variations in drug response among patients of different ethnic origins.

In recent years, pharmacogenetics research has shown significant differences in the pharmacokinetics among Caucasians, African Americans, Hispanics, and Asians, or at individual levels by stratifying groups based on genetic analysis. A good example is poor metabolizers of drugs acted on by CYP2D6. You can examine the differences based on race, since there is a large genetic variation between Caucasians, Asians, and Africans. Alternatively, you can genotype each individual looking for the non-functional alleles (*3-*8, *11-*16, *19-*21, *38, *40, *42).

Due to variations based on race and genetics, clinical research is strongly encouraged by regulatory agencies worldwide, including the FDA. It is also recommended to include patients from varied ethnic and racial groups in the clinical trials, such that the patient panel should closely resemble the makeup of the patient populations that will actually consume the medicine. Clinical pharmacokinetic data can help determine if the target drug may need to be substituted, or a dose adjustment required, to account for the potential decrease or increase in metabolism.



Drug-Drug Interactions

DDIs are one of the most important factors to consider in the course of drug development and clinical research as they may be life-threatening due to the side effects they produce or because they limit efficacy. For patients taking more than one medication at a time, there is a risk that one drug may alter the effect of another, either by reducing its effectiveness or elevating systemic concentrations to potentially dangerous levels, ultimately causing side effects. In some cases, the outcome could be severe, resulting in a dangerous drop in blood pressure, irregular heartbeat, or damage to the heart or liver. DDIs can occur between prescription medications and many over-the-counter medications (antihistamines, pain relievers, and others). Therefore, it is recommended that patients let their physicians/pharmacists know which over-the-counter drugs they are taking or may take whenever they are given a new prescription.

As per the 2017 FDA guidance entitled *Clinical Drug Interaction Studies,* "clinically relevant DDIs between an investigational drug and other drugs should therefore be:

1. Defined during drug development as part of the sponsor's assessment of the investigational drug's benefits and risks
2. Understood via nonclinical and clinical assessment at the time of the investigational drug's approval
3. Monitored after approval
4. Communicated in the labeling

The goals of studies that investigate metabolism- and transporter-mediated DDIs are to determine:

- Whether the investigational drug alters the pharmacokinetics of other drugs
- Whether other drugs alter the pharmacokinetics of the investigational drug
- The magnitude of changes in pharmacokinetic parameters
- The clinical significance of the observed or expected DDIs
- The appropriate management strategies for clinically significant DDIs

Sponsors should evaluate DDIs before the product is administered to patients who are likely to take concomitant medications that could interact with the investigational drug. Furthermore, sponsors should collect enough DDI information to prevent patients from being unnecessarily excluded from any clinical study because of their concomitant medication use."

EXAMPLES OF COMMON DRUG-DRUG INTERACTIONS INVOLVING THE CYTOCHROME P450 ENZYME SYSTEM

DRUG(S)	ENZYME INHIBITOR OR INDUCER	DRUG(S)	METABOLIZING ENZYME	POSSIBLE CLINICAL EFFECT
Amiodarone (Cordarone)	CYP2C9 and CYP3A4 inhibitor	Warfarin (Coumadin)	CYP2C9	Increased risk of bleeding caused by increased warfarin level
Carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin)	CYP3A4 inducer	Ethinyl estradiol containing contraceptives	CYP3A4	Unplanned pregnancy caused by reduced estradiol level
Clarithromycin (Biaxin), erythromycin, telithromycin (Ketek)	CYP3A4 inhibitor	Simvastatin (Zocor), verapamil (Calan)	CYP3A4	Myopathy or rhabdomyolysis caused by increased simvastatin level and Hypotension and QT interval prolongation caused by increased verapamil level
Diltiazem (Cardizem), verapamil	CYP3A4 inhibitor	Prednisone	CYP3A4	Immunosuppression caused by increased prednisolone serum levels
Fluoxetine (Prozac), paroxetine (Paxil)	CYP2D6 inhibitor	Risperidone (Risperdal), tramadol (Ultram)	CYP2D6	Increased risk of extrapyramidal adverse effects caused by increased risperidone level24; decrease in analgesic effect caused by low level of active metabolite
Metronidazole (Flagyl)	CYP2C9 inhibitor	Warfarin	CYP2C9	Increased risk of bleeding caused by increased warfarin level
Terbinafine (Lamisil)	CYP2D6 inhibitor	Amitriptyline	CYP2D6	Dry mouth, dizziness, and cardiac toxicity caused by prolonged increase in amitriptyline and nortriptyline (Pamelor) levels

PARTNERING WITH ALTASCIENCES FOR YOUR DRUG INTERACTION STUDIES

For decades, Altasciences has designed, conducted, analyzed and reported on thousands of studies exploring the effects of intrinsic and extrinsic factors, in healthy normal volunteers, special populations (elderly, by gender), and patient populations. Our clinical pharmacologists thoroughly review the pertinent literature (e.g., investigator brochure) to determine the studies required. When DDI studies are needed, they determine the ideal inhibitor, inducer, or substrate to use. Our bioanalytical department has validated methods and clinical experience with almost all common substrates and probes. We have conducted single interaction, multiple interactions across cohorts, and multiple interactions within cohort (cocktail) studies. We routinely perform genotyping to exclude or enrich certain phenotypes, or to stratify them to study a specific characteristic.

With our advanced equipment, techniques, and experienced staff, we routinely conduct studies to evaluate the effects of different intrinsic and extrinsic factors on a drug's pharmacokinetics. The information gathered from these studies can be used to improve drug safety, limit drug-related adverse events and interactions, and enable individualized drug therapy.

> "Our highly experienced scientific and clinical teams are exceptionally well versed in the conduct of a wide range of DDI trials. The delivery of high quality data on time and as promised is a particular strength for Altasciences."

Ingrid Holmes

Vice President,
Global Clinical Operations

ALTASCIENCES' CASE STUDY: DRUG-DRUG INTERACTION

Study Overview

A sponsor developing a novel treatment for cardiovascular disease approached Altasciences to conduct their first two DDI studies, assessing the effect their drug would have on the pharmacokinetics and pharmacodynamics of the commonly prescribed treatments, clopidogrel (antiplatelet) and warfarin (anticoagulant). While their drug would likely not affect the metabolism of each of the aforementioned treatments, based on its own metabolic profile, these studies were conducted to address a potential concern for excessive bleeding. This is a great example of Altasciences' expertise extending beyond a simple DDI study. Altasciences played a key role in the design, recruitment, and conduct of these studies to assess not only the pharmacokinetic impact of co-administration, but the impact on the antiplatelet and anticoagulant properties of the drugs noted above, mindful of the population required for such a trial, as well as the timing of assessments needed to sufficiently observe changes in the pharmacodynamics of the co-administered products.

Study Details

- Drug Development Phase: Phase I
- Class of Drug: Antisense oligonucleotide
- Indication: Cardiovascular disease (CVD)
- Population Type: Healthy normal volunteers (both studies)
- No. of Subjects: 18 subjects / study
- Time to Recruit Panel: 14 days
- Study Design: Open-label, single-sequence, two-treatment, two-period design (both studies)
- Key Inclusion Criteria: Males and females, non-smokers, ages 18-60, BMI 18.5-30 (inclusive), appropriate contraception use
- Key Exclusion Criteria: History of bleeding disorders, active pathological bleeding, sensitivity to the investigational products, positive drug screen, prior exposure to an investigational product in last 4 weeks
- Services Provided: Full-Service (Protocol Development, Project Management, Regulatory Submission, Clinic Conduct, Data Management, Biostatistics, Medical Writing)

Study Purpose

The primary objective of both DDI studies was to evaluate the effects of two doses of the sponsor's investigational product on the pharmacokinetics of multiple oral doses of clopidogrel and warfarin in healthy adult subjects. The studies also looked at the safety and tolerability of the investigational product when co-administered with multiple oral doses of clopidogrel and warfarin, as well as evaluating the effect on the pharmacodymanics (antiplatelet activity).

Methods

While the overall objectives and the inclusion/exclusion criteria of both studies were the same, the methodology for each trial was different. This was due to the differences in the activity and half-life of both drugs, which required slightly different washout periods and dosing schedules.

Dosing schedule for the clopidogrel interaction study:

DAY (PERIOD)	STUDY DRUG ADMINISTERED
Days 1-7 (Period 1)	A single 75 mg oral dose of clopidogrel administered alone once daily
Washout Period (Days 8-18)	
Day 19 (Period 2)	A single 75 mg oral dose of clopidogrel and a single 40 mg subcutaneous injection of investigational product administered concomitantly
Days 20-24 (Period 2)	A single 75 mg oral dose of clopidogrel administered alone once daily
Day 25 (Period 2)	A single 75 mg oral dose of clopidogrel and a single 40 mg subcutaneous injection of investigational product administered concomitantly

Dosing schedule for the warfarin interaction study:

DAY (PERIOD)	STUDY DRUG ADMINISTERED
Day 1 (Period 1)	A single 75 mg oral dose of clopidogrel administered alone once daily
Washout Period (Days 2-7)	
Day 8 (Period 2)	A single 75 mg oral dose of clopidogrel and a single 40 mg subcutaneous injection of investigational product administered concomitantly
Washout Period (Days 9-14)	
Day 15 (Period 2)	A single 25 mg oral dose of warfarin and a single 40 mg subcutaneous injection of investigational product administered concomitantly

Subjects involved in the clopidogrel interaction study were confined to the clinic for 9 nights per period, for a total of 18 overnights. In the warfarin interaction study, subjects were confined to the clinic in Period 1 for 3 nights, then 3 additional nights at the end of Period 1 and the start of Period 2. Subjects were then housed 7 additional nights when dosed in Period 2, for a total of 13 overnights.

Pharmacokinetic blood samples were taken 13 times during both Period 1 and Period 2 for the clopodigrel study pre-dose through Hour 48 (2 days post-dose). The warfarin interaction study collected pharmacokinetic blood samples through Hour 144 (6 days post-dose) during both periods: 17 samples to assess warfarin-alone pharmacokinetics in Period 1; 13 samples to assess investigational product pharmacokinetics during the first part of Period 2; another 17 samples to assess levels of both drugs during co-administration.

In the clopidogrel interaction study, pharmacodynamic blood draws were conducted a total of 7 times, twice during individual administration of each product, and 5 times during co-administration. Pharmacodynamic evaluation was done by analyzing ADP-induced platelet function. In the warfarin interaction study, 12 blood draws were taken to assess platelet function by means of hematology lab parameters focused on platelet activity: activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR) which is derived from the PT value. In addition, safety labs and adverse events were collected and evaluated throughout the course of subject participation.

Results

Both studies were conducted in a single subject panel — thus allowing for quick completion of the clinic portion of the trial.

Following multiple doses of investigational product, no clinically significant effects were observed on the pharmacokinetics and pharmacodynamics of clopidogrel.

The warfarin study showed that co-administration with the investigational product did not affect the peak concentration or extent of exposure of either product. Also, the maximum observed effect and the area under the effect-time curve for the pharmacodynamics lab parameters were not significantly affected by dosing both products together.

Both studies had no deaths or serious adverse events, and no clinically significant vital signs, ECG parameters and physical examinations.

Challenges and Solutions

Altasciences was presented with the challenge to conduct two studies with a new molecular entity in combination with another drug that had the potential to cause a serious effect on subjects. While it may have been easier or less costly to simply replicate the studies, or perhaps combine them together, the project team worked with the sponsor to design two different studies, with different timepoints of measurements, which had the same objectives. In doing so, the efficiencies of working with the same team across both projects were utilized, and both studies were treated with the utmost care, from study design, recruitment, clinic conduct, data management, all the way through biostatistical analysis, and report writing. Our success is predicated on leveraging our scientific experience in DDI studies, executing clinical trials, and in developing close partnerships with our clients to understand their goals and work to achieve them in the best way possible.

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ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.