Module 3, Video 15: Human and preclinical evidence of sex-related differences in pharmacokinetics, pharmacodynamics, and toxicology

Preliminary evidence indicates that in some cases, sex-based pharmacology differences do exist. Most of this evidence is based on human data collected during traditional pharmacokinetic, pharmacodynamic, and toxicology studies—or as they’re more commonly referred to as: PK, PD, and toxicology studies. However, some evidence of sex difference in PK, PD, and toxicology is available in animals and is important to consider in all studies, regardless of whether the intended purpose of your research program is drug discovery or not. In this module, we will describe some of the available evidence of sex-based differences in PK, PD, and toxicology in both humans and animals.

The basics of PK are Absorption, Distribution, Metabolism, and Elimination—an acronym commonly referred to as ADME. Some sex-based differences have been observed across ADME factors in both humans and animals. Many of these findings are preliminary but the available evidence indicates sex differences in the secretion of gastric acid, transit times from the stomach to the intestine [1-7], body weight, intravascular volume, organ blood flow, muscle mass [8-10], renal blood flow, glomerular filtration, tubular secretion, and tubular reabsorption [11-15], all of which are either lower or slower in women compared to men. Further, there are also sex differences in the expression and activity of hepatic enzymes related to the metabolism of drugs, including the cytochrome P450 enzyme superfamily [9, 10, 16-23]. Preliminary sex-based differences have been observed for multiple drugs including alcohol [24-26], sedatives, aspirin, and heparin [27-31].

PD is the relationship between the concentration of the drug at the site of action and the biochemical and physiological effects. PD is typically studied in the context of efficacy—the extent to which a given drug achieves its desired effect—and potency—the dose of drug required to achieve a desired effect. Efficacy is primarily measured by changes in functional outcomes.

While this video series has highlighted many instances of sex differences in functional outcome measures at baseline in the absence of any drug, some drug treatments also lead to additional sex differences in functional outcome measures that should be considered. As a result, any outcome may show a sex difference that could reflect either a baseline sex difference and/or a pharmacological sex difference. Sex-based differences in PD effects have been observed in humans for beta-blockers [33], analgesics [34, 35], antidepressants [36], antipsychotics [5, 37-40], and antimuscarinic therapies used for overactive bladder [41]. In addition, while they can influence some PK parameters, the influence of sex hormones, contraceptive use and menopause on clinical efficacy are still poorly understood for most drugs [8, 22, 42]. In rodents,
sex differences in response to tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-noradrenaline reuptake inhibitors have been observed [43-48]. Sex differences in PK and PD can also lead to sex differences in toxicology and adverse drug reactions [49].

Toxicology studies are used to assess the safety of experimental drugs and the risk for adverse drug reactions [50]. *In vitro* toxicology studies can also cover alterations in the viability, structure and/or function of a drug target [51]. The results can be used to improve the design of subsequent *in vivo* studies. *In vitro* toxicology studies are additionally widely used for screening and ranking chemicals. Most toxicology studies occur in the context of drug development, where they are highly regulated by governing bodies such as the FDA or European Medicines Agency to ensure they are conducted to the highest safety standards. This includes testing safety pharmacology, genetic toxicology, acute and subchronic toxicology, reproductive and developmental toxicity, and carcinogenic potential [52] in both sexes and multiple species, usually one rodent and one non-rodent.

Adverse drug reactions can range from mild to lethal. In humans, women tend to have more adverse drug reactions than men [10, 54]. Some evidence exists that sex differences in PK contribute to sex differences in adverse drug reactions. A 2020 study examining 86 FDA-approved drugs found that most women had elevated blood concentrations and longer elimination times, and that these differences strongly predicted sex-specific adverse drug effects in women only [55]. However, for some adverse reactions, the correlation may not be so clear. For example, drug-induced long QT syndrome is observed more often in women than in men [56]. Long QT syndrome is associated with an increased occurrence of ventricular tachyarrhythmias, which can lead to syncope, cardiac arrest or sudden death [57]. These effects are thought to be linked to changes in sex hormones across the cycle as differences in cardiac ion channels are also observed across the estrous cycle [58-61]. Thus, observed effects might be missed in the absence of PK information stratified by sex or estrous cycle stage [62]. The effect of certain drugs on drug-aquired long QT seems to be fairly consistent across species. A 2015 literature review spanning 51 years of research determined that 91% of drugs that led to prolonged QT in non-rodent animal species also did so in humans. Similarly, 88% of drugs that did not prolong the QT in non-rodent animal models also showed no QT effect in humans [63].

This video provides an introduction to sex-based differences in pharmacology. As formal PK, PD and toxicology studies are usually not performed in academic labs, many academic researchers might pay little attention to sex differences in these parameters. However, many drug compounds are used every day in academic labs. The failure to consider how biological sex influences the PK, PD or toxicological effects of various preclinically administered drugs may lead to a misinterpretation of experimental results. Thus, it is important to understand and consider potential sex differences in pharmacology at all stages of academic research.
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References


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