The Science of Sex Differences in the Pharmacokinetics and Pharmacodynamics of Drugs - Case studies
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BACKGROUND: Sex differences in pharmacokinetics (PK) and/or pharmacodynamics (PD) of drugs may result in safety and/or efficacy differences warranting dosage adjustments. A scientific understanding of sex related PK or PD of drugs is critical for adequate drug product labeling.

METHODS: Four case studies illustrate various scenarios of sex differences in the PK or PD of drugs:
Dofetilide: An antiarrhythmic drug that exhibits PK and PD sex differences. Dofetilde concentrations were 14-22% greater in women and the risk for torsades de pointes (TdP) in females is about 3 times that in males.
Heparin: An anticoagulant that shows PK and PD sex differences. Women, particularly the elderly, have a poorer outcome than men. Women have higher heparin levels and APTT values than men when given the same dose of heparin and lower dose requirements to achieve therapeutic APTT value (published article).
Alosetron: A selective 5-HT3 receptor antagonist that shows PD but no significant PK sex differences. Alosetron concentrations are 27% lower in men. Efficacy was demonstrated observed in females but not males, an observation that was not explained by PK differences.
Tedisamil: An antiarrhythmic drug that exhibits PD but no PK sex differences. A dose response was observed with more TdP-like events at doses >0.48 mg/kg in males and >0.32 mg/kg in females. Approval was not recommended.

RESULTS: Women have slower cardiac repolarization than men, which manifests as longer baseline QTc and are more prone than men to develop TdP after administration of antiarrhythmic agents. There are also age-related changes in coagulation factors which differ in men and women and sex difference have been reported in serotonin receptors and transporters. The scientific bases for the observed PK and PD sex differences will be provided.

CONCLUSION: Understanding the science of the sex differences observed during drug development is crucial for appropriate regulatory decisions and optimal dosing of drugs.