CERTARA

Modeling and Simulation Approaches Provide Insight into Herbal Supplement Safety

Scientists at Washington State University and the University of North Carolina at Greensboro used Certara's Phoenix WinNonlin and Simcyp Simulator to evaluate a previously unexplored herb-drug interaction mechanism

Background

According to the Council for Responsible Nutrition, a trade group for the $32 billion nutritional supplement industry, 68% of adults take dietary supplements.[1] Like drugs, supplements do not work the same in all patients due to a range of genetic and environmental factors. In addition, supplements are not regulated with the same rigor of as drugs. Ergo, the quality and dosage of supplements may vary widely. Moreover, herbal supplements can interact with drugs to either lessen their effectiveness or cause toxicity.

Challenge

While the study of herb-drug interactions is relatively new, modeling and simulation technology affords an opportunity to answer key safety questions. A team of scientists from Washington State University and the University of North Carolina Greensboro used modeling and simulation to evaluate an herb-drug interaction mediated via inhibition of intestinal UDP-glucoronosyl transferases (UGT).[2] Silibinin, a semi-purified milk thistle seed extract, was chosen as an exemplar herbal perpetrator. Raloxifene was selected as a clinically relevant exemplar of an intestinal UGT victim. Milk thistle is a popular supplement that is reputed to detoxify and protect vital liver function. Raloxifene, a selective estrogen receptor modulator, is used to reduce the risk of developing breast cancer and to treat osteoporosis.

Solution

Modeling and simulation technology, including physiologically-based pharmacokinetic (PBPK) modeling, is increasingly being leveraged to better understand herb-drug interactions. To test a proof-of-concept clinical study, a Simcyp PBPK model was built based on a virtual cohort of 16 healthy patients, aged 18 to 65 years, with raloxifene (60 mg) and silibinin (480 mg three times daily)

Challenge

Herbal supplements may cause interactions with conventional drugs via multiple mechanisms. While inhibition of intestinal glucuronidation has been reported as a mechanism for herb-drug interactions in pre-clinical models, its clinical relevance was unknown.

Solution

A team of academic scientists used Certara's Simcyp PBPK modeling and non-compartmental analysis software to evaluate the interaction of silibinin, an herbal supplement, with raloxifene, a selective estrogen receptor modulator.

Benefit

The mechanistic PBPK model accurately predicted the minimal impact of the silibinin-raloxifene interaction thus providing evidence that this approach may be useful for predicting herb-drug interactions mediated via alternate mechanisms.

administered in the fasted state. Pharmacokinetic outcomes were recovered by non-compartmental analysis using Phoenix WinNonlin.

The Simcyp Simulator can handle herb-drug interactions involving up to four xenobiotics plus three metabolites and accommodates simultaneously: competitive enzyme and transporter inhibition, irreversible time-based enzyme inhibition, enzyme induction, and suppression. The technology has been used to model the different and interlinking elements that contribute to an observed drug interaction and account for time-dependent changes in drug concentrations and enzyme activity levels.

In this case, the Simcyp model leveraged the ADAM model, which uses a mechanistic framework to describe the passage of drug molecules along and through the gastrointestinal tract. The ADAM module divides the intestine into multiple transit compartments, distributing any herb-drug interactions of the silibinin perpetrator and the drug victim, raloxifene, along the entire gastrointestinal tract.

Benefit

The Simcyp model predicted negligible changes in raloxifene pharmacokinetic outcomes and rapid silibinin elimination. However, some subjects demonstrated an almost two-fold increase in raloxifene exposure, suggesting further investigation is warranted. PBPK modeling should further be iterated with clinical data when possible to understand the full impact of herb-drug interactions.

Impact

Modeling and simulation can be used for the prospective evaluation of herb–drug interaction potential that will provide evidence-based information about the risk or safety of herb–drug combinations.

References

1. The Wall Street Journal, February 29, 2016. "How your supplements interact with prescription drugs." By Laura Landro

2. Gufford B, Barr J, González-Pérez V, et al. Quantitative prediction and clinical evaluation of an unexplored herb–drug interaction mechanism in healthy volunteers. *CPT: Pharmacometrics & Systems Pharmacology.* 2015;4(12):701-710. doi:10.1002/psp4.12047.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

For more information visit www.certara.com or email sales@certara.com.

CS Jul 2016 v2 041017