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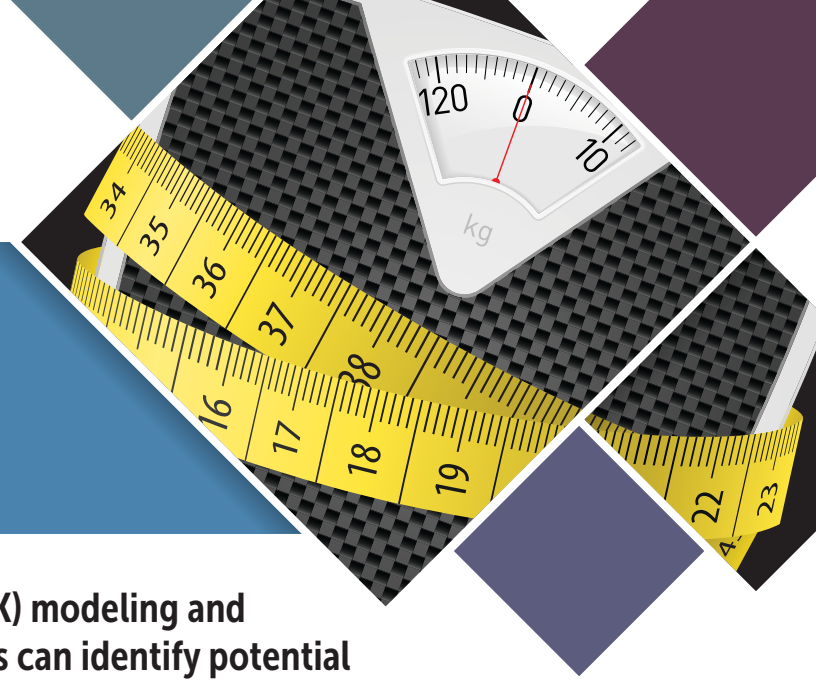

Predicting Variations in Drug Clearance in Obese Patients Using Modeling and Simulation

Physiologically-based pharmacokinetics (PBPK) modeling and simulation in virtual obese patient populations can identify potential changes in drug disposition that may impact upon drug safety and efficacy in this patient group and help guide dosing decisions

Many physiological changes are associated with obesity and can potentially impact on pharmacokinetics (PK). This can require adjustments to be made to the standard doses for normal weight patients in order to ensure safety and efficacy of drug therapy. PBPK models incorporate the known, relevant demographic, anatomical and physiological variables associated with obesity in order to predict drug clearance with reasonable accuracy in obese and morbidly obese subjects.

Models implemented in the Simcyp Simulator predicted drug clearance in obese subjects

Certara scientists applied a "systems biology" approach to identify the likelihood of observing variations in drug clearance in obesity and morbid obesity for a set of compounds for which clinical data, as well as the necessary *in vitro* information, were available. First, obese and morbidly obese virtual populations were built through collation of data on a variety of parameters including: body surface area, cardiac output, liver and kidney volumes, organ blood flow for the liver, kidney and gastrointestinal tract, enzyme activity for specific CYPs and plasma protein binding.

The models were implemented in the Simcyp Simulator and used to predict the clearance of oral alprazolam, oral caffeine, oral chlorzoxazane, oral ciclosporin, intravenous and oral midazolam, intravenous phenytoin, oral theophylline and oral triazolam. The design of the simulated studies closely matched that of the clinical studies. The PBPK modeling approach was successful in predicting clearance in obese subjects for six out of the eight drugs.[1]

The Simcyp Simulator improves decision-making regarding the need for clinical studies in obese subjects

The Simcyp Simulator allows the impact of obesity on drug clearance to be assessed using routinely generated PK data. This assists with critical decision-making on whether dedicated clinical trials in obese subjects are warranted as well as guiding elements of trial design such as initial dosing and number of participants required for the study to have sufficient power.

Highlights

The Simcyp Simulator conducts simulations in virtual patient populations based on *in vitro* and clinical data.

Virtual populations incorporating characteristics associated with obesity were developed within the Simcyp Simulator and evaluated on the ability to model changes in pharmacokinetics compared with normal weight subjects.

Identifying differences in drug clearance due to obesity can determine whether dose adjustment is necessary and help optimize the design of clinical studies.

Due to the increasing prevalence of obesity worldwide there is a pressing need for more information regarding optimal dosage regimens in this subgroup of patients. The framework is now in place to use modeling and simulation prospectively—to predict where there is likely to be a considerable impact on pharmacokinetics prior to clinical development, or retrospectively—in dose adjustment for approved drugs where clinical data in obese subjects are not available.

References

1. Ghobadi C, Johnson TN, Aarabi M, Almond LM, Allabi AC, Rowland-Yeo K, Jamei M, Rostami-Hodjegan A. Application of a systems approach to the bottom-up assessment of pharmacokinetics in obese patients: Expected variations in clearance. *Clinical Pharmacokinetics.* 2011; 50(12):809-22.

About Certara

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