Implementation of Oral Drug Absorption in Older Adults in the Physiologically Based Pharmacokinetic (PBPK) Modelling Platforms

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BACKGROUND

The older adult population, consisting of persons aged 65 years or older, is the fastest-growing population group and also the major consumer of pharmaceutical products. Due to the heterogenous aging process, this age group shows high interindividual variability in the dose-exposure-response relationship and, thus, a prediction of drug safety and efficacy is challenging. Although PBPK modelling is a well-established tool to inform and confirm drug dosing strategies during drug development for special population groups, age-related changes in absorption are poorly accounted for in current PBPK software.

OBJECTIVES & METHODS

This research aims to characterise the incorporation of physiological changes caused by increasing age that can influence the oral absorption of dosage forms in the PBPK software. The representatives of PBPK modelling platforms Open Systems Pharmacology - OSP (PK-Sim), SimCyp, and GastroPlus filled in a questionnaire concerning multiple absorption-related parameters and their implementation in the software. Besides, if the different software incorporate physiological changes in their respective older adult population databases.

RESULTS

Parameters	Software	Current incorporation in the software	Incorporated change in older population
Oral Cavity and Swallowing Capacity	All	Saliva flow rate and saliva pH can be manually altered.	No change.
Gastro-Intestinal pH	PK-Sim	Stomach acid output, and the pH of the stomach, duodenum, jejunum, ileum, cecum, ascending, and descending colon are incorporated and can be manually altered.	No change.
	GastroPlus	Stomach, duodenum, jejunum, ileum, cecum ascending and descending colon are incorporated and can be manually altered.	No change.
	Simcyp	Stomach, duodenum, jejunum, ileum and colon are incorporated and can be manually altered.	Slower rate of return of gastric pH after food intake.
GI Transit Times	PK-Sim	GET, SITT, and LITT are incorporated and can be altered manually. When taking a meal the gastric emptying time is altered based on a Weibull equation.	No change.
	GastroPlus	GET, SITT, and LITT are incorporated and can be altered manually. When taking a meal, gastric emptying time is dependent on meals, the API and the caloric intake.	Indirect change of GET after meal intake.
	Simcyp	GET, SITT, and LITT are incorporated and can be altered manually. When taking a meal the gastric emptying time is altered based on a Weibull equation.	No change.
GI Fluid Volumes	PK-Sim	Stomach, small and large intestinal luminal fluid are incorporated and can be manually altered.	No change.
	GastroPlus	Stomach, small and large intestinal luminal are depending on the fluid secretion and fluid absorption and incorporated in the dynamic fluid volume model. Herein they can be manually incorporated.	No change.
	Simcyp	Stomach, small and large intestinal luminal fluid are incorporated and can be manually altered.	No change.
Bile Acid Synthesis	PK-Sim	No mechanistic models for bile salt concentrations or micelle-mediated solubility but in vitro solubility data can be implemented manually.	No change.
	GastroPlus	Incorporates bile salt solubilization model.	No change.
	Simcyp	Incorporates Simcyp In Vitro Analysis (SIVA) toolkit to analyse dissolution profiles and solubility data of drugs.	No change.
Intestinal Epithelial Barrier Function	PK-Sim	Intestinal paracellular permeability and intestinal surface area are incorporated and can be manually altered.	No change.
	GastroPlus	Paracellular pore size and intestinal surface area are incorporated and can be manually altered.	No change.
	Simcyp	Paracellular pore size and intestinal surface area are incorporated and can be manually altered.	No change.
Active Transport and Metabolism	All	Active transporter concentrations and GI enzyme concentrations are incorporated and can be manually altered.	No change.

In the table, the absorption-related parameters are given with their incorporation in the different software. All parameters can be manually adapted but most of them do not incorporate standard changes in the older population database of all three platforms. Also, no age-dependent variability is incorporated in the different platforms for these parameters. Simcyp and OSP additionally did not inform the stomach pH, duodenum pH, gastric emptying time, small and large intestinal transit time, micelle-mediated solubility, and bile salts concentrations. Since conflicting results were observed in literature for these parameters, GastroPlus retains the parametrization for the young adults. Furthermore, none of the software providers incorporated the effect of the gut microbiome for different age groups. On the other hand, food effects are handled differently in every software. Simcyp considers a different rate of return for their older adult model. The rate of return to fasted gastric pH for subjects above the age of 65 years is described with a linear formula instead of an exponential one. For GastroPlus, age has, an indirect effect on the gastric emptying rate in fed state. The software has an inbuilt correlation between the calories in the meal and the gastric emptying time. As the calories are defined as a percentage of the total daily calorie intake which differs for gender and age, it allows scaling to all ages and gender. OSP did not report or include an age-informed rate of return to fasted pH or a difference in gastric emptying in the absorption model.

CONCLUSION

The results of the questionnaire led to the conclusion that the impact of age on several gastrointestinal physiological parameters is marginally informed and considered in the various modelling software tools. Considering the complex aged-related changes and additional extrinsic factors reported in literature, more joint efforts should be made to integrate data obtained from various *in vitro* permeability, solubility, and dissolution experiments that mimic the older population, as well as clinical studies into PBPK models. This strategy allows to better predict *in vivo* clinical response. Ultimately, the outcomes from these studies may be used to support dosing recommendations and drug development and pharmacotherapy in this population.

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