Physiologically-based absorption modeling and simulation for assessing bioavailability in elderly, children, and gastrointestinal disease states

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Introduction

Bioequivalence (BE) studies are typically performed in healthy human subjects. However, an approved generic is prescribed for the intended-to-treat patients with diverse disease background, in the presence or absence of comorbidities, and including children and elderly if approved. One common question is whether bioavailability (BA) comparisons in healthy subjects reflects that in the indicated disease population of all age groups and disease background. We assessed how gastrointestinal (GI) age or comorbidity (such as irritable bowel syndrome [IBS], ulcerative colitis [UC], and Crohn's disease [CD]) affects the in vivo performance of an orally absorbed, systemically active drug products by examining the impact on BA of GI physiological characteristics of pH, permeability, and transit time in children, in the elderly, and in patients with GI diseases. Certain GI characteristics differ significantly between the indicated subpopulations. Physiologically-based absorption (PBA) modeling was conducted for mixed amphetamine salts, omeprazole magnesium, and atorvastatin calcium. These modeled formulations were selected for the following reasons: extended-release (ER) products of amphetamine are approved for children aged 6 years and older; delayed-release (DR) omeprazole is widely prescribed and change the gastric pH (i.e. GI condition); and atorvastatin is widely prescribed for the elderly. PBA modeling and simulation compared a hypothetical generic (Test) product to the innovator (Reference) product in these populations.

Methods

Collection of GI physiological characteristics:

A comprehensive literature review of GI physiological characteristics in the elderly, in children, and in individuals with GI disease states was conducted. The following GI factors were collected: dimensions and capacity, transit times, pH, passive permeability, secretion and reabsorption of bile salts, intestinal transporters and drug-metabolizing enzymes, hepatic transporters and drug-metabolizing enzymes, and renal clearance.

PBA modeling and pharmacokinetic (PK) modeling in GastoPlus™:

Drug absorption models based on human physiology have been developed and applied to orally administered drug products . These models incorporate the physiochemical properties of the drug substance (such as molecular weight, pKa, LogP, solubility, permeability, …), the properties of the formulation/drug product (dose, dosage form, particle density, …), and physiological parameters (transit time, volume, pH, ... of GI compartments) to predict oral absorption. Commercial software, such as GastroPlus™ combine the absorption models with compartmental PK models or physiologically-based PK (PBPK) models to predict plasma concentration levels over time. In GastroPlus™, the PBA model component is called the Advanced Compartmental Absorption and Transit (ACAT) model.

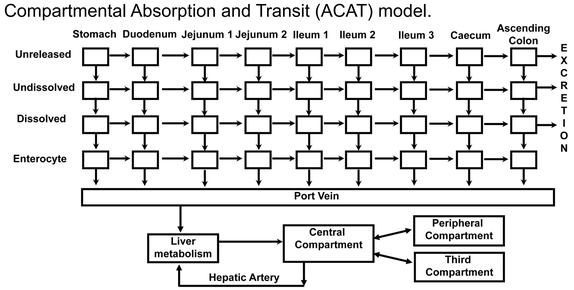

Figure 1: GastroPlus™ ACAT model

The GI parameters collected in the literature review were incorporated into GastroPlus™ to develop physiologies reflective of pediatrics, elderly, and patients with either IBS, UC, or CD. PBA models were developed for three test drugs: amphetamine, omeprazole, and atorvastatin. PK data of omeprazole in extensive, intermediate, and poor metabolizers were used for omeprazole considering CYP2C19 polymorphisms. Simulation was conducted in the developed physiologies in order to compare BA between a hypothetical generic product and the innovator product in the respective, relevant populations.

Results

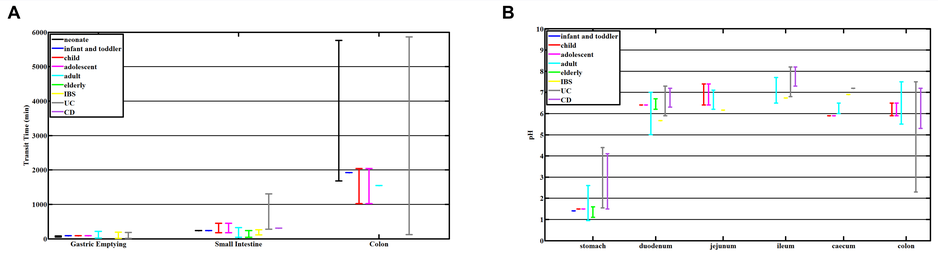

Figure 2: Example figure of two physiological parameters collected across the mentioned subpopulations: (A) reported fasting transit times in the stomach, small intestine, and colon; and (B) reported fasting pH values in the stomach, the individual subcompartments of the small intestine, the caecum, and the colon. The bars represent the range of reported values.

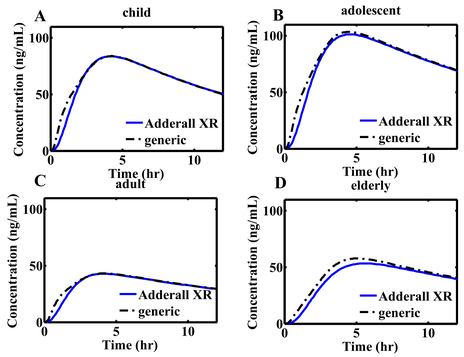

Figure 3: Simulated d-amphetamine plasma concentration vs. time profiles in the fasting condition of Adderall XR® ER capsules and a generic version which differs in release mechanism in (A) children, (B) adolescents, (C) adults, and (D) the elderly. The 1-compartment PK model fit from adult data was adjusted for pediatrics by varying the volume of the central compartment (V_c) and systemic clearance (CL) while keeping the reported pediatric elimination half-life ($T_{1/2}$) set until the reported C_{max} and $AUC_{0-\infty}$ was achieved. For adolescents and elderly, adult PK model was used.

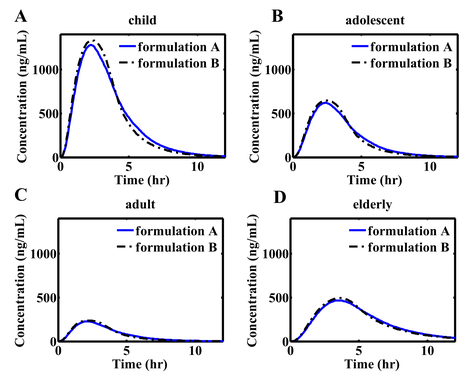

Figure 4: Simulation omeprazole plasma concentration vs. time profiles in the fasting condition of two theoretical generic formulations of Prilosec® DR capsules with different particle radii and density in (A) children, (B) adolescents, (C) adults, and (D) the elderly. Only homozygous extensive metabolizers (hmEMs) related to CYP2C19 are considered due to increased sensitization to age-related changes in CYP2C19 levels. Gut and hepatic extraction were adjusted based on percentage of CYP2C19 to adult levels. For elderly, CL was halved as reported in the product label.

Results

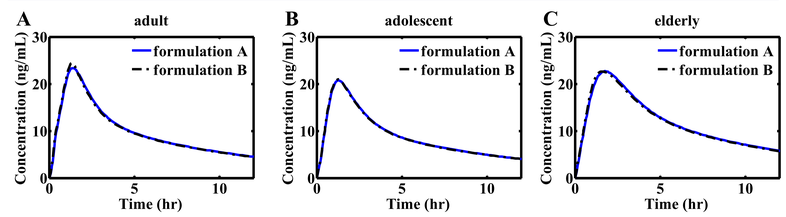

Figure 5: Simulated atorvastatin plasma concentration vs. time profiles in the fasting condition of Lipitor® tablets (formulation A) and a generic version (formulation B) in (A) adults, (B) adolescents, and (C) the elderly. The two formulations differ in the physical form of the atorvastatin, either crystalline or amorphous, which lead to variations in particle size distribution, particle density, and solubility vs. pH profiles. PK components of model kept consistent between the subpopulations; however CYP3A4 metabolism was adjusted based on age-related data.

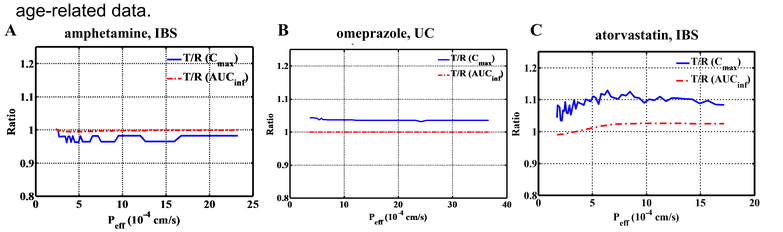

Figure 6: Test-to-reference (T/R) ratio comparison of BE metrics in the fasting condition in: (A) patients with IBS taking brand and generic Adderall XR® and a generic; (B) patients with UC taking the two theoretical generic versions of Prilosec®; and (C) patients with IBS taking brand and generic Lipitor®. GI diseases generally result in increased permeability. Since the translation of these reported increases to GastroPlus™ permeability parameters is unknown, a parameter sensitivity analysis was conducted on the effective permeability (P_{eff}) parameter examining values greater than the baseline adult value.

Conclusions

- For Adderall XR® versus generic, in the elderly, C_{max} separation was caused by slower transit times in the elderly than in younger adults due to the differences in drug release from delayed-release and sustained-release polymer systems. However, both the fasting AUC (including appropriate partial AUC) and C_{max} point estimates are well within 80-125% limits. Less significant deviations were observed in children and in adolescents.
- In hmEMs taking Prilosec®, changes in gut and hepatic extraction due to age show little-to-no risk in extrapolating fasting BA comparison from adult studies to other age groups.
- For Lipitor®, formulations differing in drug substance physical form are shown to have the fasting AUC and C_{max} estimates within 80-125% limits in the related age groups.
- Regardless of the substance taken, the increased permeability due GI disease states shows minor impact on BA. For Adderall XR® and Prilosec ®,T/R ratios remain relatively constant; while for Lipitor®, approximately 5% deviation is observed in C_{max} ratios as permeability is increased.
- PBA-centric pharmacokinetic modeling of BE provided preliminary results to further our understanding of the effects of aging, developmental changes in children aged 6 and older, and the specific GI diseases noted above on the BA of drug.
- PBA and PK modeling and simulation could be a risk assessment tool in which evidence-based differences in GI diseases and physiological GI factors are considered.

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