PBPK modeling to predict disease effects on flucytosine PK in the context of a switch from an immediate release to a sustained release formulation in the treatment of cryptococcal meningoencephalitis.

Johanna Eriksson[1], Erik Sjögren[1], Jean-Yves Gillon[2], Vishal Goyal[2], Vijay Satam[2], Stephen Robinson[2], Henri Caplain[2], Isabela Ribeiro[2], Marylore Chenel[1]
[1] Pharmetheus AB, Sweden, [2] Drugs for Neglected Diseases initiative (DNDi), Switzerland

Scan the QR code to view the e-poster

Objective

The aim of this study was to predict flucytosine (5FC) exposure in patients for both immediate release (IR) and sustained release (SR) formulations by integrating HIV-associated disease factors in a physiologically based pharmacokinetic (PBPK) model of 5FC.

This assessment aimed to evaluate the potential risk associated with transitioning from IR to SR formulations in terms of pharmacokinetic (PK) exposure.

Conclusions

Based on our PBPK modeling findings, switching from an IR to a SR formulation for treating cryptococcal meningoencephalitis is expected to maintain consistent exposure ratios (IR/SR) in most patient groups, except for those experiencing fast transit diarrhea.

Furthermore, our study highlights significant but comparable effects on drug exposure among malnourished patients, irrespective of formulation type.

Background

5FC is used for treating cryptococcal meningoencephalitis in advanced HIV patients. However, the current IR tablet, requiring four daily doses, poses adherence challenges and is unsuitable for severely ill patients, often necessitating nasogastric tube administration [1, 2].

To address these issues, a SR pellet formulation was developed. Initial PK studies in healthy volunteers revealed a 54% relative bioavailability of the SR formulation compared to IR in a fasted state, indicating incomplete absorption [3,4]. A PBPK model for 5FC has been established using these data. Based on these initial results and PBPK simulations of multiple dosing, the SR dosing regimen was adjusted to meet the exposure metrics for the IR formulation in healthy individuals. In this study, the exposure in patients was assessed for both the IR and SR formulations.

Data and methods

Study Populations. A virtual population of 200 individuals was generated using PK-Sim v9.1. This population was subsequently modified to reflect various disease components commonly associated with HIV physiology (Figure 1). Each disease component was individually incorporated into the population to assess its impact on drug exposure.

PBPK Modelling. We utilized a previously established PBPK model for 5FC, incorporating parameters such as elimination via glomerular filtration and a fraction unbound in plasma of 97% [3, 4]. The modified virtual populations were used to simulate PK exposure metrics for both the IR and SR formulation of 5FC under fasting conditions (Figure 1).

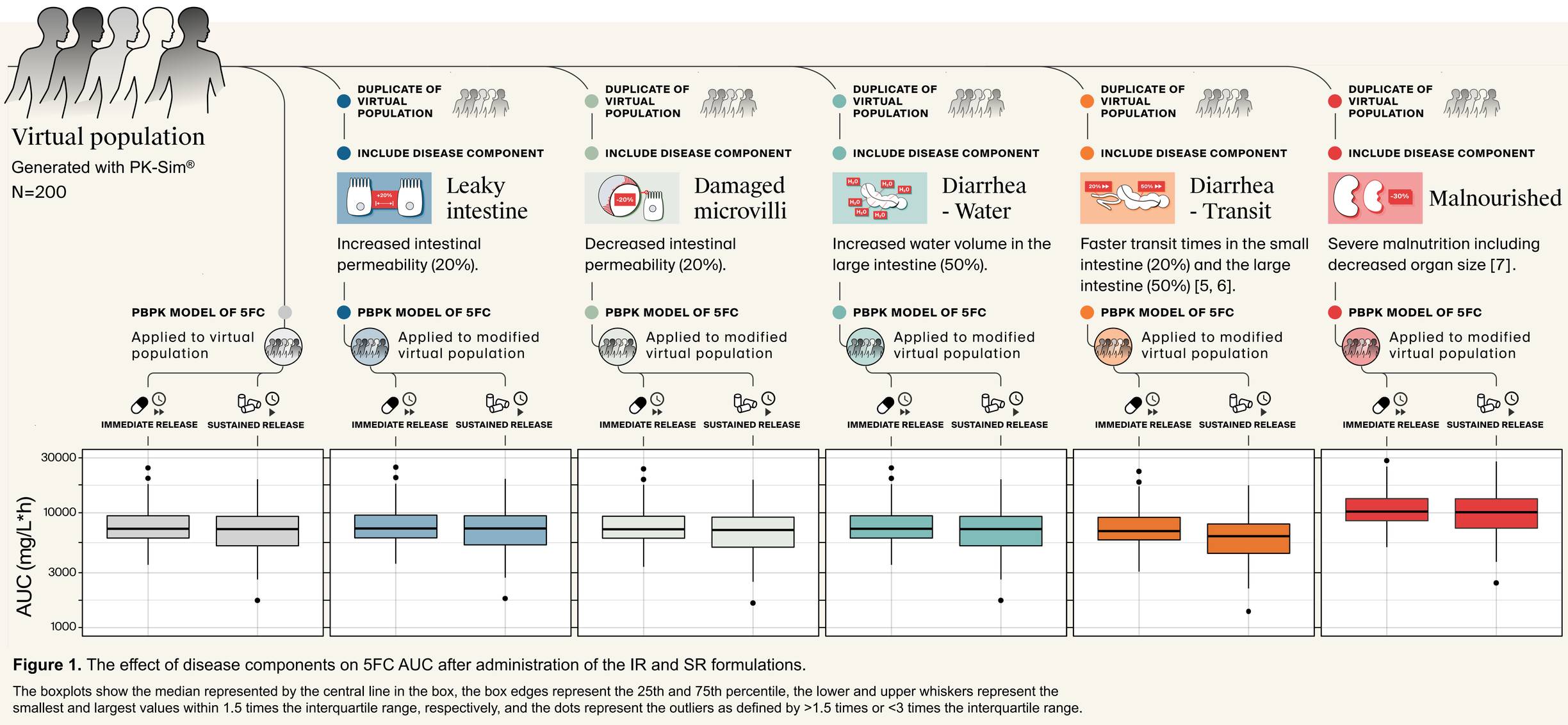

Figure 1. The effect of disease components on 5FC AUC after administration of the IR and SR formulations.

The boxplots show the median represented by the central line in the box, the box edges represent the 25th and 75th percentile, the lower and upper whiskers represent the smallest and largest values within 1.5 times the interquartile range, respectively, and the dots represent the outliers as defined by >1.5 times or <3 times the interquartile range.

Results

The primary disease-related risk affecting a switch in formulation was identified to be diarrhea caused by fast gastrointestinal transit times (Figure 1). Simulated exposure ratios (SR/IR) were approximately 10% lower in populations with fast transit diarrhea compared to a healthy population.

This observation is attributed to the shortened absorption time in patients experiencing diarrhea, which affect the SR formulation more significantly than the IR formulation.

In addition, severe malnutrition significantly influenced the PK of both SR and IR formulations of 5FC (Figure 1). In severe malnourished patients, there was a notable increase in median exposure (15-18%) and maximum concentration (Cmax) (13-15%) due to reduced renal clearance [7].

This impact was consistent across both formulations, suggesting that transitioning from IR to SR cannot be considered a specific risk for treating cryptococcal meningoencephalitis in severely malnourished individuals.

References

1. Vermes A. et al. The Journal of antimicrobial chemotherapy 2000; 46(2): 171-9.
2. Archibald L.K. et al. Emerging infectious diseases 2004; 10(1): 143-5.
3. Goyal V. et al. Clinical Translational Science, 2024; accepted for publication.
4. Eriksson J. et al. PAGE abstract 2023.
5. Sharpstone D. et al. Gut 1999; 45.1: 70-76.
6. Ohe M.R. et al. New England Journal of Medicine 1993; 329.15: 1073-1078.
7 Sjögren E. et al. Pharmaceutics 2021; 13.2: 204.

Disclosures and funding

This project (grant RIA2018CO-2516) is part of the European and Developing Countries Clinical Trials Partnership Association (EDCTP2) programme supported by the European Union, with support by the Drugs for Neglected Diseases initiative (DNDi).

Contact

marylore.chenel@pharmetheus.com
www.pharmetheus.com