Predicting disease effect on the pharmacokinetics (PK) of sustained and immediate release formulations of flucytosine by applying physiologically based pharmacokinetic (PBPK) modeling

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BACKGROUND

WHO recommends flucytosine (5FC) as an essential component of cryptococcal meningitis (CM) treatment regimens. The currently available 5FC formulation, an immediate release (IR) tablet, needs to be administered four times a day and is sub-optimal for administration via naso-gastric tube. To address this problem, DNDi is developing a sustained release (SR) formulation. Two PK studies in healthy subjects have already been performed in South Africa, which evaluated the immediate release and SR formulations. A PBPK model was developed using concentration-time profile data from the two studies in healthy volunteers[1].

To assess the risk of the SR formulation leading to over- or underexposure of 5FC in an upcoming Phase 2 trial (due to alterations in the gastrointestinal (GI) tract associated with the disease), PBPK modeling was used to assess the potential impact of the disease on 5FC PK.

METHODS

A healthy population was generated in PK-Sim® and modified to include different disease components.

The disease components considered in this analysis, were:
1) increased (20%) intestinal permeability as a consequence of "leaky" intestine,
2) decreased (20%) intestinal permeability as a consequence of damaged microvilli,
3) diarrhea due to faster transit time in the small (20%) and large intestine (50%),
4) diarrhea due to higher water volume in the large intestine (50%), and
5) severe malnutrition, as described in the literature[2].

Simulations using the legacy PBPK model with modified populations, including disease components, were performed according to scenarios listed above (1 to 5).

For each scenario and each treatment, i.e., IR (weight-based dosing, 100mg/kg/day) and SR (6000 mg bid), the following PK parameters were derived from the PK profiles simulated for repeated dosages (steady-state):

- AUC_t (Area Under the Curve up to 7.5 days)
- C_{max} (maximal concentration at steady-state)
- C_{trough} (concentration at through at steady-state)

RESULTS

Being malnourished was the disease component with the greatest impact on 5FC PK, irrespective of the formulation (IR or SR), with an increase in exposure compared to healthy subjects. Diarrhoea due to faster transit tends to slightly decrease 5FC exposure. Other disease states have a very limited impact (Figure 1).

> **Switching from an immediate release to sustained release formulation of flucytosine for the treatment of cryptococcal menigitis, is not predicted to cause over- or underexposure in a patient population**
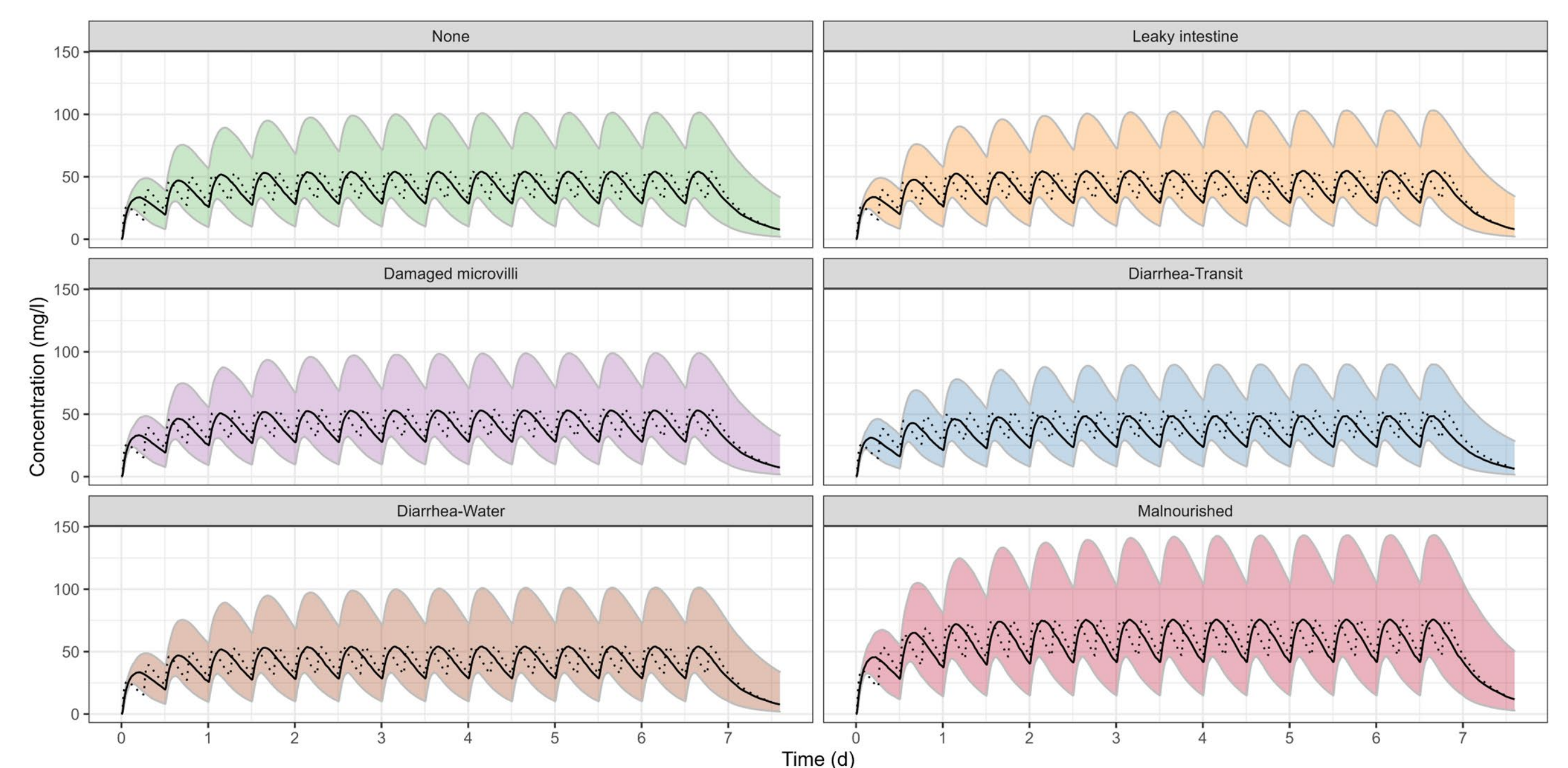

Figure 1: The effect of disease components on 5FC PK profiles after administration of the IR and SR formulations. The black and dotted lines correspond to the medians of simulated profiles after administration of the SR and IR formulations, respectively. The coloured shaded areas correspond to the 90% prediction intervals of the SR formulation.

The PK parameters, expressed as geometric mean ratios comparing the SR to the IR formulation (Table 1), show that the exposure of the SR formulation is about 10% lower than the IR formulation in patients having diarrhea, due to fast intestinal transit (which corresponds clinically to bowel movements three or more times a day with liquid or loose stools[3]).

For the other disease components, the exposure of the SR and IR formulations were similar, as was also the case in healthy subjects.

Table 1: The effect of disease components on the relative exposure of the SR and IR formulations. Values are expressed as geometric mean ratios (SR/IR).

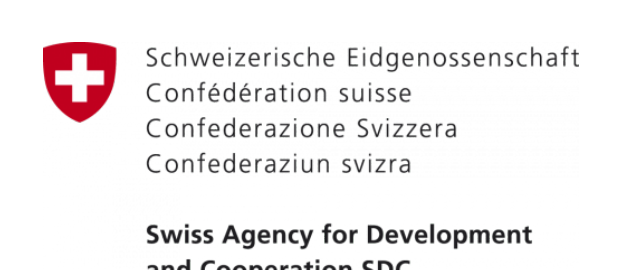| Disease component	AUC_t	C_{max}	C_{trough}
None	0.92	0.94	0.80
Leaky intestine (1)	0.93	0.95	0.82
Damaged microvilli (2)	0.91	0.93	0.79
Diarrhea due to fast intestinal transit (3)	0.83	0.88	0.70
Diarrhea due to high water content (4)	0.92	0.94	0.80
Malnutrition (5)	0.92	0.94	0.81

CONCLUSIONS

Switching from an immediate release to a sustained release formulation of 5FC for the treatment of CM is not predicted to cause over- or underexposure in patients, with the exception of patients with diarrhea.

REFERENCES

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ACKNOWLEDGMENTS