

PK modelling of flucytosine in HIV-positive adults with cryptococcal meningitis in Africa

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Introduction

Flucytosine (5-FC) is commonly used in combination therapy for the treatment of cryptococcal meningitis. Historically, its use has been limited due to accessibility issues. However, as flucytosine becomes increasingly available globally, there is new potential for its use in the treatment of other fungal infections. To optimise dosing and inform future trials, a greater understanding of flucytosine's pharmacokinetics (PK) and pharmacodynamics (PD) is required.

Methods

Analysis was conducted with data from the phase 3 AMBITION-CM trial (1) involving HIV-positive adults with cryptococcal meningitis from five African countries across up to 7 days. Model fitting and exploration were performed using non-linear mixed effect modelling using nlmixr2 (version 2.1.1.9) in R (version 4.3.1). Allometric scaling was included as a prior. Creatinine, creatinine clearance, and neutrophil count were tested as model covariates. Serum levels below the limit of quantification were handled using the M3 method.

Results

The final dataset comprised 383 adults. Median weight (max, min) was 53kg (34, 119); age 37 years (18, 71); males n = 220 (57%). Pharmacokinetic data was described using one plasma and one CSF compartment disposition model. Typical values for the absorption rate constant, clearance and volume of distribution were 0.727 hour⁻¹, 7.9 L/h, and 133 L. The intercompartmental clearance for CSF was 0.344 L/h, and the volume of distribution for CSF was 5.13 L. A proportional error model was employed for the estimation of plasma concentration, and a proportional-additive error model was employed for the estimation of CSF concentration. The model benefited from inter-individual variability on all parameters. No covariates were retained in the model.

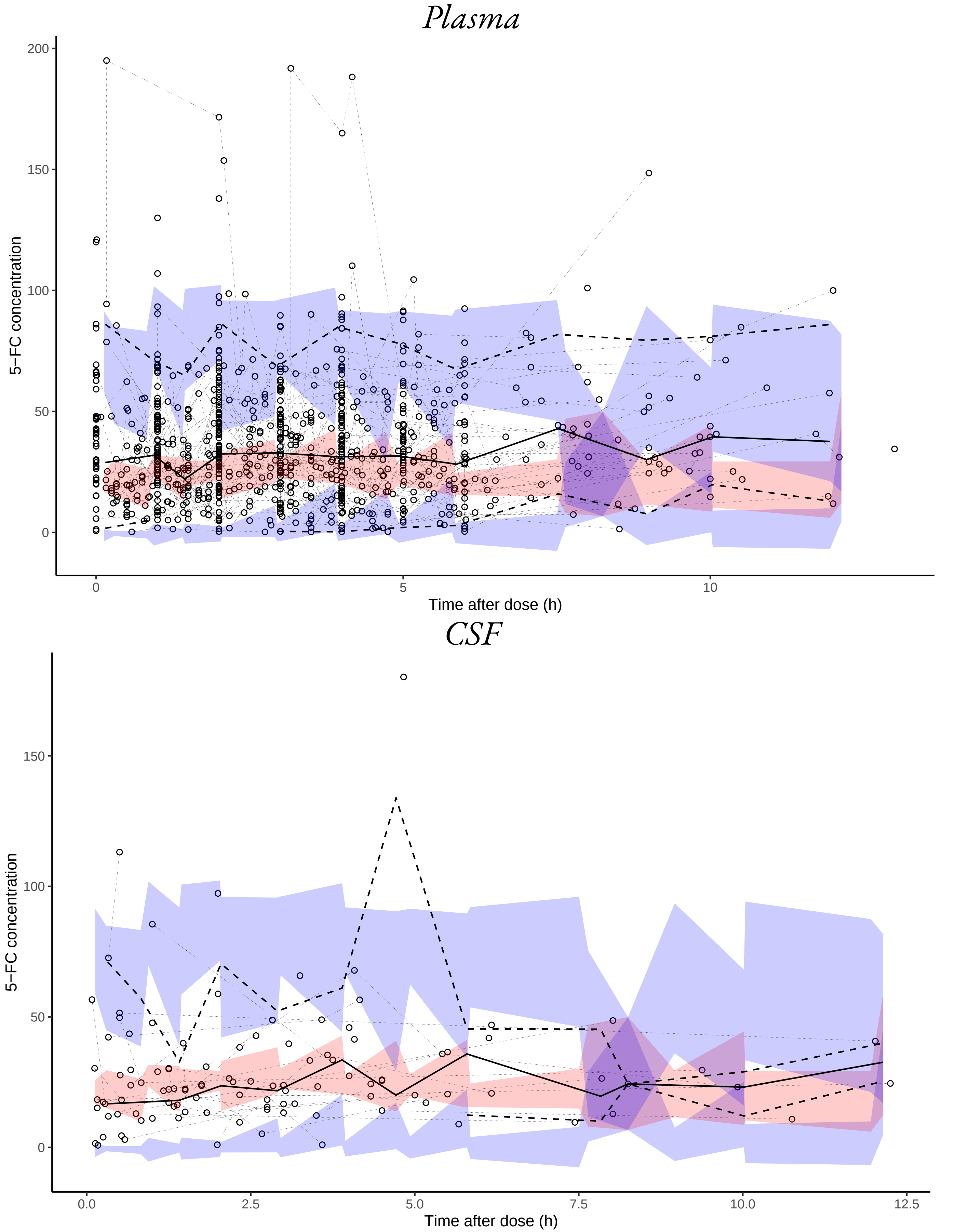


Figure 1: Visual Predictive Check, where black line is the median, dots are observed data. Dashed line is 5th and 95th intervals. Red shading is prediction intervals for median. Purple shading is prediction intervals for 5th and 95th intervals.

Conclusions

We reliably described the PK of 5-FC and its movement into the CSF. Future work will include utilising CFU counts to assess the impact of drug exposure on fungal clearance, to ultimately provide clinically relevant insights for current and future dosing strategies.

Key points

Data were collected from the phase 3 AMBITION-CM trial of adults with cryptococcal meningitis.

We created a PK model consisting of plasma and CSF observations.

Future work will include incorporating CFU values into the model to make clinical dosing suggestions.

References

[1] Joseph N Jarvis, David S Lawrence, David B Meya, Enock Kagimu, John Kasibante, Edward Mpoza, Morris K Rutakingirwa, Kenneth Ssebambulidde, Lillian Tugume, Joshua Rhein, David R Boulware, Henry C Mwandumba, Melanie Moyo, Henry Mzinganjira, Cecilia Kanyama, Mina C Hosseinipour, Chimwemwe Chawinga, Graeme Meintjes, Charlotte Schutz, Kyla Comins, Achita Singh, Conrad Muzoora, Samuel Jjunju, Edwin Nuwagira, Mosepele Mosepele, Tshepo Leeme, Keatlaetse Siamisang, Chiratidzo E Ndhlovu, Admire Hlupeni, Constantine Mutata, Erik van Widenfelt, Tao Chen, Duolao Wang, William Hope, Timothée Boyer-Chammard, Angela Loyse, Sile F Molloy, Nabila Youssouf, Olivier Lortholary, David G Lalloo, Shabbar Jaffar, Thomas S Harrison, and Ambition Study Group. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. *N. Engl. J. Med.*, 386(12):1109–1120, March 2022.

Parameter	Population Estimate (95%CI)	%RSE	BSV(CV%)
K_a (hour ⁻¹)	0.727 (0.555, 0.952)	43.2	80.5
CL/F (L/hour)	7.9 (7.78, 8.02)	0.383	43.7
$V_{(L)}$	133 (126, 140)	0.559	80.5
Q/F (L/hour)	0.344 (0.283, 0.419)	9.37	80.5
$V2_{(L)}$	5.13 (4.17, 6.13)	6.46	
prop.err _{plasma}	0.607		
prop.err _{CSF}	0.458		
add.err _{CSF}	0.956		
coeff _{weight on CL}	0.750 (fix)		
coeff _{weight on V}	1.00 (fix)		

Table 1: Parameter Estimates