

POPULATION PHARMACOKINETIC MODEL FOR FLUOROURACIL (5-FU) ACCOUNTING FOR IRREGULARITIES IN INFUSION RATE

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Introduction and Objectives

Although numerous studies have shown that BSA poorly predicts drug exposure^{1,2}, it is still common practice to adjust the dose according to the patient's body surface area (BSA). Recently, a dose adaptation strategy based on a target exposure was successfully applied for 5-FU³. Gamelin et al⁴ reported that after continuous infusion of 5-FU, a target AUC of 20-24 mg·h·L⁻¹ was associated with better tumor response and less toxicity compared to BSA-based dosing.

However, a reliable estimation of AUC requires a number of blood samples which is unfeasible to be carried out in clinical routine. A population pharmacokinetic (PK) approach may overcome this problem and can identify the factors affecting 5-FU PK as well as estimate interindividual and interoccasion PK variability.

The aim of this study was to develop a population PK model of 5-FU accounting for deviating infusion rates at the end of infusion and identify potential covariates explaining PK variability of 5-FU exposure during continuous intravenous infusion (c.i.v.).

Patients and Methods

1023 plasma concentrations from 93 patients receiving 5-FU c.i.v. for more than 18 hours were pooled from four clinical studies. All studies were conducted with ethics committee approval and patient informed consent was obtained prior to inclusion. Blood samples for 5-FU measurement were put on ice immediately after collection. Individual 5-FU concentrations were determined either by HPLC or the My5-FU® homogeneous immunoassay.

The pharmacokinetic model was developed using NONMEM 7.2.1 with first-order conditional estimation with interaction (FOCE Inter). Population PK parameters were estimated, a flexible infusion rate was included and potential covariates such as sex, age, BSA and dose were tested. Final model selection was done according to the objective function value (OFV). The criterion for inclusion a covariate into the model was a decrease in OFV of ≥ 6.63 units ($p=0.01$) and a reduction in interindividual variability. For the backward elimination procedure, a change in OFV of ≥ 7.88 was required to reach statistical significance at $p=0.005$. Goodness-of-fit (GOF) plots and successful convergence were also considered to select the final model.

Model evaluation was performed using visual predictive checks (VPCs), bootstrap methods and by Bayesian prediction of 272 plasma concentrations from 25 patients.

Results

A one-compartment PK model was successfully fitted to the data. The model parameters are systemic clearance (CL) and central volume of distribution (V). Interindividual variability (IIV) and interoccasion variability (IOV) were described by exponential models.

Since in clinical routine deviations from the infusion rate frequently occur at the end of infusion, a flexible infusion rate was introduced during the last 10% of the infusion duration leading to a smaller OFV and a reduction in interindividual variability.

Sex was the only covariate found: Clearance (CL) of female patients was estimated to be 77% of male patients' CL. PK parameters are shown in Table 1.

Figure 1. Goodness of fit plots.

A. DV vs IPRED,
B. WRES vs PRED.

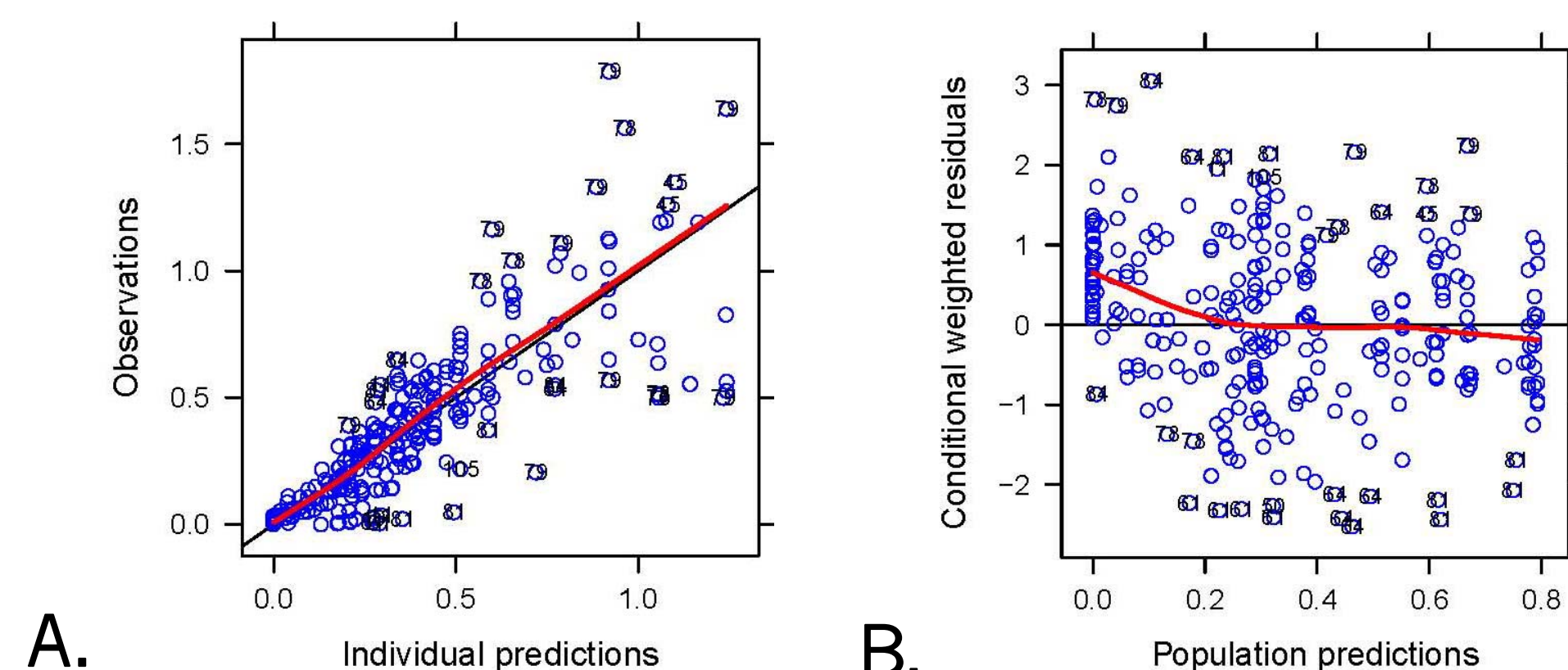


Table 1. Parameter estimates for 5-FU and confidence intervals (CIs) obtained by bootstrapping

Parameter	Estimate (95% CI)	IIV (%CV, 95% CI)	IOV (%CV, 95% CI)
CL (L/h)	297 (273 – 327)	37.4 (31.5 – 43.2)	12.8 (7.8 – 16.0)
V (L)	31.2 (26.2 – 39.7)	42.2 (30.1 – 57.2)	-
Flexible infusion rate (%CV)	1.7 (1.1 – 2.3)	-	-
Θ (covariate of females on clearance)	0.8 (0.7 – 0.9)	-	-
ρ (CL, V)	0.8 (0.5 – 0.95)	-	-
Residual error			
$\sigma_{\text{prop, HPLC}}$ (%)	48.9 (43.1 – 54.8)		-
$\sigma_{\text{add, HPLC}}$ (mg/L)	2.8 (1.7 – 4.0)	23.1 (13.6 – 30.3)	-
$\sigma_{\text{prop, Immunoassay}}$ (%)	29.8 (24.0 – 34.8)		-

IIV, interindividual variability; CV, coefficient of variation (%); IOV, interoccasion variability; CL, clearance; V, central volume of distribution; ρ , correlation coefficient; σ_{prop} , proportional residual variability (CV); σ_{add} , additive residual variability (SD).

The fact that IOV of CL is lower than IIV suggests that 5-FU target exposure might be achieved by adapting the dose in subsequent cycles based on measured plasma concentrations from previous cycles.

Model evaluation and Bayesian estimation revealed that the population PK model predicts individual plasma concentrations with satisfactory precision. Result from bootstrapping are shown in Table 1. The GOF plots and VPCs (only 24 hours and 120 hours infusion duration are presented) for model evaluation are shown in Figure 1 and 2.

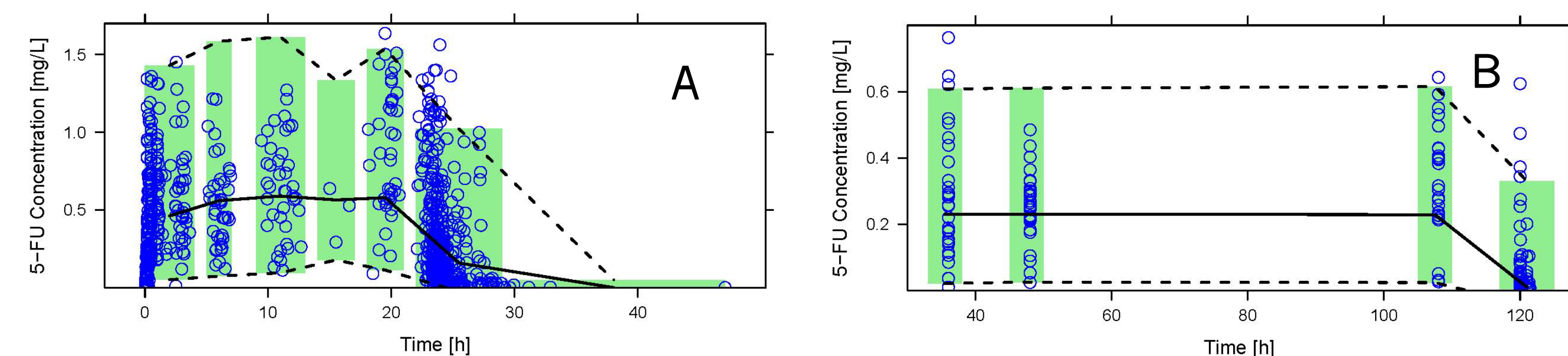


Figure 2.

Visual predictive checks (VPCs) after a 5-FU infusion over A. 24 hours, and B. 120 hours.

The 5th and 95th percentiles (dashed lines) and the median (solid line) of model-simulated 1,000 data are shown, along with the actual observations (open circles).

Conclusions

- Accounting for irregularities of infusion rates is a promising approach to improve estimation of PK parameters of 5-FU during continuous intravenous infusion.
- 5-FU target exposure may be achieved by adapting the dose in subsequent cycles based on measured plasma concentrations from previous cycles.
- Our model should be further evaluated for its potential to individualize 5-FU dosing maximizing efficacy and minimizing toxicity.

References

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