POPULATION PHARMACOKINETICS OF 5FU AND ITS MAJOR METABOLITE 5-FDHU IN COLORECTAL CANCER PATIENTS

Abstract n°1890

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CONTEXT

The anticancer drug 5-fluorouracile (5FU) which is indicated for the treatment of solid malignancies especially colorectal, breast, head and neck neoplasms is extensively biotransformed to 5-fluoro-5,6-dihydrouracil (5-FDHU) by the dihydropyrimidine deshydrogenase enzyme (DPD). DPD deficiency is recognized as an important risk factor, predisposing patient to undergo severe toxicity [1]. The aim of this study is to develop a population pharmacokinetic model for both 5FU and 5FDHU to explore mechanisms and factors affecting the 5-FU metabolism.

METHODS

Data

Data came from a retrospective study on 129 colorectal cancer patients who received 6 cycles of 5-FU 370 mg/m2/day i.v. boluses (5 days every 4 weeks) and L-leucovorin 100 mg/m2/day, one month later after chirurgical resection. Demographic and biological data were recorded from patient files and considered as covariates (Table 1).
Individual plasma concentrations of 5-FU and 5-FDHU were determined on day 1 of the first cycle from 5 min up to 3 h after drug administration with a validated high performance liquid chromatography method.

Population Pharmacokinetic model

A simultaneous model for the 5FU/5-FDHU concentration-time data system was performed using the population approach implemented in NONMEM VI. The FOCE-Interaction method was used for the estimation of the structural model parameter. Base model selection was realized according to the lower value of the objective function (OFV), goodness-of-fit plots, successful convergence, the absence of shrinkage on parameter estimate.
For the detection of atypical individuals, a leave-one-out procedure was performed followed by a principal component analysis (PCA). The interest was to evaluate the impact of removing these patients from the database on the base model population pharmacokinetic parameter estimate.
The covariate screening procedure was done using a PCA, then covariates selected according to their clinical interest were introduced as a power function in the final model. Validation of the final model was done using a bootstrap procedure.

RESULTS

Base Model

The pharmacokinetic of 5FU and 5-FDHU was well described by a three compartment model. Central and peripheral compartment were associated with 5FU and a single compartment was associated with 5-FDHU. The metabolism of 5FU to 5-FDHU was best described by a nonlinear Michaelis-Menten process and the eliminations of 5FU and of 5-FDHU, by a first order linear process (Figure 1).
Population parameter interindividual variability (IV) was described by an exponential model and residual variability (RV) by a proportional error model. Structural hypotheses were considered: Vm was fixed equal to V1 for structural identifiability purposes, V2 was fixed to three times V1 and interindividual variability of Q was fixed to 70% (following a sensitivity analysis of the results with respect to the Q variations in the range of 10 to 120%).
The leave-one-out procedure detected two atypical 5FU/5-FDHU kinetic profiles. The corresponding patients were excluded from the study but no significant impact was observed on the population parameter estimation.

Final Model

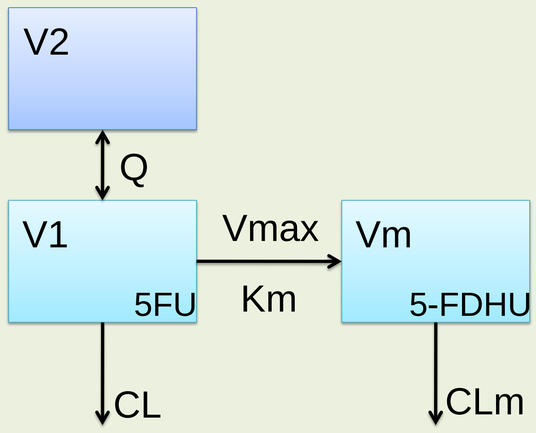
Two covariates, weight on 5FU central compartment distribution volume and body surface area on 5FU clearance and 5FU metabolism rate were included in the final model. None of the other covariates (ALAT, ASAT, GGT, creatinine clearance, age, sex) have been found significatively associated with 5-FDHU clearance .DPD activity has not been found to explain 5FU clearance IV or metabolism rate IV, however a slightly correlation (r=-0.369, *p<0.01*) has appeared with the inter-compartmental clearance Q of 5FU, suggesting a reserve compartment for 5FU depending on the value of the DPD activity.
Final model parameter and bootstrap estimate (Table 2) enhance the validation of the model, goodness-of-fit plots have not shown any bias (Figure 2).

CONCLUSION

This population PK model is the first one which integrates a nonlinear process describing the metabolism of 5FU to 5-FDHU. It could be used to assess the relationships between exposures of both 5FU and 5-FDHU and related toxicities or efficacy.

CHARACTERISTICS	MALE median	MALE range	FEMALE median	FEMALE range	ALL median	ALL range
Demography						
n	83		46		129	
Age (year)	62	(57 - 69)	58	(52-64)	61	(56-68)
Height (cm)	169	(161-174)	155	(150-162)	165	(156-171)
Weight(kg)	66	(59-75)	58	(49-64)	62	(56-72)
*BSA**	1.73	(1.60-1.90)	1.59	(1.44-1.65)	1.65	(1.51-1.86)
Biology						
Creatinine CL	0.90	(0.81-1.04)	0.80	(0.68-0.90)	0.88	(0.75-1.00)
ALAT (UI/L)	18	(15-21)	17	(14-20)	18	(15-20)
ASAT(UI/L)	22	(18-27)	20	(16-24)	21	(17-26)
GGT(UI/L)	31	(25-45)	26	(21-35)	30	(22-43)
DPD						
n	50		34		84	
PBMC-Activity (pmol/mn/mg)	165	(119-264)	190	(115-218)	169	(118-260)
Dose (mg)	640	(590-703)	588	(532-611)	611	(559-688)

Table 1 : Patients characteristic



CL : 5FU clearance
Q : 5FU inter-compartmental clearance
V1: 5FU central distribution volume
V2: 5FU peripheral distribution volume
Vmax: 5FU metabolism rate
Km: 5FU Michaelis-Menten constant
Vm: 5-FDHU distribution volume
CLm: 5-FDHU clearance

Figure 1: The base model structure and the implied parameters

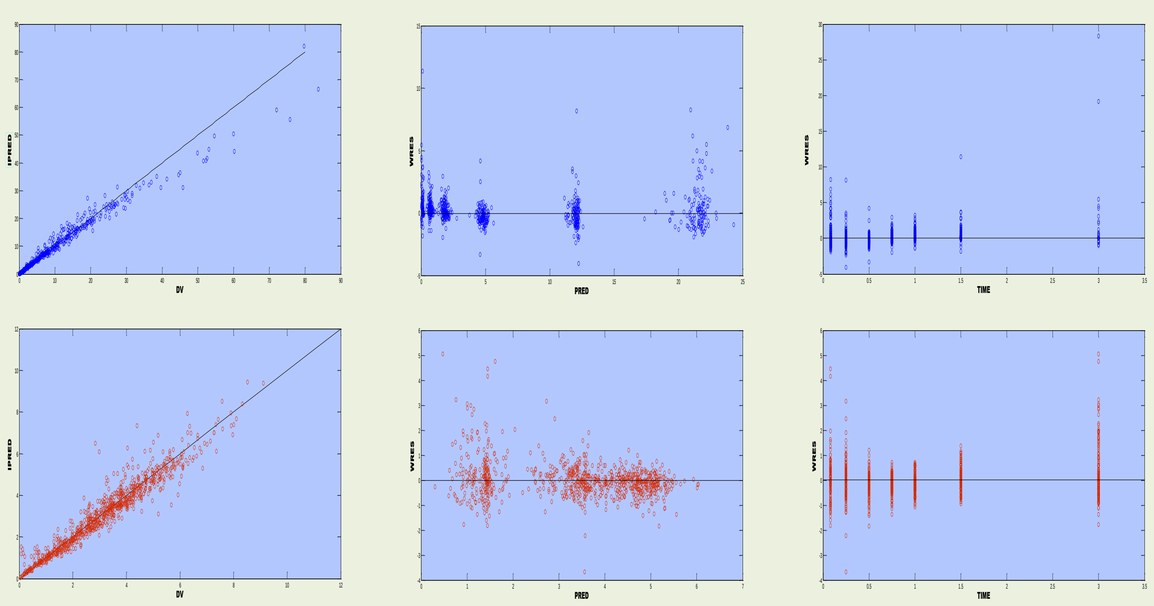


Figure 2: Goodness-of-fit plots (IPRED vs DV, WRES vs PRED, TIME)
Top pannel : 5FU
Down pannel : 5-FDHU

POPULATION PARAMETERS			BOOTSTRAP	
Parameter	Estimate	RSE(%)	Median	Confidence interval (95%)
CL (L/h)	33.6	11.8	32.9	32.7 - 34.0
Q (L/h)	5.81	7.8	5.74	5.69 - 5.89
V1 (L)	21.6	4.3	21.5	21.4 - 21.7
Vmax (mg/h)	396	25.2	400	390 - 415
Km (mg/L)	24.5	13.1	24.6	24.4 - 25.6
CLm (L/h)	15.6	6	15.5	15.3 - 15.7
Covariate				
Θ1 (V1/WEIGHT)	0.755	25.9	0.73	0.71 - 0.77
Θ2(CL/BSA)	0.823	27.2	0.86	0.81 - 0.89
Θ3(Vmax/BSA)	1.27	37	1.25	1.22 - 1.38
Interindividual Variability				
ω_{CL}	41.7	11.3	41.7	40.9 - 42.1
ω_{V1}	49.8	15.8	49.6	48.4 - 50.2
ω_{Vmax}	67	20.1	67.1	65.9 - 68.2
ω_{Km}	65.2	27.8	66.1	65.0 - 68.8
ω_{CLm}	68.6	10.8	67.6	67.4 - 69.6
Residual variability				
σ_{5FU}	14.7	16.1	14.3	14.3 - 14.9
$\sigma_{5\text{-}FDHU}$	19.7	13.3	19.4	19.3 - 19.8

Table 2 : Final model parameters estimate

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[1] Di Paolo A, Danesi R, Falcone A, Cionini L, Vannozzi F, Masi G, Allegroni G, Mini E, Bocci G, Conte PF, Del Tacca M. Relationship between 5-fluorouracil disposition, toxicity and dihydropyrimidine dehydrogenase activity in cancer patients. Ann Oncol 2001;12(9):1301-6