

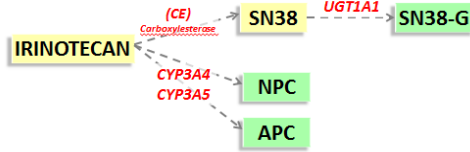
A PK-PGx study of irinotecan: Influence of genetic polymorphisms of xenoreceptors CAR and PXR

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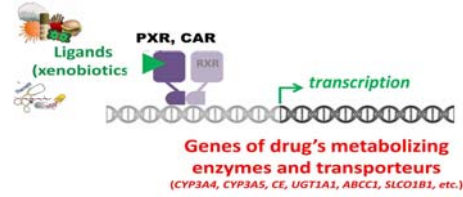
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INTRODUCTION

Irinotecan is an anticancer agent broadly used in the treatment of colorectal cancer. It's a prodrug and has a complex metabolism which includes one active metabolite, (SN38) and 3 inactive compounds (SN38G, APC, and NPC).



The xenoreceptors PXR (gene *NR1I2*) and CAR (gene *NR1I3*) which are activated by xenobiotics (endogens, and exogens chemicals) can regulate the expression of all the genes which control the metabolism of irinotecan, including UGT1A1⁽²⁾.



Pharmacogenetics (PGx) study the influence of interindividual genetic variability on drug response. The main genetic factor associated with the PK of irinotecan is a polymorphism of *UGT1A1* (*UGT1A1*28*), the enzyme which detoxify the SN38 into an inactive glucuronide form (SN38G)⁽¹⁾.

This poster focus on the PK of irinotecan as a chemical entity, which is the first step of the complete metabolism of this drug.

HYPOTHESIS : the genetic variability of PXR and CAR can explain a part of the pharmacokinetic variability of irinotecan

DATA

« Protocol BIOCOLON »

A french study about the response to colorectal cancer therapy

200 patients



109 patients treated by irinotecan

Perfusion 180mg/m² during 2h (FOLFIRI or FOLFIRINOX)



5 blood samples

1.5h/4.5h/7.5h/28.5h/46h



Irinotecan and metabolites quantification by HPLC

PK model-building : We've built a model for the prodrug in order to use the individual estimates of the parameters as regressor in the PK models of its metabolites (next analysis). We use **Monolix™** (V 4.1.3) which estimates parameters thanks to the algorithm **SAEM**.

Structural model : it was chosen on the basis of changes in - log likelihood and qualitative assessment of diagnostic plots. Various error models and 3 types of elimination of irinotecan (linear, non linear, and mixt) were tested

Covariates analysis (2 steps) :

- (1) An **exploratory study of genetic covariables** was conducted by testing the correlation between the empirical Bayesian estimation (EBE) of the PK parameter of irinotecan with the genotype of the patients for PXR (13 SNP, Single Nucleotide Polymorphism), and CAR (5SNP). We used the package **SNPassoc of the R software** which perform a generalized linear model to determine the genetic effect of the minor allele (dominant, recessive, and additive)⁽³⁾. The genetic covariables tested were chosen thanks to the Software Haploview™ to ensure a good coverage of their genetic variability of PXR and CAR and also on the basis of their association with the PK of other drugs in the literature.
- (2) Finally, **the SNP which were significantly correlated with the EBE (p=0.05) were introduced in the PK model** with other physiological covariates (sex, age, weight, performans status (PS)), and their impact on the model were evaluated by performing a the log-likelihood ratio test (**LRT**) between the basic model and models including each of the covariates.

METHODS

STRUCTURAL MODEL

Objective function

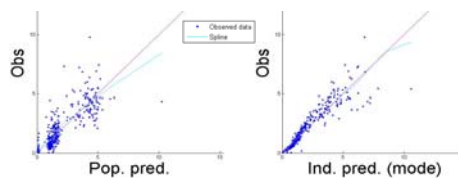
Population parameters

Goodness of the fit between the observed concentrations and the predictions for the population and for the individuals

VPC (Visual Predictive Check)

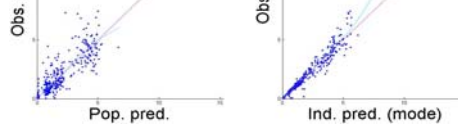
(M1) Linear elimination	Lin		IS
	-2LL	-286.21	-234.02
	AIC	-258.21	-206.02

parameter	s.e. (lin)	r.s.e.(%)
V	7.81	4.5
k	1.6	0.95
k12	1.2	0.72
k21	0.00361	0.00085
k13	16	9.8
k31	0.784	0.049
(error) b	0.238	0.013
(error) c	1.16	0.054



(M2) Non-linear elimination	Lin		IS
	-2LL	-258.05	-342.91
	AIC	-224.05	-308.91

parameter	s.e. (lin)	r.s.e.(%)
V	17.7	0.7
k12	0.584	0.014
k21	0.078	0.0026
k13	17.2	0.75
k31	3.31	0.11
Vm	156	17
Km	5.45	0.49
corr(Vm,Km)	1	0.002
(error) b	0.196	0.011
(error) c	1.12	0.045



In both models the residus were independent of the time, and of the predictions. The estimation of the likelihood by linearization and by important sampling led to conflicting conclusions. We've chosen the model M2 because it better estimates the parameters, and because the fit and the prediction are better. A mixt elimination has also been tested ; but the diagnostic criteria for M2 were better.

We've chosen a 3 compartments model with a proportional error , a nonlinear elimination of irinotecan and a correlation between Vm and Km.

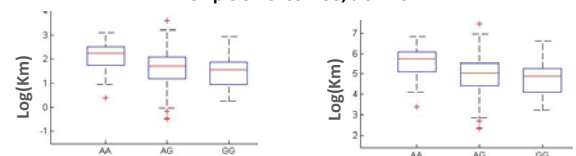
COVARIATES ANALYSIS

The EBE of Km is correlated with 4 SNP of PXR and CAR (same results for Vm)

Common homozygote (hmzC) ; heterozygote (htz) ; homozygote variant (hmzV)

SNP	hmzC vs (htz and hmzV) (hmzC and htz) vs hmzV		hmzC=0/ htz=1/ hmzV=2
	Dominant	Recessive	log-additive
rs3814055 (PXR)	0.04613	0.48794	0.09277
rs1523127 (PXR)	0.03491	0.73033	0.12751
rs10934498 (PXR)	0.47274	0.02240	0.07148
rs2502815 (CAR)	0.02675	0.30622	0.02232

Boxplot : Km distribution by genotype Example of rs1094498, a SNP of PXR



The differences between the likelihood of the basic model and the likelihood of the models including each of the 4 genetics covariates were not significant (P_{value} of the LRT between 0.2 and 1). Physiological covariates either did not improve the model.

CONCLUSION, PERSPECTIVES

We described the PK of irinotecan using a 3 compartmental model with a proportional error and a non linear elimination. 80% of irinotecan underwent a hepatic metabolism, and 20% was excreted in the urine (4). Most of the studies described a linear elimination for irinotecan (5-6). However, the non linearity that we observed can be explained by a saturable hepatic metabolism, and a saturable cellular transport during the renal excretion process. Some polymorphisms of the genes encoding the xenoreceptor PXR and CAR were associated to the EBE of Vm and Km. Nevertheless, these genetic covariables covariates did not improve the model. These results are only the first step of a more exhaustive analysis, and PK models of the metabolites of irinotecan have to be designed to test the influence of genetic covariates. We also planned to validate all the steps of the analysis thanks to a bootstrap methodology.