Assessment of pharmacokinetic variability of fondaparinux in 809 patients treated after major orthopedic surgery: the POP-A-RIX study

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Introduction

- Fondaparinux: 1st synthetic factor Xa inhibitor, renal excretion
- Better efficacy in prevention of venous thromboembolic events in patients undergoing major orthopedic surgery than low-molecular-weight heparin (LMWH) [1].

Aim of the study

- But Increase risk of hemorrhage compare to LMWH
- Is the risk of hemorrhage predictable?
- Modeling anti-Xa activities of fondaparinux
- Assessment of the correlation between anti-Xa levels and risk of hemorrhage

Anti-Xa activity

- Chromogenic assay
- Expressed in mg/L
- LOQ < 0.07 mg/L

Center	Analyser	Reagent	Conversion
CHU St Etienne	BCS	Biogenic	1750 UI ↔ 2.5 mg
AP-HP Cochin	STAR	STA	1 µg/ml ↔ 1.34 UI/ml
Reims	STAR	Stachrom	1 µg/ml ↔ 1 UI/ml
Caen	?	?	4000 UI↔2.5 mg
Annonay	STAR	STA	1750 UI↔2.5 mg
Rouen	STAR	Rotachrom	Directement en mg/L
Lyon	BCS	Biophen	1750 UI↔2.5 mg

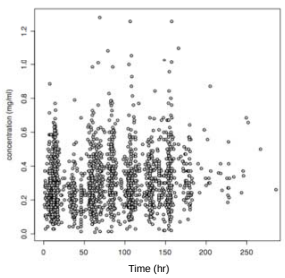
Description population

Population

• 809 orthopaedic patients: 36% hip fracture, 33% total hip replacement, 26% total knee replacement, 5% others

Samples

- 2467 samples
- 2.5 samples per patient on average (0 to 4)



Patient characteristics

Demographics	
Age (yrs)	73.6 ± 12.3 [20-100]
Womem	71%
BW (kg)	70.5 ± 16.8 [35-172]
BMI (Kg/m²)	26.6 ± 5 [13-54]
CrCl (mL/mn)	76 ± 31 [18-263]
Risk factors of hemorrhage	
Age > 75 ans	50%
BW < 50 Kg	13%
ClCr < 50 mL/mi	20%
HBP	55%
DVT/PE	23%
Cancer	13%
Diabetes	20%

Methods

Design

• French multicenter prospective study in major orthopedic surgery
• Patients treated with 2.5 mg of s.c. fondaparinux once daily for at least 5 days

Covariates

• Age, gender, body weight (BW), serum creatinine (Scr), creatinine clearance (CrCl)
• Diabetes, cancer, arterial hypertension

Modeling

• Structural models: 1 and 2 compartments, absorption 0 and first order
• Inter-individual variability on clearance (Cl), central volume of distribution (Vc), peripheral volume (Vp), inter-compartmental clearance (Q) and absorption rate (Ka)
• Selection of covariates based on the likelihood ratio test
• NONMEM® VI, FOCE

Model validation

• Numerical Predictive Check (NPC)
• External validation by splitting dataset in 2/3, 1/3

Results

Structural model

• 2 cpt., 1st order absorption
• Proportional and additive error model

Covariates

• Cl = *f* (CrCl, gender)
• Vc =*f* (BW)

External validation (validation dataset)

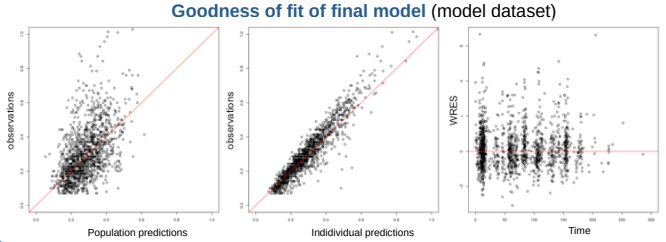
Parameters	*Without covariate*	*Final model*
Biais (ME)	-0.3089	-0.0187
Precision (MSE)	0.2447	0.0208
(RMSE)	0.1109	0.1018

Pharmacokinetics parameters (model)

Parameters	*Mean (Se)*	*Inter-indiv (Se)*
Cl = Θ1 + CrCL*Θ6 (*Θ7 males)		65% (0.20)
Θ1 ($L*h^{-1}$)	0.0842 (0.5)	
Θ6	0.00203 (0.11)	
Θ7	1.84 (0.25)	
V2 = Θ2 * [Wt/median(Wt)] ^{Θ8}		57% (0.20)
Θ2 ($L*h^{-1}$)	8.03 (0.03)	
Θ8	0.53 (0.19)	
Q ($L*h^{-1}$)	0.0987 (0.41)	69% (0.57)
V3 (L)	25.9 (0.90)	132% (0.27)
Ka	0.677 (0.12)	99% (0.23)
Residual variability p(%), a(mg/l)	12.7 (0.25)	0.04 (0.16)

NPC 500 simulated datasets, 4.2 % observations outside the 95% prediction interval

Goodness of fit of final model (model dataset)

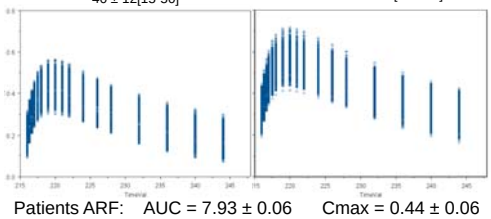


Simulations

500 simulated patients after 10 day of 2.5 mg fondaparinux

Normal renal function (NRF)
40 ± 12[15-50]

Altered renal function (ARF)
76 ± 13 [50-100]



Patients ARF: AUC = 7.93 ± 0.06 Cmax = 0.44 ± 0.06
Patients NRF: AUC = 11.16 ± 1.41 Cmax = 0.57 ± 0.06

Discussion

- Inter-individual variability of anti-Xa activities explained in part by BW, gender and renal function
- Unexplained variability + + + but what is the clinical impact of this variability?
- Are the anti-Xa correlated with risk of hemorrhage in patients treated with fondaparinux?
- Therapeutic drug monitoring required?

➔Multivariate logistic model to predict the risk of hemorrhage
➔Ongoing work

Reference

[1] Turpie AG, Arch Intern Med 2002;162:1833-40

Fundings

• PHRC 2006
• Année Recherche Clinique Fédération Hospitalière de France et LEEM