Pharmacokinetic Variability of the Absorption of Enoxaparin Used Subcuteanously for Venous Thromboembolism Prophylaxis

S. Chantel (1,2), P. Martin (1,2), P.Y. Petit (3), D. Massignon (4), X. Dode (1), P. Maire (5), R.W. Jelliffe (6), G. Aulagner (1,2)

(1) Department of Pharmacy, Hôpital Cardiologique, Bron, France, (2) EA 3452, University H. Poincaré, Nancy, France, (3) Department of Anaesthesia, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France, (4) Department of Haematology, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France, (5) ADCAPT, Department of Pharmacy, Hôpital A. Charial, Francheville, France, (6) Laboratory of Applied Pharmacokinetics, University of South California, Los Angeles, USA

Introduction

➤ The use of enoxaparin for the prophylaxis of venous thromboembolism (VTE) after orthopaedic surgery leads to an important pharmacokinetic variability, particularly for the absorption of the drug.

➤ The aim of this study was to ***determine the influence of morphological patients' characteristics on the absorption*** (absorbed fraction - Fa, absorption rate constant - Ka) ***of enoxaparin used subcuteaneously*** for VTE prophylaxis in orthopaedic surgery.

Patients and methods

➤ Sixty-nine patients (57 for total hip replacement, 12 for total knee replacement) were treated with ***subcutaneous enoxaparin, 4000 IU od at 7 am***. Enoxaparin was administered according to the recommendations for the method of administration of the summary of product characteristics of Lovenox® (Sanofi-Aventis).

➤ ***Three blood samples for anti-Xa activity measurement*** were taken in each patient. Population pharmacokinetic analysis was performed using the ***NPEM2 program*** (version 11.7), with a ***one-compartment linear model*** which was found to best describe the distribution of pharmacokinetic parameters in the population.

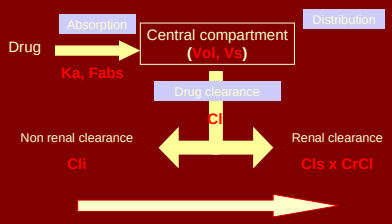
➤ Individual parameters (Fa, Ka, clearance) were estimated by MAP (Maximum A posteriori Probability) Bayesian method. ***Correlations between each individual parameter value and the patient's covariates*** (weight, height, body mass index - BMI, body surface area - BSA, overweight, ...) were tested.

Results - Discussion

Characteristic	Mean	Standard deviation	Range
Age (years)	65	13	36-84
Males / females	38/31	-	-
Body weight (kg)	79	14	53-120
Height (cm)	168	9	150-183
BMI (kg/m²)	26.9	3.3	18.8-33.8
CrCl (ml/min/1.73m²)	78	21	25-134

Table 1 – Patients' characteristics

CrCl: creatinine clearance (Jelliffe and Jelliffe)



	Cl (l/h)	Vol (l)	Fa	Ka (h^{-1})
Median	0.983	3.8	0.774	0.781
Standard deviation	0.449	2.6	0.169	0.347
Coefficient of variation	46%	68%	22%	61%

Table 2 – NPEM estimates of population pharmacokinetic parameters

19 patients (28%) → BMI > 30 kg/m²

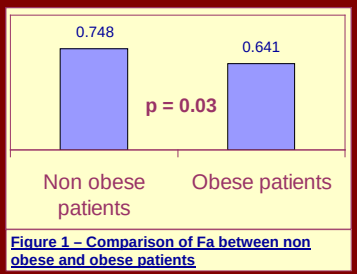


Figure 1 – Comparison of Fa between non obese and obese patients

	Age	Weight	Height	BMI	BSA	Overweight	PIBW
Ka	r = 0.032 NS	r = 0.032 NS	r = -0.055 NS	r = 0.063 NS	r = -0.000 NS	r = 0.045 NS	r = 0.055 NS
Fabs	r = 0.032 NS	**r = -0.282 p = 0.02**	**r = -0.273 p = 0.05**	r = -0.145 NS	**r = -0.308 p = 0.02**	r = -0.171 NS	r = -0.131 NS

Table 3 – Correlations between individual pharmacokinetic parameters and patients' covariates

Overweight = Weight – Ideal Body Weight

PIBW (Percentage above Ideal Body Weight) = Overweight / Body Weight x 100

NS: non significant

➤ Enoxaparin is absorbed in a lesser fraction in the heaviest patients than in the lightest

➤ The multiple regression analysis shows that the clearance is mainly explained by 2 independent factors: the body weight (p=0.03) and the absorbed fraction (p<0.001).

Conclusion

➤ The absorption of enoxaparin is clearly related to the patients' weight, and this could explain why the exposure to the drug is less in the heaviest patients than in the lightest. Therefore, a weight-adapted dose may reduce the pharmacokinetic variability of enoxaparin.