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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00622115
		Study Code:	ENOXA_C_02537
Generic drug name:	enoxaparin	**Date:**	10 March 2011

Title of the study: A phase I, pharmacokinetic and tolerability study of intravenous unfractionated heparin after subcutaneous enoxaparin 1 mg/kg b.i.d. repeated administration in healthy subjects. (STUDY No : ENOXA_C_02537)

Investigator(s): Evelyne, GUÉNOLÉ, MD (Therapharm Recherches, France)

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Publications (reference):

Study period:

Date first subject enrolled: 25 July 2007

Date last subject completed: 17 November 2007

Phase of development: I (Clinical pharmacology)

Objectives:

Primary objective:

- to characterize the pharmacokinetic and the pharmacodynamic profile after intravenous bolus injection of unfractionated heparin (UFH) after repeated subcutaneous (sc) 100 IU anti-Xa/kg (corresponding to 1 mg/kg) q12 ± 2h administrations of enoxaparin in Caucasian healthy subjects.

Secondary objective(s):

- to compare the pharmacokinetic and the pharmacodynamic profile between 3 different timing of administration of the UFH
- to assess the tolerability of the different anticoagulation protocols

Methodology: Single-center, repeated doses, randomized, 3 parallel groups, open-label study

Number of subjects/patients:	Planned: 72	Treated: 72	Randomized: 72
Evaluated:	Pharmacodynamic: 72	Safety: 72	Pharmacokinetics: 72

Diagnosis and criteria for inclusion:

- Healthy subjects (male and female), between 40 and 60 years of age
- Body Mass Index between 18 and 29 kg/m2

Investigational product:

- Enoxaparin: solution in individual pre-filled syringe
- UFH: solution

Dose:

- Enoxaparin: 100 IU anti-Xa/kg (corresponding to 1 mg/kg)
- UFH: 70 U/kg

Administration:

- Enoxaparin: subcutaneous injection twice a day for 2.5 days
- UFH: single intravenous injection 4 hours, 6 hours or 10 hours after last enoxaparin injection on Day 3

Duration of treatment:

- Enoxaparin: 2.5 days
- UFH: 1 day

Duration of observation: 2.5 days

Reference therapy: Not applicable

Criteria for evaluation:

Pharmacodynamic: Emax, AUEC(0-14) and Emin were estimated for ACT, TGT_{PPP}, TGT_{PRP}, aPPT and PTTK anticoagulation tests. Mean values were estimated for PFA100. ETP, velocity index, lag time, peak and time to peak were assessed for TGT_{PPP} and TGT_{PRP}.

Safety: The safety evaluation was based on the recording of adverse events during the observation period and on physical examination, clinical laboratory evaluations, vital signs and ECG parameters measurement at screening, before first dose and at the end of the study.

Pharmacokinetics: PK was assessed by calculation of Amax, AUC(0-14) and Amin parameters for anti-Xa and anti-IIa activity values

Pharmacokinetic sampling times and bioanalytical methods: Blood sampling times were as follows:

All subjects: pre-dose, 1 h, 3 h, 4 h, 6 h, 10 h and 14 h post enoxaparine dose at Day 2

- UFH 4 group: pre-dose, 1 h, 3 h, 4 h, 4.17 h, 4.5, 5, 6 h, 8, 10 h and 14 h post enoxaparine dose.
- UFH 6 group: pre-dose, 1 h, 3 h, 4 h, 6 h, 6.17 h, 6.5 h, 7 h, 8, 10 h and 14 h post enoxaparine dose.
- UFH 10 group: pre-dose, 1 h, 3 h, 4 h, 6 h, 8, 10 h, 10.17 h, 10.5 h, 11 h, 12 h and 14 h post enoxaparine dose.

Anti-Xa and anti-IIa activities measurements were performed using a validated commercially available chromogenic method.

Same sampling times were used for PK and PD variables assessment that were determined using non-compartmental model.

Statistical methods: In case of non normality, Amax, AUC(0-14) and Amin values were log-transformed.
Intergroup differences in these parameters were analyzed using an analysis of variance with UFH as fixed term and using Tukey adjustment for multiplicity.

The level of significance was fixed at 0.05.

95% CI of differences between means were computed.
In case of non normality data, 95% CI of the ratio were computed by converting the 95% CI of the difference between means of log values by the antilog transformation.
Pharmacodynamic parameters were analyzed as PK parameters.

Descriptive analysis was performed on the safety parameters.

Summary:

72 healthy subjects were enrolled and completed the study as initially planned. No major protocol deviation occurred during the trial All subjects were included in the PD, safety and PK analyses.

Efficacy/pharmacodynamic results:

All subjects were analyzed for PD purpose. Primary PD analysis consisted in the ETP and velocity index assessments for TGT_{PPP} and TGT_{PRP} anticoagulation tests.

Median ETP levels from TGT_{PPP} measured 12 h after the previous enoxaparin SC dose, were substantially decreased compared with the standard normal values in healthy young volunteers measured with the method and technical conditions used (2300 $\pm$ 200 nM·min; Calibrated Automated Thrombogram®, Diagnostica Stago). On day 3, 3 h after the final enoxaparin SC dose, median (IQR) ETP levels were further decreased by approximately 40% in all groups. The administration of UFH at all three time points resulted in a rapid and complete abolition of thrombin generation. ETP levels returned to pre-UFH levels about 4 h after the stack-on IV UFH bolus was given.

These modifications of ETP values were statistically confirmed with significantly lower values ($p<0.0001$ for each) at Day 3 than at Day 2 in each group for TGT_{PPP} and TGT_{PRP}. Changes were comprised between -300 nM/min and -1169 nM/min for UFH4 and UFH10 groups respectively for TGT_{PPP} and between -858 nM/mL in UFH6 and -1122 nM/mL in UFH10 groups for TGT_{PRP}.

Similar results were reported for TTprp test.

Median ACT levels measured while patients were receiving enoxaparin alone did not reflect any relevant anticoagulation effect with a median (IQR) peak level of 172 s (162–180). Similarly, following UFH administration, ACT levels remained within the range commonly observed in subjects receiving UFH, with peak levels between 259 and 267 s within 10 min regardless of whether UFH was administered at 4, 6 or 10 h after the last SC enoxaparin dose.

Safety results:

No death, no serious TEAE and no withdrawal due to TEAE occurred during the study.

Incidence of TEAE was similar between UFH4 and UFH10 groups and was higher in UFH6 group (29.2% versus 50.0%). All TEAEs were of mild to moderate intensity. Investigations and nervous system disorders were the most affected SOC during the study. Incidence of drug-related TEAEs was higher in UFH6 group with 5 out of 8 TEAE related to enoxaparin and 7 out of 12 TEAEs related to UFH. Drug-related TEAEs were mainly ALAT increases due to enoxaparin and UFH injection and hot flushes due to UFH injection.

Study treatments were considered as well-tolerated during this study.

Pharmacokinetic results:

UFH injection at 4 hours, 6 hours and 10 hours post-enoxaparin induced a transitory increase in anti-Xa and anti-IIa levels. This increase was maintained during approximately 4 hours in each group.

AUC(0-14) of anti-Xa (LMWH) and anti-IIa were significantly increased at Day 3 following UFH ($p<0.0001$) in each group of subjects (between +4.5 in UFH10 group and +5.8 h*"U/mL in UFH4 group). Significant peak values increases were also reported: 2.7 fold increase ($p<0.0001$) for anti-Xa (LMWH) and 4.0 fold increase ($p<0.0001$) for anti-IIa.

Date of report: 07 October 2008