Anti-factor Xa kinetics after intravenous enoxaparin in patients undergoing percutaneous coronary intervention: a population model analysis

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Aim

Recent studies have suggested that intravenous (i.v.) enoxaparin could be used as antithrombotic therapy in patients ongoing percutaneous coronary intervention (PCI). However, anti-Xa pharmacokinetics following different i.v. dosing regimens is not clearly established.

Methods

A population pharmacokinetic analysis was developed using anti-Xa activities measured in 546 patients who received a single 0.5 mg kg⁻¹ i.v. dose of enoxaparin immediately before PCI. Effects of higher doses (0.75 mg kg⁻¹ and 1 mg kg⁻¹) and/or additional bolus after the initial administration were similarly simulated.

Results

Enoxaparin anti-Xa time profiles were best described by a one-compartment model with zero-order kinetics. Mean population parameters (intersubject variability, %) were CL 1.2 l h⁻¹ (33), V 2.9 l (30) and zero-order input 0.25 h (24). With a single bolus of 0.5 mg kg⁻¹, the totality of the patients reached an effective anticoagulation level (anti-Xa >0.5 IU ml⁻¹) and only 2.5% reached levels above 1.5 IU ml⁻¹. Simulations showed that greater doses (0.75 mg kg⁻¹ and 1 mg kg⁻¹) prolonged the duration of anticoagulation (3.4 and 4.1 h, respectively) compared with the 0.5 mg kg⁻¹ bolus (2.7 h) and markedly increased the proportion (48% and 79%, respectively) of patients with anti-Xa levels >1.5 IU ml⁻¹. For delayed and/or prolonged procedures, patients could be administered a second bolus of half the initial dose in a time interval between 90 min to 2 h after in order to maintain similar anticoagulation profile levels.

Conclusions

A single 0.5 mg kg⁻¹ i.v. dose of enoxaparin reached anticoagulation levels adequately and should be safer compared with greater doses for anticoagulation in patients undergoing an elective PCI. An additional second bolus could be proposed in patients with delayed or prolonged procedures.

Introduction

Angiography and percutaneous coronary intervention (PCI) are increasingly widespread in the management of patients with coronary artery disease [1]. Because these procedures may induce thrombotic complications, they require a concomitant use of anticoagulant drugs, traditionally unfractionated heparin (UFH) [2–6]. Nonetheless, there are many disadvantages with UFH, the primary one being a poorly predictable anticoagulant effect for a given dose.

Subcutaneous administration of the low-molecular-weight heparin (LMWH) enoxaparin has emerged as a better antithrombotic therapy for the management of patients with acute coronary syndromes [7–9], including when they undergo PCI [10, 11].

In patients who are not pretreated by anticoagulants before the catheterization procedure, the use of intravenous (i.v.) enoxaparin has recently been proposed as an alternative therapy with or without coadministration of a glycoprotein IIb/IIIa inhibitor [12]. Compared with subcutaneous administration, the i.v. route should provide both faster anticoagulation profiles and equivalent effect for PCI procedures. If disposition mainly includes distribution and different decay phases, the disposition of enoxaparin would be the same irrespective of the route of administration. However, when using short infusion there are two main components that cannot be easily derived: the rapidity of onset and the true levels of observed concentrations, because with the subcutaneous route, there is a fraction of the dose that is not bioavailable [13]. Therefore the anti-Xa time profiles following i.v. administration are not predictable from subcutaneous studies.

Other studies have already studied enoxaparin i.v. administration in patients undergoing PCI but often with an associated administration of subcutaneous enoxaparin or i.v. UFH [13–20]. The use of a single i.v. bolus of 1 mg kg⁻¹ enoxaparin (NICE-1 trial [16]) may lead to important peak anticoagulation levels (mean anti-Xa activity around 2.1 IU ml⁻¹), which results in a more important bleeding risk and delayed sheath withdrawal, both complicating procedural feasibility. In the NICE-4 [21] and ELECT studies [18] using a moderate i.v. enoxaparin dose (0.75 mg kg⁻¹) in combination with GPIIb/IIIa inhibitors, bleeding complications were (7% and 8.5%, respectively), comparable with those surveyed with the 1 mg kg⁻¹ dose in NICE-1. On the other hand, Choussat *et al.* [22] reported that the dose of 0.5 mg kg⁻¹ i.v. enoxaparin produced anticoagulation levels >0.5 IU ml⁻¹ in more than 95% of patients, and seemed to be both effective in thrombotic prevention (2.5% for the composite end of all death causes and myocardial

infarction at 30 days) and safe regarding immediate sheath removal, major and minor bleeding complications. The anticoagulation target is not clearly established in PCI patients. Published data differ in defining the best therapeutic target in terms of efficacy and safety. Martin *et al.* suggested a target between 0.6 and 1.8 IU ml⁻¹ as the best for PCI procedures in a series of 55 patients [17]. Others [18, 23, 24] have suggested that levels >0.5 IU ml⁻¹ for prevention of thrombosis and between 1.5 and 1.8 IU ml⁻¹ for safety considerations should be a good therapy. Finally, the ELECT [18] study reported a target therapeutic range between 0.8 and 1.8 IU ml⁻¹ anti-Xa.

However, limited data on antifactor Xa kinetics following these different regimens are available and anticoagulation profiles over time have never been previously described. Thus, our objective was to conduct a pharmacokinetic population analysis in 556 patients undergoing PCI all receiving 0.5 mg kg⁻¹ i.v. bolus of enoxaparin in order to describe anticoagulation profiles after a single i.v. dose to establish the appropriate dosing regimens.

Simulations were also conducted to describe anti-Xa kinetics following the administration of 0.75 mg kg⁻¹ and 1 mg kg⁻¹ i.v. doses of enoxaparin and re-administration of a second enoxaparin bolus.

Methods

Patient population

Consecutive patients scheduled to undergo elective PCI in the catheterization laboratory of the Institute of Cardiology at the Pitié-Salpêtrière University Hospital in Paris, France were enrolled in this cohort. All patients were >18 years old and were referred for elective PCI of a coronary artery or vein graft stenosis of >70%. Exclusion criteria were primary PCI for ST-elevation myocardial infarction, LMWH or UFH within the last 48 h before PCI, or a GPIIb/IIIa antagonist within the previous 2 weeks. This study was in agreement with French research legislation for studies based on therapeutic drug monitoring data. It was approved by the ethics committee of the Pitié-Salpêtrière Hospital in Paris, France.

Procedures for PCI

PCI was usually performed immediately after a coronary angiogram (*ad hoc* angioplasty) using standard techniques, and 6-F guiding catheters in all patients. Sheaths were removed immediately after PCI irrespective of the use of GPIIb/IIIa inhibitors. Vascular closure devices were not used. Patients were allowed to walk on the next morning (bed-rest time >12 h) and left the hospital on the day following PCI.

Study medications

Intravenous enoxaparin, 0.5 mg kg⁻¹ single bolus, was used in all patients. There was no weight-related upper limit for the dose of enoxaparin. All patients received a loading dose of aspirin (500 mg i.v.) before the start of the procedure, followed by a daily oral aspirin dose of 75 mg. PCI was performed without the administration of UFH or of any additional bolus of enoxaparin, and no antithrombin treatment was administered after the procedure. Sheaths and catheters were flushed with a saline solution containing 23 mg l⁻¹ of enoxaparin. Such a solution represents a negligible quantity of enoxaparin, less than 1% (by 10 ml volume) of total enoxaparin-administered doses. Eptifibatide (bolus regimen of 180 µg kg⁻¹ followed by a 2.0 µg kg⁻¹ min⁻¹ continuous infusion) or abciximab (bolus of 0.25 mg kg⁻¹ followed by an infusion of 0.125 µg kg⁻¹ min⁻¹) were the only GPIIb/IIIa inhibitors used in this study.

Determination of anti-Xa activity

Serial blood samples were taken to measure anti-Xa activity: before the i.v. bolus of enoxaparin, 10 min after the bolus (start of PCI), at the end of the PCI (mean time = 45 min), 3 h after the PCI, and on the morning after PCI. The measurement of the anti-Xa activity was performed using a validated chromogenic assay (STA[®]-Rotachrom[®] Heparin 8; Diagnostica Stago, Asnières, France), with a lower limit of assay detection of 0.01 IU ml⁻¹. The quality of anti-Xa activity determination was assessed by the use of control human plasmas containing a predetermined level of LMWH (STA[®]-Quality LMWH; Diagnostica Stago). The interbatch assay precision (coefficient of variation, %) of control human plasmas was between 6 and 8% during the study period.

Population pharmacokinetic modelling

Pharmacokinetic analysis was carried out using the non-linear mixed-effect modelling program NONMEM version V with the Digital Fortran Compiler 6.5 (double precision, level 1.1) [25]. One and two-compartment models with first-order or zero input were investigated to describe anti-Xa kinetics. Different error models were investigated for intersubject (ISV, η) and residual (ϵ) variabilities.

Standard goodness of fit criteria to assess model suitability was adopted by evaluation of the objective function value (OFV), parameter estimates as well as their precision and goodness-of-fit. Full and reduced models (one parameter less) were compared by the χ^2 test of the difference between their respective OFV. The influence

of covariates collected at inclusion (age, gender, weight, serum creatinine and creatinine clearance) on the pharmacokinetic parameters was investigated. A classical graphical approach was performed by plotting individual estimates of pharmacokinetic estimates against each tested covariate. The inclusion of a covariate was then considered to have improved the fit if (i) it produced a significant decrease in the OFV of at least 4 units ($P < 0.05$, one degree of freedom), (ii) there was a reduction in the ISV of the associated pharmacokinetic parameter, and (iii) its effect was biologically plausible. In order to keep only the covariates with the largest contribution to predict enoxaparin pharmacokinetics in a final multivariate model, a change of 7 units ($P < 0.01$, one degree of freedom) of the OFV was required for the retention of a single parameter during backward stepwise multiple regression analysis.

The accuracy and robustness of the final population model were then assessed using a bootstrap method [26]. From the original dataset of patients, 1000 bootstraps were drawn with resampling. For each of the 1000 bootstrap sets, the population pharmacokinetic parameters were estimated. Then, the mean, median and standard deviation of these 1000 estimates were compared with those obtained in the original population set. The model was considered validated if no significant differences were observed.

Finally, given the mean and variance parameters, 200 simulations were carried out to describe population time courses, 5th, median and 95th percentiles. To identify a suitable dosing therapeutic regimen, a series of simulations were performed. The anti-Xa time profiles following i.v. administration of 0.5, 0.75 and 1 mg kg⁻¹ of enoxaparin were then generated.

As mentioned before, an anticoagulation target is not clearly established in PCI patients. Using as reference the actual published data [17, 18, 23, 24], anticoagulation profiles have been analysed by means of minimal and maximal levels as follows: lower anticoagulation threshold was considered as an anti-Xa level >0.5 or >0.8 IU ml⁻¹ and upper anticoagulation threshold was considered as anti-Xa level >1.5 or >1.8 IU ml⁻¹. Time and proportion of patients within these targets are reported.

Since some patients may require a prolonged anticoagulation time (delayed start of PCI after the i.v. injection or prolonged procedure), a second i.v. enoxaparin bolus was studied. The anti-Xa kinetics of an additional bolus after the initial one were then simulated in order to determine the optimal timing and dose of this second bolus. Results are expressed as mean $\pm$ SD unless otherwise specified.

Results

Demographic data

A total of 556 patients participated in the study. Their baseline characteristics are shown in Table 1. Eptifibatide and abciximab were concomitant treatments in 146 and 29 patients, respectively. Renal function assessed by the Cockcroft and Gault formula was $<60 \text{ ml min}^{-1}$ in 208 patients and $\leq 30 \text{ ml min}^{-1}$ in 23 patients. Eighty-three patients were aged >75 years. Mean dose of enoxaparin was $38 \pm 7 \text{ mg}$ ($3830 \pm 730 \text{ IU}$).

Pharmacokinetics analysis

Data description A total of 2016 anti-Xa activity measurements were obtained (with a mean of three anti-Xa measurements per patient) from the 556 patients. Data from 10 (1.8%) patients (38 anti-Xa activity measurements) were excluded from the following analysis because of probable misadministration of enoxaparin or misplaced IV line as assessed by the lack of acute increase in anti-Xa activities that remained in the physiological range ($<0.3 \text{ IU ml}^{-1}$). Adding these data in the

final model did not, however, change estimates of pharmacokinetic parameters.

Population pharmacokinetics

The time course of anti-Xa activity was best described by a one-compartment model with zero-order input. The parameters of the model were the clearance (CL), the distribution volume (V) and zero-order input time (T₀). ISVs for CL and V were ascribed to an exponential model. ISV for zero-order input (T₀) and residual variability were best described by an additive error model.

During the covariate submodelling, it appeared that V and CL were influenced by bodyweight (OFV decreases of 146 and 122 units, respectively). CL was also influenced to a lesser degree by creatinine clearance and serum creatinine. In the final model, only the body weight (BW) was identified as a significant covariate as follows:

$$\text{CL} = \text{TV CL} \times (\text{BW}/75)^{0.9}$$

$$\text{V} = \text{TV V} \times (\text{BW}/75)^{0.7}$$

This covariate submodelling, where TV means typical value, resulted in a decrease of the ISVs for CL and V from 38 to 33% and from 35 to 30%, respectively. The final model was subjected to a bootstrap analysis. Table 2 summarizes the results. Figure 1 shows the predicted vs. observed anti-Xa time course and individual predicted vs. observed anti-Xa activities.

Bleeding complications after administration of 0.5 mg kg^{-1} of i.v. enoxaparin Bleeding incidence was 1.7% considering the TIMI score (Thrombolysis In Myocardial Infarction [27]) for bleeding complications. Only two patients out of 546 had a major bleeding complication during the intervention: one had a fatal haemorrhage (massive haemoptysis in a patient with a history of pulmonary cancer); the other had a haematoma at the site of ponction with major bleeding resulting in a haemoglobin drop of 3 g dl^{-1} needing transfusion. Eight patients had minor bleeding complications: seven haematomas associated with false aneurysms resolved after manual compression and one macroscopic haematuria. None of the 10 patients had observed anti-Xa levels above 1.1 IU ml^{-1} (last measure 24 h after intervention). Mean maximal concentration estimated by the pharmacokinetic analysis was 1.1 IU ml^{-1} . The anticoagulation profiles of these patients were not different from the rest of the population. Therefore, the potential relationship between anti-Xa activity and occurrence of bleeding could not be characterized in this study.

Table 1

Baseline characteristics

Characteristic	Overall sample (n = 556)
<i>Gender (number and percentage)</i>	
Men	442 (79%)
Women	114 (21%)
<i>Age (years)</i>	
Mean (SD)	63 (11)
Range	21–93
<i>Body weight (kg)</i>	
Mean (SD)	76 (15)
Range	35–153
<i>Serum creatinine ($\mu\text{mol l}^{-1}$)</i>	
Mean (SD)	118 (95)
Range	48–883
<i>Creatinine clearance (ml min^{-1})*</i>	
Mean (SD)	69 (27)
<i>Number of patients (%)</i>	
$\geq 60 \text{ ml min}^{-1}$	346 (62%)
$31\text{--}59 \text{ ml min}^{-1}$	185 (33%)
$\leq 30 \text{ ml min}^{-1}$	23 (4%)
<i>Enoxaparin dose (mg)</i>	
Mean (SD)	38.1 (0.7)
Range	17.5–76.5

*Calculated according to the Cockcroft and Gault formula.

Table 2

Population pharmacokinetic parameters of enoxaparin for the 546 patients and bootstrap validation

Parameter	Final model, mean $\pm$ SE	Bootstrap* Median	2.5th–97.5th
<i>Structural model</i>			
TV.CL (l h ⁻¹)	1.20 $\pm$ 0.03	1.17	0.95–1.26
BW effect on CL	0.9 $\pm$ 0.1	0.9	0.63–1.17
TV.V (L)	2.9 $\pm$ 0.1	2.9	2.7–4.1
BW effect on V	0.7 $\pm$ 0.1	0.7	0.5–1.0
T ₀ (h)	0.25 $\pm$ 0.01	0.24	0.16–0.28
Basal anti-Xa (IU ml ⁻¹)	0.0725 (fixed)		
<i>Statistical model</i>			
Residual variability, IU ml ⁻¹	0.09 $\pm$ 0.02	0.09	0.07–0.15
ISV (CL) (% CV)	33 $\pm$ 3	34	27–39
ISV (V) (% CV)	30 $\pm$ 7	29	18–51
ISV (T ₀) (h)	0.06 $\pm$ 0.02	0.06	0.03–0.14

*Statistics on 917 bootstrap runs (1000 programmed, 917 runs were successful). Nonparametric confidence interval based on the 2.5th–97.5th percentiles. SE, Standard error of estimate; TV, typical value; CL, clearance; V, distribution volume; T₀, zero-order input time; ISV, intersubject variability; CV, coefficient of variation; BW, body weight.

Description of individual anti-Xa profiles following 0.5 mg kg⁻¹, 0.75 mg kg⁻¹ or 1 mg kg⁻¹ intravenous bolus For the 0.5 mg kg⁻¹ dose, anti-Xa activity rose above 0.5 IU ml⁻¹ in all patients and 97% were within the range of 0.5–1.5 IU ml⁻¹. Minimum levels of anticoagulation (>0.5 IU ml⁻¹) were rapidly obtained after administration in 100% of simulated patients and were maintained on average during 2.7 $\pm$ 0.9 h; 75% of simulated patients reached levels above 0.8 IU ml⁻¹ for a mean time of 1.7 $\pm$ 0.6 h. The distribution of time during which anti-Xa levels were above 0.5 IU ml⁻¹ is depicted in Figure 2. Figure 3a shows the 5th, 50th and 95th percentiles of anti-Xa levels over time. Anticoagulation levels >1.5 IU ml⁻¹ were observed in only 2.5%. No simulated patients reached levels above 1.8 IU ml⁻¹.

For the 0.75 mg kg⁻¹ dose, all simulated patients reached anticoagulation levels >0.5 and >0.8 IU ml⁻¹, with mean durations of 3.4 $\pm$ 1.1 h and 2.3 $\pm$ 0.8 h, respectively. Figure 3b shows the 5th, 50th and 95th percentiles of anti-Xa levels over time. Anticoagulation levels >1.5 IU ml⁻¹ were found in 48% of simulated patients, of whom 28% reached levels >1.8 IU ml⁻¹.

With 1 mg kg⁻¹, all simulated patients reached anticoagulation levels >0.5 IU ml⁻¹ and >0.8 IU ml⁻¹ as well, but the mean duration of such a level was again increased (4.1 $\pm$ 1.3 and 3.0 $\pm$ 1 h, respectively). Figure 3c shows the 5th, 50th and 95th percentiles of

anti-Xa levels over time. Anticoagulation levels >1.5 IU ml⁻¹ were found for 79% of simulated patients, of whom 57% reached levels >1.8 IU ml⁻¹.

Table 3 summarizes the proportion of patients and duration obtained for different anticoagulation levels of anti-Xa after the three single different doses.

Simulation of anticoagulation profile after a second bolus of enoxaparin i.v. (Figure 4) For patients with a delayed or prolonged intervention after anticoagulation therapy has been initiated, anticoagulation levels may not be maintained for a sufficient time after the initial i.v. bolus. We therefore evaluated the effects of a second bolus at different doses and at different time intervals in order to reach the same anti-Xa peak as the one provided by the first bolus. This evaluation was conducted only with the dose regimens of 0.5 mg kg⁻¹ and 0.75 mg kg⁻¹ given the higher and prolonged levels obtained with 1 mg kg⁻¹ dose. Considering the anti-Xa activity kinetics described in Figure 3, the optimal timing for re-administration appeared to be between 90 min and 2 h. At this time, the eliminated dose after the first 0.5 mg kg⁻¹ bolus was estimated to be 50% (47 and 57%, respectively). The dose needed to reach a similar peak after a second injection was in the range of 0.2–0.25 mg kg⁻¹ in this 90–120-min time interval. The anticoagulation profiles over time (5th, 50th and 95th percentiles) after a second 0.25 mg kg⁻¹ bolus 2 h

Figure 1

a) Observed vs. predicted anti-Xa activity after a 0.5 mg kg⁻¹ dose of i.v. enoxaparin. b) Observed vs. individual predicted anti-Xa activity after a 0.5 mg kg⁻¹ dose of i.v. enoxaparin

after the initial 0.5 mg kg⁻¹ bolus are shown in Figure 4a. With the 0.75 mg kg⁻¹ regimen, the dose needed to reach a similar anti-Xa peak was in the range 0.25–0.375 mg kg⁻¹ in the same time. Such a second bolus respects the target of anticoagulation provided by the initial 0.75 mg kg⁻¹ bolus during the first 2 h and prolonged this effect for 2 h (Figure 4b).

Figure 2

Distribution of effective anticoagulation duration (>0.5 IU ml⁻¹ of anti-Xa activity) after 0.5 mg kg⁻¹ dose of i.v. enoxaparin

Discussion

Our study is the first one to describe antifactor Xa kinetics following intravenous enoxaparin. This result was obtained from a population pharmacokinetics analysis conducted in 546 patients undergoing PCI.

Our modelling showed that (i) all tested doses (0.5, 0.75 and 1 mg kg⁻¹) of i.v. enoxaparin were able to reach an anticoagulation level of >0.5 IU ml⁻¹ and 75% of patients reached levels >0.8 IU ml⁻¹ after the dose of 0.5 mg kg⁻¹, compared with all patients with 0.75 mg kg⁻¹ and 1 mg kg⁻¹ (100%); (ii) a rapid onset was observed with all dosing regimens; and (iii) significantly fewer patients reached anti-Xa activity levels above 1.5 and 1.8 IU ml⁻¹ after a dose of 0.5 mg kg⁻¹ (2.5% and none) compared with 0.75 mg kg⁻¹ (48% and 28%) and 1 mg kg⁻¹ (79% and 57%, respectively).

Pharmacokinetic simulations suggested the possibility of re-administering a fixed dose of i.v. enoxaparin after the initial bolus in order to maintain a similar anticoagulation level. The 0.5 mg kg⁻¹ dose provided an anticoagulation level >0.5 IU ml⁻¹ in all patients and for 90–120 min in the majority of patients. Even if such a duration appeared to be convenient for most procedures, it could be insufficient in some cases such as abnormally long or delayed procedures (i.e. transfer or long waiting after the initial i.v. bolus of enoxaparin). With both reg-

Figure 3

Antifactor Xa kinetics (5th, 50th and 95th percentiles) after (a) a 0.5 mg kg⁻¹ i.v. dose; (b) a simulated 0.75 mg kg⁻¹ i.v.; (c) a simulated 1 mg kg⁻¹ i.v. dose of enoxaparin

Table 3

Patients reaching minimum and maximum anticoagulation levels and mean duration time for the three different intravenous doses

Dose (mg kg ⁻¹)	Patients with anti-Xa >0.5 IU ml ⁻¹ , /mean duration (h) ± SD	Patients with anti-Xa >0.8 IU ml ⁻¹ , /mean duration (h) ± SD	Patients with anti-Xa >1.5 IU ml ⁻¹ , /mean duration (h) ± SD	Patients with anti-Xa >1.8 IU ml ⁻¹ , /mean duration (h) ± SD
0.5	100%/2.7 ± 0.9	75%/1.7 ± 0.6	2.5%/0.5 ± 0.2	–
0.75	100%/3.4 ± 1.1	100%/2.3 ± 0.8	48%/1.7 ± 0.6	28%/1.2 ± 0.4
1	100%/4.1 ± 1.0	100%/3.0 ± 1	79%/0.9 ± 0.3	57%/1.0 ± 0.3

SD, Standard deviation.

imens (0.5 and 0.75 mg kg⁻¹), the administration of half the dose of the initial bolus (0.25 and 0.375 mg kg⁻¹, respectively) 2 h afterwards should provide a new cycle of anticoagulation similar to the first one. These new available data and regimens offer practical advantages for clinicians but obviously need to be validated in terms of risk–benefit in clinical practice.

Although UFH is used as the standard anticoagulant in the catheterization laboratory, LMWHs offer many theoretical advantages over UFH for this indication, in particular a more stable and predictable anticoagulant dose–response and a greater anti-Xa/anti-IIa ratio, resulting in less thrombin generation and activation [28]. The regimen of i.v. enoxaparin bolus administrated just before PCI procedures is clinically undefined, since anti-Xa levels and peak concentrations have been poorly reported in clinical trials [12, 14]. Choussat *et al.* [22]

suggested that the 0.5 mg kg⁻¹ i.v. dose is a good option in PCI patients, providing an adequate and rapid anticoagulation level to perform the procedure and providing a safe anticoagulation regimen in patients irrespective of age, renal function, sex, overweight or use of antiplatelet treatments. This information is confirmed by anticoagulation profiles observed in these 546 patients if the minimum anticoagulation level is to be fixed above 0.5 IU ml⁻¹.

Our findings (Figure 3) are also in agreement with those reported in the NICE-1 and 4 trials, where anti-Xa peak levels were 1.5 ± 0.6 IU ml⁻¹ for a dose of 0.75 mg kg⁻¹ and 2.1 ± 0.7 IU ml⁻¹ for a dose of 1 mg kg⁻¹. Major and minor haemorrhagic incidences were reported to be 6.1% (1 mg kg⁻¹ of enoxaparin alone) and 7% (0.75 mg kg⁻¹ associated with an antiplatelet agent, abciximab) and sheath withdrawals were

Figure 4

Antifactor Xa kinetics (5th, 50th and 95th percentiles) obtained from the simulation of (a) 0.5 mg kg^{-1} followed 2 h later by a second bolus of 0.25 mg kg^{-1} and of (b) 0.75 mg kg^{-1} followed 2 h later by a second bolus of 0.375 mg kg^{-1}

delayed in both studies with these anti-Xa mean values. On the other hand, a lower bleeding incidence (1.3–1.6%) has been reported with the use of the reduced 0.5 mg kg^{-1} dose [14, 22]. The incidence of bleeding complications in our study is concordant with these previous publications. As described in other pharmacokinetic studies [13], our results confirm the differences between i.v. and subcutaneous enoxaparin administra-

tion. Peak anti-Xa activities were almost doubled when enoxaparin was administered intravenously, although bioavailability was supposed to be similar.

Some studies have suggested dose adjustment for subcutaneous enoxaparin in patients with non-ST elevation acute coronary syndromes and an altered renal function, whether following PCI or not [15, 29–31]. At the same time, renal insufficiency has been shown to be a risk factor for bleeding and ischaemic events [32–34]. Although creatinine clearance appears to be associated with enoxaparin elimination rate in our model as well as in previous studies, no significant improvement in the population pharmacokinetic model was observed when this covariate was taken into account. This could mean that with acute i.v. bolus administration, as opposed to repeated subcutaneous administrations, no dose adjustment is necessary according to renal function. This might be in accordance with the fact that with the objective of a short anticoagulation duration, the volume of distribution is the main determinant of plasma concentration levels (during a short period of time after administration – 1 or 2 h) for a given bolus dose, justifying an adjustment for enoxaparin dosage by weight but not by renal function. This dose adjustment was confirmed by our model. Since only 4% of patients had a creatinine clearance $<30 \text{ ml min}^{-1}$, the absence of dose adjustment in patients with severe renal failure for a single i.v. enoxaparin bolus would need to be confirmed.

In terms of bleeding complications, the incidence with the dose of 0.5 mg kg^{-1} was confirmed comparable to other clinical studies with a 0.5 mg kg^{-1} i.v. dose. According to anticoagulation profiles, this bleeding could not be imputed to i.v. enoxaparin administration and might be due to other risk factors, since no significant elevations in anti-Xa activity were observed.

Finally, our modelling study provides new pharmacological information concerning enoxaparin administered intravenously. The information on anti-Xa activity evolution over time would then allow clinicians to correlate it with efficacy and safety outcomes and our data would be essential for clinical interpretation of forthcoming studies. Our study was not designed to assess efficacy on clinical outcomes and only a randomized study with clinical events as primary endpoint would answer this dose issue. The ongoing multicentre randomized STEEPLE (Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation) study investigates the hypothesis of a superiority of enoxaparin over unfractionated heparin in elective PCI, with enoxaparin being evaluated in two different arms (0.75 and 0.5 mg kg^{-1}). Our findings would help interpretation of results from this study

enrolling 2700 patients, which will have the power to answer the question of the enoxaparin dose in terms of efficacy and safety outcomes. With the assumption of a therapeutic target anti-Xa range of 0.5–1.5 IU ml⁻¹ and regarding the low incidence of bleeding complication in our population (1.7%), our results suggest that the 0.5 mg kg⁻¹ dose may have the best benefit–risk ratio.

Competing interests: None declared.

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