

Study PK 133: A Phase I, Open, Randomized, 3-Period, Cross-Over Study
Comparing the Pharmacokinetic Profile of Two Formulations of RP54563: Single
Concentration Ampule (1-Shot / 2-Shots) Versus Double Concentration Ampules,
Administered as 1.5 mg/kg^{-1} Once a Day Subcutaneous Treatment for 5 Days to
Healthy Male and Female Volunteers. *Final Study Report*. 17 September 1996.
[Vol. 9, pages 6-4-58 to 59]

Kinetic profiles of treatment C (200 mg.ml⁻¹) versus treatment A (100 mg.ml⁻¹)

The two formulations exhibit comparable disposition profiles (Table 59 p.127). The rate of absorption (t_{max}), the distribution (MRT) and the elimination ($t_{1/2}$) processes of the two formulations are similar ($p > 0.05$). Some differences are observed with slightly higher circulating plasma [REDACTED] clotting time prolongation [$+ 6.4$ s on mean values of $A(\Delta t)_{max}$, $p < 0.02$] and extent of absorption : AUCs from treatment C are 6 % higher than AUCs from treatment A ($p < 0.001$) following repeated administration. The overall exposure (A average) to Heptest® activity are close ($+55$ s Treatment A - $+58.4$ s Treatment C) though statistically significantly different ($p < 0.05$).

Kinetic profiles of treatment B (100 mg.ml⁻¹-2 shots) versus treatment A (100 mg.ml⁻¹-1 shot)

There is no statistically significant difference (Table 59 p.127) between the pharmacokinetic parameters of the two schemes of administration of the 1.0 mg.ml⁻¹ concentration solution. The overall exposure (A_{ave}) to [REDACTED] activity ($+55$ s treatment A and treatment B) is similar ($p > 0.05$). The plateau activity is achieved at the same rate following repeated administration.

7.5. APTT clotting time prolongation

7.5.1. Mean APTT clotting time prolongation

Individual data : figures and curves, are presented in Appendix A.4.2.. Mean curves are portrayed Figures 13 to 16. The analytical validation of data is reported in the Drug Disposition technical report Appendix A.5.1.

From Day 1 to Day 5 and on Day 6, the time-course of APTT profiles are similar for the three treatments (Figure 13 p.146). The mean values of the APTT activity generated in plasma of each group of patients (males and females) are similar for treatments A and B (Figure 14 p.147, Figure 15 p.148). Females in the treatment group C exhibit lower clotting time prolongation than males (Figure 16 p.149).

7.5.2. APTT clotting time prolongation parameters

Individual data are presented in Table 46 to Table 48. Statistical analysis is reported Appendix A.3.2. Statistical results are summarized Table 61.

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The mean values of parameters at steady state are summarized Table 8 p.58 for the three treatment groups :

Table 8 : Summary of Pharmacokinetic parameters of APTT clotting time prolongation at steady state (Day 5) for the three treatments

	Treatment A 100 mg.ml ⁻¹ (single shot)	Treatment B 100 mg.ml ⁻¹ (double shot)	Treatment C 200 mg.ml ⁻¹ (single shot)
A(Δ t)max (s)	+19.3 \pm 4.7	+20.1 \pm 6.4	+22.0 \pm 6.7
t max (h)*	3.0 [2.0-4.5]	3.0 [2.0-5.0]	3.0 [2.0-5.0]
ratio max	1.6 \pm 0.1	1.7 \pm 0.2	1.7 \pm 0.2

Mean \pm SD or * median and range (Extracted from Table 46)

- Parameters of plasma APTT activity exhibit a gaussian distribution pattern according to the conclusions of the test of normality (Table 61 p.129).
- According to the Proc mixed performed on log transformed bioavailability parameters : A(Δ t)max and on tmax and the ratio max :
 - there is no statistically significant « treatment », « period », « sequence » or « sex » effects.
 - a statistically significant « subject(sequence) » is observed on A(Δ t)max (p<0.05).
- The Schuirmann two one-sided test (Table 61 p.129) shows that the three treatments corresponding to two formulations (100 mg.ml⁻¹ and 200 mg.ml⁻¹) and the schemes of administration for the 100 mg.ml⁻¹ formulation (single or double shot) are bioequivalent in terms of maximum plasma APTT clotting time prolongation at $\alpha = 0.1$, the 90 % confidence intervals being inside the accepted 80-125% bioequivalence interval .

The APTT disposition profiles of the three treatments A, B and C are comparable in terms of APTT clotting time prolongation. The clotting time recorded at t=0 hour and at t= 3 hours are similar indicating that the steady state is achieved after the first administration.

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ATTACHMENT 6

Lovenox
Supplemental NDA 20-164/SE1-015 and SE1-016

- c) Provide a tabular summary of data (including study number, design, enoxaparin sodium dose, dosing frequency, patient population, aPTT results) that supports the last sentence of the first paragraph related to the effects of dosing on aPTT parameters. Clarify if any other studies were used to support this sentence as both study reports K9001006 (taken to be the report listed as « PK91006:RP54563 ») and PK 91107 listed in footnote 9 are single dose studies

For clarification, RPR points out that PK 91107 was a repeat dose study with enoxaparin (1.5 mg/kg SC once a day for seven days).

Study number	Dose/Route	Baseline (s) Mean ± SD	aPTT max (s) Mean ± SD	Ratio M/C Mean ± SD
Healthy volunteers				
K 91006 (S-015/016) - single dose (n=16 males)	Day 1			
	1.0 mg/kg/SC	29.6 ± 3.4	41.0 ± 4.6	1.4 ± 0.2
	1.25 mg/kg/SC	30.3 ± 3.9	43.5 ± 5.6	1.5 ± 0.2
	1.5 mg/kg/SC	29.2 ± 3.2	44.8 ± 6.6	1.6 ± 0.3
	2.0 mg/kg/SC	29.6 ± 2.6	51.4 ± 7.4	1.8 ± 0.3
PK 133 (S-015/016) BE (3 arms) Multiple dose n=24 males +females	Day 5			
	1.5 mg/kg (A)/SC	31.7 ± 3.1	49.9 ± 6.7	1.6 ± 0.1
	1.5 mg/kg (B)/SC	31.3 ± 2.9	50.5 ± 8.5	1.7 ± 0.2
	1.5 mg/kg (C)/SC	31.3 ± 3.3	51.7 ± 8.1	1.7 ± 0.2
Patients				
K 91107 (S-015/016) - Multiple dose DVT treatment (n=16 patients)	1.5 mg/kg /SC			
	Day 2	30.3 ± 6.6	46.3 ± 12.8	1.6 ± 0.4
	Day 7	30.4 ± 4.7	42.5 ± 6.8	1.5 ± 0.2

Ratio M/C = maximum aPTT of the subject or patient/control plasma

- d) In the "Pharmacodynamics" subsection :

- (1) Provide the reference and information supporting the fifth sentence of the first paragraph related to clearance of enoxaparin including the enoxaparin sodium dose at which this estimate was obtained.

Clearance was determined at an IV dose of 40 mg in 8 subjects. The correct value for the label is 26 ml/min. See table below for individual data per subject and mean values. Calculation of Cl/f is also shown below. Original NDA #20-164 30 Dec 1991 RP 54563 - 100536 (Vol 2.11, Table VI, page 298, attachment 8).

ATTACHMENT 7

Lovenox
Supplemental NDA 20-164/SE1-015 and SE1-016

Pharmacokinetics and biodistribution of technetium 99m labelled standard heparin and a low molecular weight heparin (enoxaparin) after intravenous injection in normal volunteers

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Summary. For a better understanding of low molecular weight heparin pharmacokinetics, 99m technetium labelled heparin and enoxaparin were injected intravenously to four normal volunteers, after approval by the Ethics Committee and preliminary animals studies.

In vitro and *in vivo*, the labelled products proved to be stable and identical to the non-labelled drugs.

Radioactivity curves in blood, organs and urines were similar for both products. Anti Xa plasma half-life was 3 times longer for enoxaparin than for heparin. Anti IIa plasma half-lives were similar. However, radioactivity persisted much longer than biological activities for both products. After

chromatography, most of the radioactivity was bound to AT III, where an anti Xa activity peak was also detected. The anti Xa activity peak seen after adding AT III to plasma was much higher with heparin than with enoxaparin. In urine, biological activities, measured with AT III supplementation, were higher with enoxaparin than with heparin.

These results suggest that phenomena other than biodistribution are responsible for the differences in pharmacokinetics observed between these two products. The two most likely explanations are differences in metabolism and/or a release of an endogenous factor.

The recent introduction of low molecular weight heparin (LMWH) has raised a number of questions concerning their pharmacokinetics. The biological activities anti Xa and anti IIa as measured in blood do not completely account for the antithrombotic activity of these products (Thomas, 1986). Direct measurement of these compounds in the blood and excreta is also difficult, because of their molecular heterogeneity.

It is therefore difficult to explain the prolonged action of LMWH preparations. Some hypotheses have been proposed: they may be retained by the organism for longer than heparin (Larsen *et al.* 1986), they may be metabolized more slowly (Uzan *et al.* 1987), inhibited more slowly by platelet factor 4 (Lane *et al.* 1985), or finally, an endogenous antithrombotic factor may be released (Dawes *et al.* 1986a).

Studies in human volunteers given enoxaparin or heparin subcutaneously have shown differences in bioavailability.

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This may be due to different resorption kinetics in the vicinity of the injection site (Bara *et al.* 1985; Frydman *et al.* 1988).

To our knowledge, there have been no measurements of both heparin, LMWH and their metabolites in blood, urine and organs in the same subjects.

We have therefore studied the activity and metabolism of ^{99m}Tc-labelled heparin and enoxaparin in a group of human subjects. Each subject was given both heparin and enoxaparin. The short-lived gamma emitting isotope ^{99m}Tc can be measured by scintigraphy, and is suitable for measurements in humans under conditions which satisfy the requirements of Ethics Committee.

MATERIALS AND METHODS

Subjects. Four healthy volunteers (Table I) were studied after having given their informed consent. Preliminary complete biological and haematological surveys were normal. Plasma volumes were measured using ⁵¹Cr as an erythrocyte marker. Heparin and enoxaparin were injected

Table I. Subjects characteristics

Subject	Sex	Age (yr)	Height (cm)	Weight (kg)	Plasma volume (ml)	Injected radioactivity (mCi)	
						Heparin	Enoxaparin
BB	M	47	183	76	3325	20.8	16
LG	F	43	165	65	2308	18.7	15
MDL	F	23	174	70	2774	16.4	15.4
CB	M	25	173	63	3187	18.4	15.4

i.v. (30 mg per subject). Successive injections were given at least 1 week apart.

Products. Heparin (mean molecular weight: 15000 Da: 160 U anti Xa and anti IIa versus the fourth international heparin standard) and enoxaparin (depolymerized heparin preparation achieved through alkaline cleavage of heparin benzyl ester: mean molecular weight: 4500 Da: 93 U anti Xa and 30 U anti IIa versus first international standard for low molecular weight heparin) (Rhône-Poulenc Santé, Alfortville, France) preparations were labelled with ^{99m}Tc prior to each injection as follows: a sterile, pyrogen-free solution of stannous chloride (40 mg/ml) was prepared by diluting a stock solution (200 mg/ml) with water under a stream of nitrogen and filtering through a millipore filter (Millex 0.22 μm). A 0.5 ml aliquot (20 mg) was then mixed with 1 ml NaCl (63 g/l) plus 5 ml heparin or enoxaparin (150 mg). 3.7 GBq ^{99m}Tc pertechnetate (CEA, Saclay, France) was then added and the solution mixed for 5 min at room temperature. Aliquots, containing 30 mg of heparin or enoxaparin (0.7 GBq), were removed for injection. The remaining solution was used for controls.

Controls. The labelling efficiency was measured after chromatography on Whatman no. 1 paper with acetone, after 0, 3 and 24 h of incubation with ^{99m}Tc . Free pertechnetate was eluted with acetone, while heparin and enoxaparin stayed at deposit site. Labelling was expressed as the percentage total pertechnetate coupled to heparin or enoxaparin. The biological activities (anti Xa and anti IIa) of the labelled products were measured by standard amidolytic techniques, using the chromogenic synthetic substrates CBS 3139 (Stago) for the anti Xa, and S 2238 (Kabi) for the anti IIa assays, in the presence of bovine factor Xa (Stago), or human thrombin (Ortho). Briefly, the techniques were as follows: (i) anti Xa activity: citrated plasma and bovine factor Xa diluted in tris EDTA buffer were incubated (37°C) for 30 s (high doses), or 60 s (low doses); (ii) anti IIa activity: citrated plasma and human thrombin, diluted in tris EDTA buffer, were incubated (37°C) for 30 s with S2238. The delta optical density were measured on a Gilford 3500 spectrophotometer.

Sterility was checked by preparing solutions under conditions identical to those used for the injectates, and incubating them on Petri dishes (nutrient gelatin and Sabouraud medium) and in broth (trypticase-soy bean and thioglycolate broth).

Experimental protocol. Control blood samples were taken 15 min prior to injection of the radiolabelled products. Two series of blood samples were taken at 5, 15, 30, 45, 60, 90,

150, 180, 210, 300, 460 and 1440 min after injection. The first set of test samples (4.5 ml) were placed in 0.5 ml of 3.8% sodium citrate. The plasmas were separated by centrifugation (3500 g at 15°C for 15 min), and the radioactivities of plasma and erythrocyte samples were determined immediately. Partial thromboplastin times were determined with activator on the fresh plasmas. The remaining plasmas were frozen and stored at -20°C.

The second set of samples were placed in glass vials and were incubated for 1 h at 37°C, and then centrifuged (5 min at 3500 g and 15°C), the serum was recovered and kept at -20°C for residual prothrombin assays. Additional blood samples (10 ml) were taken at 30 min and placed in citrate for fractionation studies.

Urine samples were collected prior to heparin/enoxaparin injections and at 45, 75, 180, 210, 360, 480, 720 and 1440 min after injection. Total volumes were measured and aliquots were taken for radioactivity assays, for anti Xa and anti IIa assays, and to check eliminated products for product degradation.

Scintigraphic measurements were made from frontal thoracic and abdominal images using a tomography type gamma camera (Gammatome II, Sopha Medical) linked to a SIMIS 4 computer (Sopha Medical). Pictures were taken every 1.5 s for the first 30 min after injection to provide a dynamic record. Static images were obtained with 1, 5 or 15 min exposures at various times and were used to calculate total organ (heart, liver) total and unit surface radioactivity. Tomographic images were taken at 120 min for two subjects, and at 120 and 300 min for the other two.

The *in vivo* stability of the label was checked by recording images of the thyroid for each subject, as free pertechnetate is taken up by the thyroid.

Plasma and urine sample fractionation. Plasma samples were chromatographed on an Ultrogel ACA 54 column (height: 79 cm; diameter: 1.6 cm). Fractions (3 ml) were eluted with NaCl 0.15 M at 10 ml/h. The radioactivity and the anti Xa activity with and without AT III supplementation were measured. Urine samples were fractionated on a DEAE-trisacryl M column (height: 3.5 cm; diameter: 1.5 cm); 3 ml fractions were eluted with 3 M NaCl, followed by 1.2 M.

Measurement of biological activities. The anti Xa and anti IIa activities in samples of frozen plasma were measured as described above. Measurements on urine and plasma samples were made before and after adding purified human AT III.

The prothrombin consumption, reflecting the prothrombinase generation, was determined in serum by chromometric

technique: briefly, serum was added to deficient plasma (Stago) and clotting time performed in the presence of calcium thromboplastin (neoplastin Stago) in an automate: Coagamate X2. This residual prothrombin was measured 1 h after coagulation on serum. Activated partial thromboplastin times were measured in fresh plasma using the Diacellin assay (Diamed, France).

Data analysis. (1) Both recovered radioactivity and biological activities were expressed as percentage of the totals injected, corrected for the subjects plasma volume. However, radioactivity and biological assays do not necessarily provide comparable indices of the molecular heterogeneities (in terms of molecular weights and in terms of affinities) of the two products.

(2) The cardiac and hepatic elimination curves were fitted to a single component exponential curve.

(3) Elimination from the blood followed an alpha-phase pattern for the first 5 min post injection (Gravlee *et al.* 1988). From 5 min to 8 h the elimination could be fitted to a single component exponential curve, and from 8 to 24 h elimination was apparently slow, but the number of samples was too small for analysis.

RESULTS

Injected preparations

The ^{99m}Tc -labelling did not significantly alter the biological activities of enoxaparin and heparin: (anti Xa IU/mg were 91 and 161 before, and 93 and 157 after labelling for enoxaparin and heparin respectively. Anti IIa IU/mg were 29 and 161 before and after labelling, for enoxaparin and heparin respectively). *In vitro*, free pertechnetate ($^{99m}\text{TcO}_4^-$) accounted for less than 2% of the total radioactivity during the first 6 h, and for about 5% at 24 h. This label stability was confirmed *in vivo* by counting the centrifuged erythrocytes in each sample from all subjects. The radioactivity remained below 5% of the total injected radioactivity. Thyroid images showed no pertechnetate fixation in the four subjects. All sample sterility tests were negative and clinical tolerance was excellent.

Plasma studies

The average values of radioactivity clearance from plasma, expressed as half-lives (mean \pm SD), were very similar for heparin (345.7 ± 14.2 min) and enoxaparin (325.6 ± 14.2 min).

Fig 1 shows the changes in anti Xa and anti IIa activities and in radioactivity with time after injection.

The half-lives of plasma heparin elimination calculated from anti Xa and anti IIa activities were similar (51 ± 6 min and 53 ± 9 min), but were quite different for enoxaparin (anti Xa: 147 ± 17.5 min and anti IIa: 73 ± 9.6 min). The short heparin half-life resulted in no biological activity being detected after 5 h. By contrast, detectable enoxaparin anti Xa activity was still present in three subjects 5 h after injection.

The percentage of anti Xa activity found 5 min after injection (87% for enoxaparin; 76% for heparin) was higher than the percentage of radioactivity found at the same time

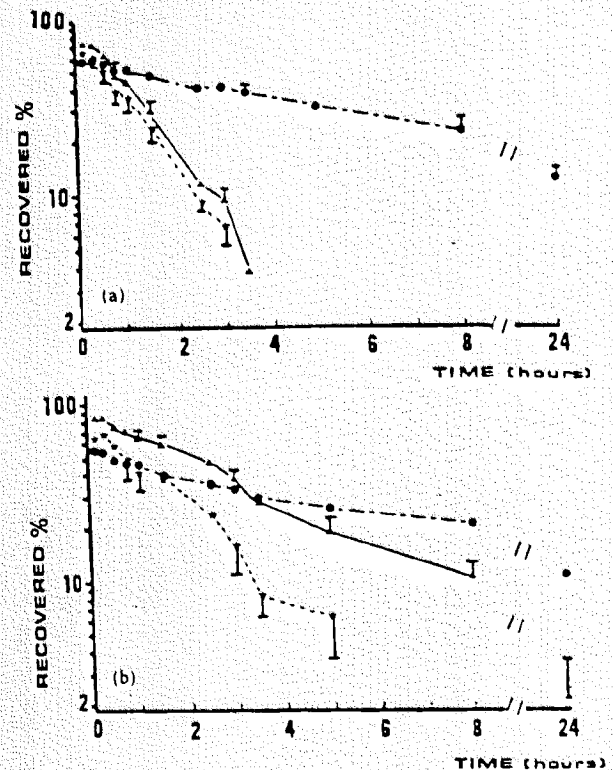


Fig 1. Plasma kinetics of radioactivity, anti Xa and anti IIa activities after heparin (a) and enoxaparin (b) injection. ●: radioactivity; ▲: anti Xa activity; ★: anti IIa activity.

(59% for enoxaparin and 63% for heparin). These differences persisted during the first 4 h for enoxaparin, and during the first 2 h for heparin.

The activated partial thromboplastin times were longer for heparin than for enoxaparin. The average values obtained were 233 s (30 min) and 135 s (60 min) for heparin, and 43 s (30 min) and 35 s (60 min) for enoxaparin.

Prothrombin consumption was perturbed for 90 min after heparin injection, and for about 180 min after enoxaparin injection (CV = 5%). This perturbation was greater 5 min after heparin injection than 5 min after enoxaparin.

Plasma fractionation studies

The radioactivity peak coincided roughly with the anti Xa peak (molecular weight about 70 000 Da) in all the plasma samples. The coincidence cannot be expected to be perfect, since the methods used are completely different: the radioactivity correspond to all anticoagulant and non-anticoagulant fractions present in this peak fraction zone, whereas the anti Xa activity correspond only to the fraction bound to AT III. This might explain the non-absolute coincidence.

A second peak was also present around molecular weight 5000 Da, outside the protein fraction zone. The anti Xa peak for enoxaparin was higher than the corresponding radioactivity peak (Fig 2b). For heparin, the situation was reversed (Fig 2a). Addition of antithrombin III (1 U/ml) to the eluted

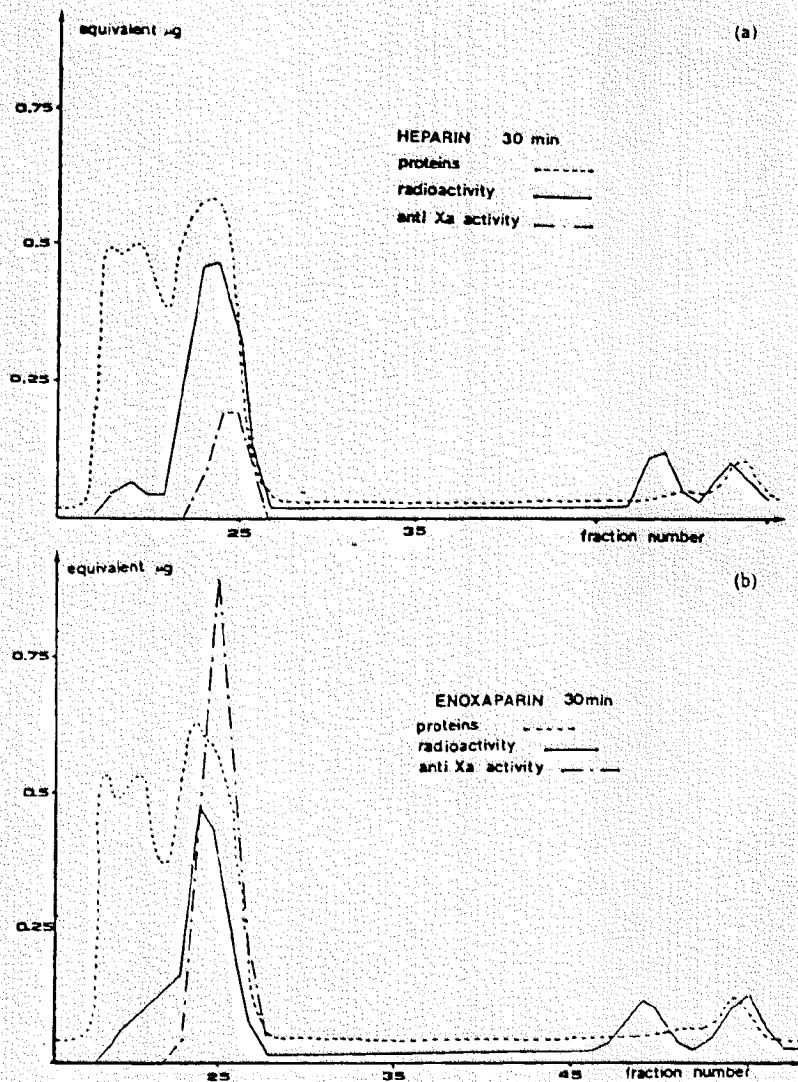


Fig 2. Radioactivity and anti Xa activity after AT III supplementation in plasma eluted fractions 30 min after heparin (a) and Enoxaparin (b) injection in one of the subjects.

Table II. Effect of antithrombin III (AT III) addition on anti Xa activity of protein fractions eluted from heparin or enoxaparin plasma

Compound	Anti Xa activity of protein eluted fraction (μg equivalents/ml)					
	Total		Peak level			
	Without AT III supplementation	With AT III supplementation	Ratio	Without AT III supplementation	With AT III supplementation	Ratio
Heparin	1.02	4.04	3.9	0.1	2.91	27.5
Enoxaparin	2.33	4.44	1.9	0.58	1.84	3.1

radioactivity peak fractions for heparin-injected plasmas greatly increased the anti Xa activities but produced only moderate increases in anti Xa activities of enoxaparin-injected plasmas (Table II).

Radioactivity in organs

Fig 3 shows heparin and enoxaparin scintigraphies at 35 and 360 min for one of the subjects. At 35 min, most of the radioactivity is localized within the heart. At 360 min, it is

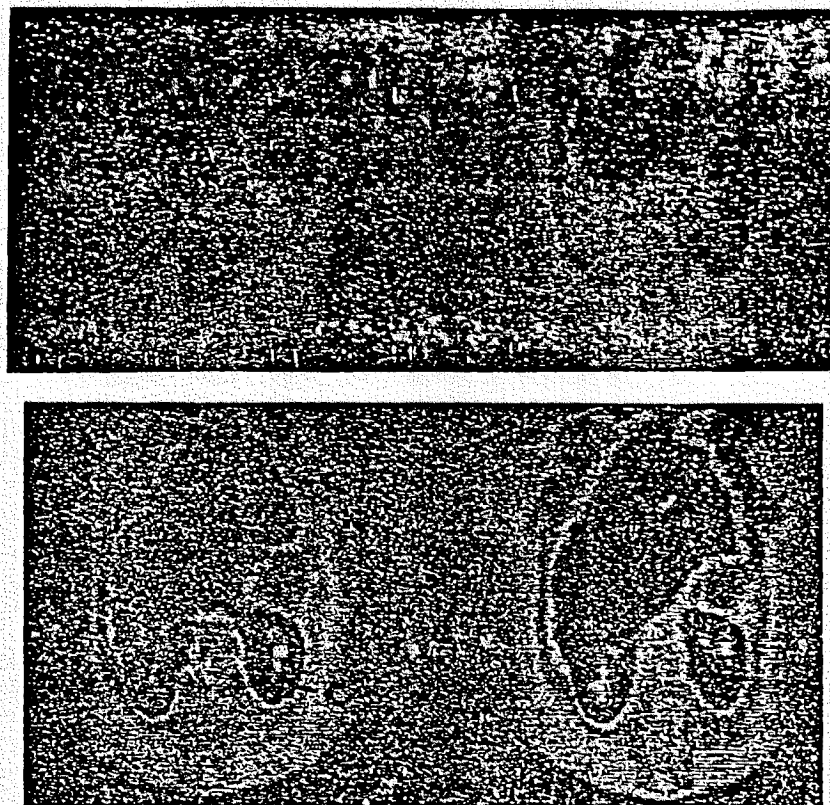


Fig 3. Heparin and enoxaparin scintigraphies at 35 min (above) and 360 min (below) after injection for one of the subjects. (A) heart. (B) liver. (C) kidneys.

distributed preferentially within heart, liver and kidneys.

The fitted curves for the hepatic (Fig 4a) and cardiac (Fig 4b) elimination of the two products were similar in all the subjects tested.

Statistical analysis of these data (analysis of variance and *t*-test) showed no difference between heparin and enoxaparin ($P < 0.05$), neither in terms of their average values in the four subjects, nor in two-by-two differences. There was no detectable thyroid uptake of either heparin or enoxaparin.

Urinary kinetics

The cumulative eliminated radioactivities of heparin and enoxaparin were not significantly different ($22.4 \pm 3.6\%$ for heparin and $20.6 \pm 3.6\%$ for enoxaparin at 210 min, $32.7 \pm 6.5\%$ for heparin and $29.2 \pm 3.6\%$ for enoxaparin at 480 min, $46.1 \pm 9.1\%$ for heparin and $41.3 \pm 4.0\%$ for enoxaparin at 1440 min), confirming their similar metabolic behaviours, plasma kinetics and organ fixations. Urinary elimination of the two radiolabelled products was fast, with an average of 43% being eliminated in 24 h.

Anti Xa and anti IIa measurements in urine, after addition of AT III, reveal a much higher cumulated anti Xa activity (in four subjects) and much higher cumulated anti IIa activity (in three subjects) for enoxaparin than for heparin at 1440 min (Table III).

Table III. Cumulated AT III dependent biological activities excreted in urines 24 h after heparin or Enoxaparin injection

Subject	Heparin (per cent of injected activities)		Enoxaparin (per cent of injected activities)	
	Anti Xa	Anti IIa	Anti Xa	Anti IIa
BB	1	2	10	12.2
LG	3	17	19	8
MDL	2.3	5.5	7.5	21
CB	4	4	8	10

DISCUSSION

Several radioisotopes (^{99m}Tc, ¹³¹I, ¹²⁵I) have been used to label heparin and heparin derivatives in animal studies and some have also been used in humans. The short-lived (6 h) single energy gamma emitter (E = 140 keV) ^{99m}Tc is well suited for studies in man, because of its suitability for use with gamma imaging techniques and because it results in low irradiation doses. ^{99m}Tc forms very stable complexes with

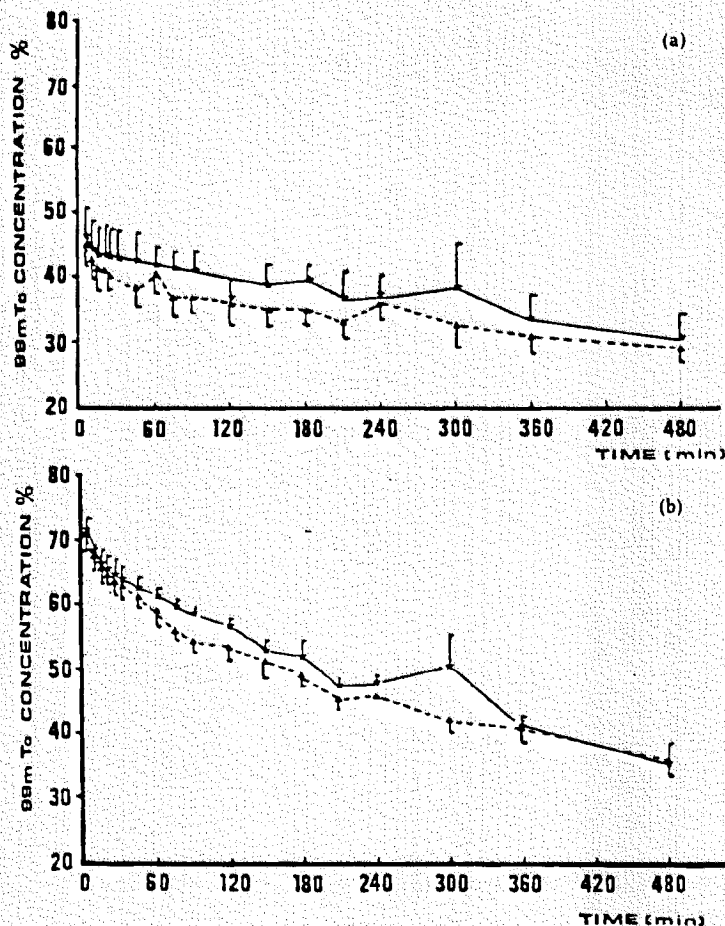


Fig 4. Organs radioactivity kinetics: (a) liver. (b) heart, after heparin and enoxaparin injection. ★: heparin; ▲: enoxaparin.

chelating ligands and, unlike ³⁵S, is not removed when such molecules are desulphated. Animal studies have shown that ^{99m}Tc-labelled heparin and heparin derivatives are stable *in vivo* (Perdrisot *et al.* 1984). In man, the absence of thyroid ^{99m}Tc fixation, and erythrocytes fixation up to 24 h after injection, indicates that free ^{99m}Tc is not produced *in vivo*. The radioactivity and biological activities of ^{99m}Tc heparin and enoxaparin are found in the same plasma fraction, or elution peak, 30 min after injection, showing that the pertechnetate is still bound to heparin and enoxaparin.

In order to assess the radiation exposure, a dosimetric study was performed, based on extrapolation from animal experiments (to be published), and was submitted to the Ethics Committee of Hôpital Beaujon, before the present study was undertaken.

The results of the present study show that the radiation exposures of our four volunteers were similar for heparin and Enoxaparin. Despite the differences in weight and height of the four subjects, the doses received by each of them (whole body: 1.2 μ Gy/MBq) were similar. These doses were smaller than those received by patients during standard routine hepatic scintigraphy (5.4 μ Gy/MBq).

It must be noted that, despite the physical differences of the volunteers (sex, age, height and weight), the kinetics of

distribution and elimination were very similar within the four of them.

The single-compartment fitting of the blood kinetic corresponds to the beta elimination phase between 5 min and 8 h.

There was an initial rapid distribution phase for both heparin and enoxaparin since only about 60% of the radioactivity was found in the blood 5 min after injection. Similar results have been obtained by others (Gravlee *et al.* 1988). This rapid phase could be due to endothelial binding of the labelled substances (Van Rijn *et al.* 1987), but this was not measured in our study. As we used i.v. injection, we assumed 100% of the activity to be present at 0 min. There appears to be a slow elimination phase from 8 to 24 h post-injection, but the small number of measurements did not permit satisfactory quantification of these phases.

The data indicate that the blood kinetics of heparin and enoxaparin are similar, based on radioactivity studies. The anti IIa activities are in agreement with earlier studies (Bara *et al.* 1985; Dawes *et al.* 1986b), as well as the finding that the plasma half-life of anti Xa activity for enoxaparin was longer than that for heparin (Bara *et al.* 1985; Dawes *et al.* 1986b).

The reported half-lives obtained by tracer studies after intravenous injection in humans vary considerably. Esquerre *et al.* (1979), who used ^{99m}Tc, found values for normal