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Safety Profile of Tinzaparin Administered Once Daily at a Standard Curative Dose in Two Hundred Very Elderly Patients

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Abstract

Objectives: Too few very elderly patients with an age-related renal impairment are included in clinical trials. We conducted a study in order to evaluate the safety profile of tinzaparin, a low molecular weight heparin (LMWH), given at a curative dose (175 IU/kg once daily) in very elderly patients treated for up to 30 days.
Setting: An 800-bed geriatric hospital.
Design: A 1-year prescribing study.
Patients: Consecutive in-patients older than age 70, whose creatinine clearance was above 20 ml/min, and requiring full anticoagulation with LMWH were included.
Measurements: Safety parameters (major bleeding/heparin-induced thrombocytopenia/death) were recorded. Plasma anti-Xa activity levels were regularly measured throughout the treatment period.
Results: Two-hundred in-patients, mean age 85.2 ± 6.9 years (70 to 102), mean creatinine clearance 51.2 ± 22.9 ml/min, were given tinzaparin. Six patients died during the treatment period: only one could be related to the anticoagulation treatment. Three major bleeding episodes (1.5%) were reported. Antithrombotic drug interactions likely contributed to the bleeding event in two of them. Heparin-induced thrombocytopenia was confirmed in two patients (1%). No correlation was found between anti-Xa activity and creatinine clearance or age.
Conclusions: Tinzaparin can be used safely at a curative dose in very elderly patients as long as (i) the accurate bodyweight-adjusted dose is given; (ii) platelet counts and anti-Xa levels are regularly monitored and; (iii) the interaction with other antithrombotic drugs is correctly managed.

Background

The incidence of venous thromboembolism and atrial fibrillation increases with advanced age.[1,2] Therefore, anticoagulants are frequently prescribed in the geriatric patient population. Among heparins, low molecular weight heparins (LMWHs) given at a bodyweight-adjusted dose are now commonly used in the treatment of acute thromboembolic disease.[3] They are at least as effective and safe as unfractionated heparin (UFH) in the treatment of deep venous thrombosis with or without pulmonary embolism, and are more convenient.[3-9]

The development of LMWHs for clinical use was stimulated by their superior pharmacokinetic properties: LMWHs have a longer half-life and higher bioavailability than UFH as well as a more predictable dose response.[10] Thus, laboratory monitoring of LMWH therapy is usually not necessary.

Age is well recognised as a factor that may affect the drug pharmacokinetics. Indeed, aging is frequently associated with impaired renal function which may lead to accumulation of drugs mainly eliminated by the kidney, such as LMWHs.[11] Thus, repeated administration of curative doses of LMWHs may lead to overdosage and/or an accumulation effect with a risk of bleeding. Dose finding studies with LMWHs have shown that the rate of major bleeding was significantly increased in patients receiving the higher dosage. As an example, in the Thrombolysis in Myocardial Infarction (TIMI)-11A study, it was clearly shown that increasing the dose of enoxaparin by 25% resulted in an unacceptable rate of major bleedings (6.5 *vs* 1.9%), associated with very high anti-Xa levels compared with the usual therapeutic range.[12] Another dose-finding study conducted with dalteparin showed similar results.[13]

To date it has not been clearly demonstrated in any clinical trial that testing of anti-Xa correlates to outcome. Nevertheless, consistent data and experts' recommendations[3,10,14,15] suggest that anti-Xa monitoring could improve the safety of LMWHs especially in select patient populations with high haemorrhagic risk. In patients with renal impairment, the monitoring of anti-Xa level can detect an accumulation effect that could lead to an overdosage.[16,17] Monitoring of anti-Xa activity may be recommended to detect an overdosage in older patients with age-related renal impairment.

Because most clinical trials include too few very elderly patients, they provide little reliable evidence concerning the bleeding rate in older patients treated with curative doses of LMWH.[18] Thus, the safety profile of LMWHs in this frail elderly population remains unclear.

We conducted a one-year prescribing study of a LMWH, tinzaparin, at curative dose (175 anti-Xa IU/kg) given once daily to very elderly patients hospitalised in an 800-bed geriatric hospital. The main objectives of the study were to evaluate: (i) the safety profile of tinzaparin in older patients for up to 30 days in routine practice; (ii) the anti-Xa activity throughout a maximum of a 30-day treatment period; (iii) the correlation between anti-Xa activity and age, weight, or creatinine clearance.

Methods

Study Design

Between September 1999 and August 2000, we conducted an observational study, initiated by the Local Committee for Drug Management, and which included records of pharmacovigilance data. The aim of the study was to evaluate the safety profile of a LMWH, tinzaparin, given at curative dose in elderly patients. This study reflects the current practice in all clinical departments of the Charles Foix University Hospital, including 800 short stay geriatric, continuing care and rehabilitation or long stay care beds.

All patients older than 70 and requiring full anticoagulation with LMWH were included. In our institution, tinzaparin (Innohep®[1], Leo Pharmaceutical Products, Ballerup, Denmark) was the only available LMWH preparation for the treatment of acute thromboembolic disease. Exclusion criteria were: (i) any contraindication to the use of curative dose LMWH; and (ii) a creatinine clearance value calculated using the Cockcroft formula of below 20 ml/min.[19]

Data were collected throughout the duration of treatment up to a maximum of 30 days.

Safety data including all major events in patients receiving tinzaparin at curative dose were prospectively recorded: (i) deaths or; (ii) any major bleeding defined as overt bleeding with a haemoglobin decrease of at least 2.0 g/dl, bleeding

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

requiring transfusion of two (or more) units of red blood cells, intra-cerebral, retro-peritoneal, gastro-intestinal or genitourinary tract bleeding. A clinical expert was appointed to review all major adverse events. Minor bleedings were not systematically recorded and for this reason not analysed.

Biological data were systematically recorded: (i) creatinine clearance calculated using the Cockcroft formula; (ii) full blood counts (haemoglobin level, platelet count) and; (iii) plasma anti-Xa activities.

Treatment Regimen and Blood Processing

The patients were to receive the recommended initial dose of 175 IU anti-Xa/kg of tinzaparin (Innohep®) given as a single daily subcutaneous injection. By convention, the first day of tinzaparin treatment was referred to as D1. The injections were administered in the morning at 10.00 am. Monitoring of tinzaparin was performed according to the recommendations formulated by the Authority for Health Products in France and other European countries.[20] Anti-Xa activity was measured at peak level (5 hours after the injection) when tinzaparin treatment was started and then once per week thereafter.[20] Studies conducted in healthy volunteers and population pharmacodynamic studies conducted in patients receiving tinzaparin at curative dose showed that the mean anti-Xa peak level was approximatively 0.8 IU/ml.[21-23] In these studies, 90% of the patients had an anti-Xa peak level between 0.5 and 1.5 IU/ml due to inter-subject variability. Thus, the National Health Authorities consider that the acceptable upper limit of anti-Xa is 1.5 IU/ml for tinzaparin. A dose adjustment is recommended if this upper limit is reached. In our study, a 20% reduction of the dose regimen was suggested if the anti-Xa level was ≥1.4 IU/ml. In contrast, no anti-Xa lower limit has been defined. For this reason, we did not recommend any increase of the dose. Platelet count was performed twice weekly for the first 3 weeks on treatment and then once weekly, according to the recommendations.[20]

As no extra-sampling was required, the informed consent of the patients was not mandatory. All these administration and monitoring guidelines were recorded on an anti-coagulant prescribing guidance chart distributed to all prescribers in the hospital under the authority of the Charles Foix Hospital Drugs Committee.

Haemostasis Tests

Venous blood was withdrawn into sodium citrate tubes (0.105 mmol/L, 1vol/9vol) [Beckton Dickinson, San Jose, CA, USA]. Platelet-depleted plasma was obtained by centrifuging at 2500g at 15°C for 15 min. Measurement of anti-Xa activity was routinely performed on fresh plasma. Anti-Xa activity was determined using a chromogenic assay (Stachrom® heparin, Diagnostica Stago, Asnières, France), as previously described.[24] Confirmatory laboratory tests for heparin-induced thrombocytopenia (HIT) were performed at the Hôtel-Dieu Central Haematology Laboratory using a combination of a functional test (platelet aggregation) and testing for anti-platelet factor 4-heparin antibodies (ELISA), as previously described.[25]

Statistical Analysis

The statistical analysis was performed on SAS software (SAS® Institute Inc., Cary, NC, USA). Results are expressed as mean ± standard deviation (minimum to maximum). The significance threshold was defined as $p = 0.05$. Pearson correlation coefficients were determined.

Results

Patient and Treatment Characteristics

Of the 239 hospitalised patients receiving tinzaparin treatment at a curative dose, 200 consecutive in-patients (44 men, 156 women), aged 85.2 ± 6.9 years (range 70 to 102), met eligibility criteria for the study. Thirty-nine patients were excluded: 21 were below the age of 70 years; nine had a creatinine clearance below 20 ml/min; nine patients had been previously enrolled in the study. The baseline

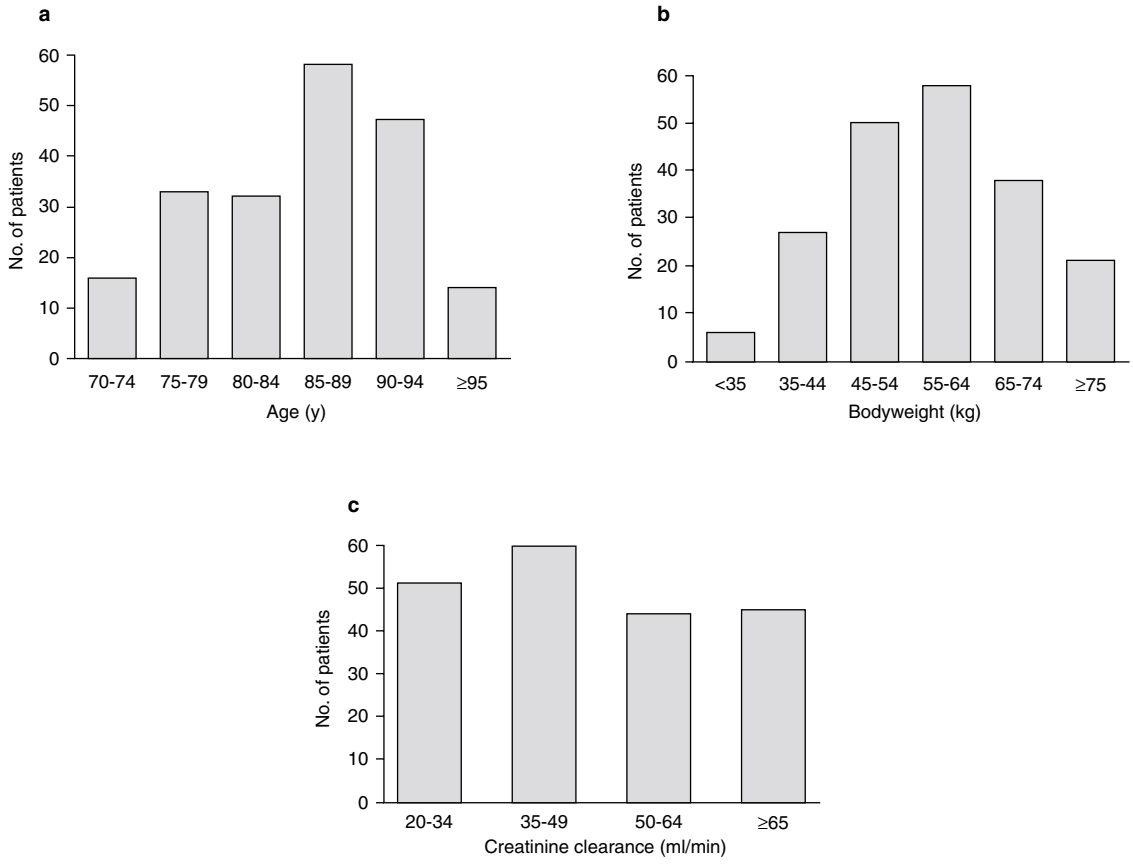

Fig. 1. Characteristics of the 200 patients included in the study. (**a**) The distribution of the population by age bands; (**b**) the distribution of the population by bodyweight bands; (**c**) the distribution of creatinine clearance in the population by four subgroups.

characteristics of the included patients are shown in figure 1. The mean bodyweight was 58.2 ± 13.7kg (range 32 to 109). The mean creatinine clearance was 51.2 ± 22.9 ml/min (range 20 to 161) [median 46 ml/min].

The indications for curative dose tinzaparin were: (i) venous thromboembolic disease in 132 patients (107 deep vein thrombosis, 25 pulmonary emboli); (ii) acute atrial fibrillation in 43 patients and; (iii) other reasons in 25 patients.

The mean duration of treatment in the 200 patients followed for a maximum period of 30 days was 19.1 ± 10.1 days (range 1 to 30). In 145 patients (72.5%), tinzaparin treatment was continued beyond 10 days.

Of the 200 included patients, 153 (76.5%) received a mean actual dose of 173 IU/kg/24h; 47 patients received a dose differing by more than 15 IU/kg of the recommended dose (i.e. 175 IU/kg): 14 patients (7%) received a dose higher than >190 IU/kg/24h and 33 patients (16.5%) received a dose lower than 160 IU/kg/24h. The analysis of the collected data (initial dose, bodyweight) showed that many cases of incorrect administration (i.e. <160

or >190 IU/kg/24h) were due to a lack of a recent measurement of the patient's bodyweight in the clinical departments.

Safety Events

The safety events are summarised in table I.

Six deaths occurred during or immediately after stopping tinzaparin treatment. Only one death could be linked to the anticoagulation treatment.

Three major bleeding episodes, one of which was fatal, were reported. A 88-year-old woman (bodyweight 80kg, creatinine clearance 45 ml/min) developed a subdural haematoma on D13 which was fatal on D14. In this patient, the overlap of tinzaparin/warfarin, which was started on D5, was badly performed: on D8, anti-Xa level reached 2.0 IU/ml without any change in the tinzaparin dose till D13; at the same time her international normalised ratio (INR) was >7.0 from D10 to D12 (due to a probable interaction with fluconazole prescribed for a oropharyngeal candidiasis).

A 74-year-old man (bodyweight 86kg, creatinine clearance 68 ml/min) developed a haemorrhagic transformation of an ischaemic stroke on D15, as he was receiving the combination of tinzaparin, warfarin (INR = 2.0 at the time of the bleeding), aspirin (acetylsalicylic acid) and dipyridamole. The patient recovered spontaneously and completely from the haemorrhagic accident.

A 87-year-old woman (bodyweight 100kg, creatinine clearance 68 ml/min) developed a post-traumatic muscular haematoma in the right leg on D9 associated with a 2.6 g/dl drop in haemoglobin level. On D11, the rupture of the haematoma led to a surgical repair and the patient received two units of red blood cells.

Of the 200 patients, HIT was suspected in three patients and was confirmed by laboratory tests in two of them. Platelet counts rose after tinzaparin had been discontinued in the three cases. No clinical complications of HIT were found in these three patients.

Anti-Xa Monitoring

Figure 2 shows the distribution of anti-Xa activity values in the 200 patients by creatinine clearance subgroups. A total of 630 anti-Xa activity measurements were performed throughout the treatment period in the 200 patients. A similar dispersion of anti-Xa activity levels was observed in the four creatinine clearance subgroups.

Table I. Summary of safety events

Critical event	Description	Causality		
		TZ	OAC	Other
Death (n = 6)	Subdural haematoma	++	++	–
	Acute ischaemia of the small intestine	–	–	–
	Legionella	–	–	–
	Aspiration pneumonia	–	–	–
	Aspiration pneumonia	–	–	–
	Heart failure	–	–	–
Major bleeding (n = 3)	Subdural haematoma[a]	++	+	–
	Haemorrhage into ischaemic stroke	+	+	+
	Post-traumatic muscular haematoma	++	–	–
HIT (n = 3)	On D8 – no laboratory confirmation	±		±
	On D12 – laboratory confirmation	++		–
	On D5 – laboratory confirmation	++		–

Causality: – not associated; ± dubious; + possible; ++ probable.

a The subdural haematoma was fatal (see deaths).

D = day; **HIT** = heparin-induced thrombocytopenia; **OAC** = oral anticoagulation; **TZ** = tinzaparin.

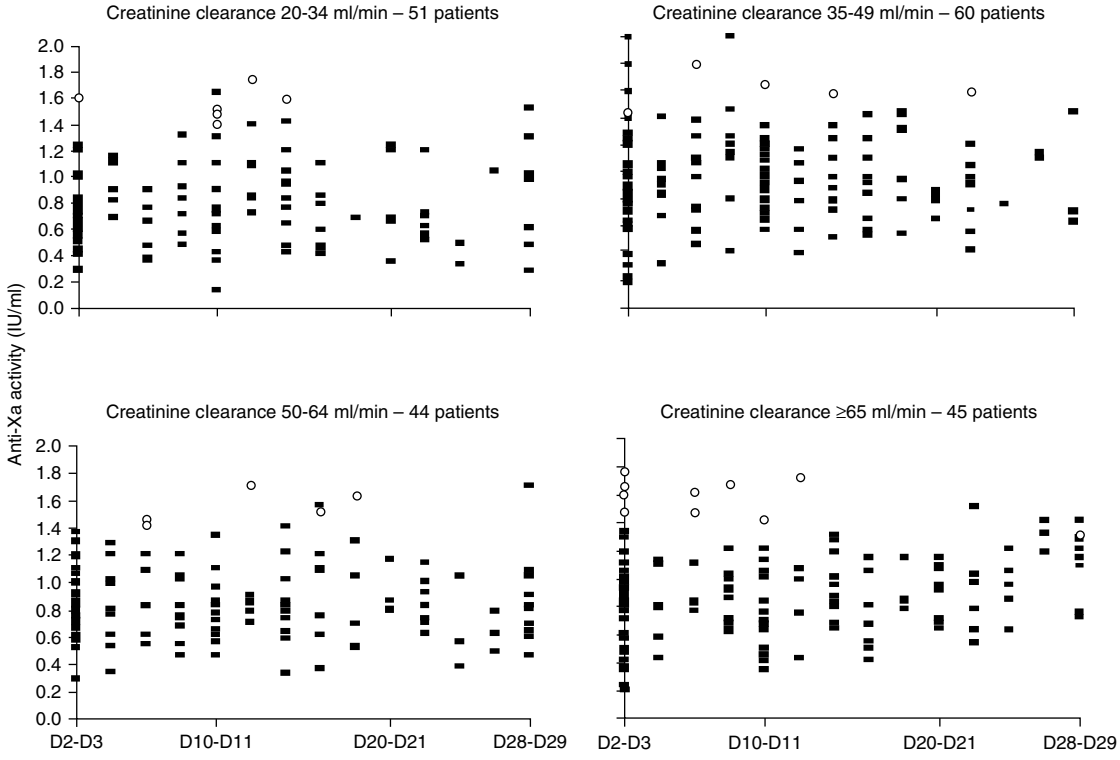

Fig. 2. Anti-Xa activity by creatinine clearance subgroup. Plasma anti-Xa activity values were followed up to a maximum of 30 days. The mean anti-Xa activity at the start of treatment was 0.81 ± 0.31 IU/ml (n = 151 anti-Xa values) in agreement with previous data.[23,24] The rings show the anti-Xa activities of patients in whom an anti-Xa ≥ 1.4 IU/ml led to an adjustment in the initial dosage (26 patients in total). The patients in whom doses were changed were distributed throughout the four creatinine clearance subgroups. **D** = day.

Twenty-six patients had a dose changed because of an anti-Xa activity ≥1.4 IU/ml. Interestingly, they were distributed throughout the four creatinine clearance subgroups (figure 2). Six received an initial dose higher than 190 IU/kg/24h and thus, the monitoring of the anti-Xa activity allowed the physicians to correct the tinzaparin dosage. In the 20 patients receiving a dose ≤190 IU/kg/24h, a 20% dose decrease was followed by anti Xa levels in the therapeutic range for 17 patients, and a subsequent 20% dose adjustment was required in three patients.

In ten patients with an anti-Xa activity level between 1.4 and 1.5 IU/ml, the physicians chose not to change the dose and the later anti-Xa activities of these patients were within the therapeutic range.

Correlation Between Anti-Xa Activities and Age/Bodyweight/Creatinine Clearance

No correlation was found between anti-Xa activity and patient characteristics such as age, bodyweight and creatinine clearance.

Discussion

In controlled clinical trials, major bleeding episodes occurred in about 1 to 3% of patients treated with LMWHs at curative dose.[4-9] The mean age of patients in these clinical trials was about 60 to

65 years. Only a few data are available concerning the safety of LMWHs in geriatric practice. In a recent review, Merli[18] analysed the current literature with respect to the pharmacology, safety, and efficacy of LMWHs in elderly patients, and concluded that there was no evidence of an increased risk of major bleeding based on the patient age. However, recent pharmacovigilance data reported major and fatal bleeding episodes in elderly patients treated with various LMWHs in France.[26] A Dear Doctor Letter was issued by the French Drug Agency concerning the prescribing rules of LMWHs in special populations such as elderly patients with age-related renal impairment.[27] In our study, very elderly in-patients, mean age 85 years, were included. In the conditions of routine practice, the rate of major bleeding in our patients treated with tinzaparin at curative dose was 1.5%, which is not higher than the incidence of such bleedings in younger patients.[28,29]

In our study, antithrombotic drug interactions likely contributed to the bleeding in two of the three patients who developed major bleeding. In geriatric patients, comorbid conditions lead to frequent polypharmacy which may increase the risk of bleeding. In the third case of bleeding reported, the patient was obese. It is not yet established if bodyweight-based LMWHs dosing recommendations are appropriate for obese patients.[10]

HIT is a threatening complication of heparin treatment. However, there are no data as to the incidence of HIT in older medical patients treated with curative dose of LMWH.[30] The incidence of HIT in patients who received unfractionated heparin or LMWH for antithrombotic prophylaxis after surgery varies according to the studies.[31] In our study, serologically-confirmed HIT occurred in two patients (1%) without any clinical manifestations of the HIT syndrome. The sample size does not allow a definitive estimation of the rate of HIT in older medical patients. However, the incidence of 1% would suggest that regular monitoring of platelet count during treatment with LMWH at curative dose is required.

In the present study, about 25% of our patients did not receive the precise recommended dose. In most cases, that was due to an absence of a recent weight measurement. Only estimating bodyweight by eye frequently leads to error in dosage. For example, for a patient weighing 60kg, an error of 5kg leads to a deviation of 15 IU/kg in tinzaparin dosage. Current bodyweight should be required, especially in long stay units or institutions, in order to determine the accurate dose of LMWH.

Prolonged duration of treatment with curative dose of tinzaparin was frequently observed in our study. This is attributable to the characteristics of our patients who are very old and frail. Indeed, in these patients with comorbidities, polypharmacy, cognitive and functional impairment, the use of oral anticoagulation (OAC) may be challenging.[32,33] For example, comorbidities requiring invasive procedures frequently delay LMWH to OAC overlap; cognitive impairment may predict a bad compliance with OAC. These reasons may explain the physician's preference for a long-term treatment with LMWH. Interestingly, recent clinical trials show that prolonged LMWH treatment is a well tolerated and effective alternative for patients with venous thromboembolism who have a contraindication to OAC.[34-36]

Since LMWHs are mainly eliminated by the kidney, the prolongation of LMWH treatment at a curative dose exposes elderly patients to a theoretical risk of accumulation, especially those with age-related renal impairment. In order to detect an accumulation of LMWH, the measurement of the anti-Xa activity at peak level may be recommended.[10,14,15] The only two studies conducted previously in older patients treated with two LMWHs, nadroparin and tinzaparin, at curative dose, showed differences in the pharmacodynamic profile of the two compounds.[16,24] Mismetti et al.[16] showed an accumulation of nadroparin administered once daily, over 6 to 9 days (180 IU/kg/24h), in older subjects, with a significant correlation between anti-Xa activity levels and creatinine clearance. In contrast, we found no significant

increase in mean anti-Xa activity over a 10-day treatment period in 30 elderly patients treated with tinzaparin administered once daily (175 IU/kg/24h), without any correlation between anti-Xa activity and creatinine clearance.[24] In the present study, in a larger sample of elderly patients, no correlation was observed between anti-Xa level and creatinine clearance or age, in agreement with previous data.[23,24] These results highlight that the pharmacodynamic properties of the different LMWHs are not clinically interchangeable.[3,15]

While laboratory monitoring of LMWH therapy is usually not considered necessary, it is, however, recommended in certain clinical situations such as renal failure, advanced age, obesity.[10,14,15] In our study, the monitoring of anti-Xa activity may have contributed to the safety of tinzaparin therapy at curative dose. Indeed, on one hand, it allowed the detection, and correction, of the misuse of tinzaparin in six patients. On the other hand, 20 patients with a high anti-Xa activity showed a good response to the 20% dose reduction, as shown by the subsequent decrease in the anti-Xa activity level. It is noteworthy that most of anti-Xa values did not exceed 1.5 IU/ml. Thus, the recommended upper limit of 1.5 IU/ml at peak level seems adequate for tinzaparin at curative dose.[20] The clinical relevance of such an anti-Xa monitoring and dose reduction cannot be definitely established in the present study. Nevertheless, a comparative study with and without anti-Xa monitoring would probably confirm the utility of anti-Xa monitoring in elderly frail patients. Furthermore, the observations with tinzaparin cannot be applied to other LMWHs since they have different pharmacodynamic profiles. Specific studies are needed in order to establish therapeutic levels for each LMWH preparation in special populations.

In conclusion, tinzaparin can be used safely at curative dose in very elderly patients, as long as an accurate dose is given. Case-control studies should be conducted in order to evaluate the clinical relevance of anti-Xa activity monitoring in elderly and other frail patients, especially in case of prolonged treatment with LMWH at curative dose.

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References

1. Kniffin WD, Baron JA, Barrett J. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. Arch Intern Med 1994; 154: 861-6
2. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. Arch Intern Med 1995; 155: 469-73
3. Hirsh J. Guide to anticoagulant therapy: heparin. Circulation 2001; 103: 2994-3018
4. Leizorovicz A, Simonneau G, Decousus H, et al. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis. BMJ 1994; 309: 299-304
5. Lensing AWA, Prins MH, Davidson BL, et al. Treatment of deep venous thrombosis with low-molecular-weight heparins. Arch Intern Med 1995; 155: 601-7
6. Siragusa S, Cosmi B, Piovella F, et al. Low molecular weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. Am J Med 1996; 100: 269-77
7. Gould MK, Dembitzer AD, Doyle RL, et al. Low molecular weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. Ann Intern Med 1999; 130: 800-9
8. Dolovich LR, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low molecular weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000; 160: 181-8
9. Couturaud F, Julian JA, Kearon C. Low molecular weight heparin administered once versus twice daily in patients with venous thromboembolism: a meta-analysis. Thromb Haemost 2001; 86: 980-4
10. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low molecular weight heparins. Chest 2001; 119: 64S-94S
11. Epstein M. Aging and the kidneys. J Am Soc Nephrol 1996; 7: 1106-22
12. The Thrombolysis In Myocardial Infarction (TIMI) 11A trial investigators. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. J Am Coll Cardiol 1997; 29: 1474-82
13. Bratt G, Törnebohm E, Granqvist S, et al. A comparison between low molecular weight heparin (Kabi 2165) and standard heparin in the intravenous treatment of deep venous thrombosis. Thromb Haemost 1985; 54: 813-7

14. Abbate R, Gori AM, Farsi A, et al. Monitoring of low molecular weight heparins in cardiovascular disease. Am J Cardiol 1998; 82: 331-61
15. Boneu B, de Moerloose P. How and when to monitor a patient treated with low molecular weight heparin. Semin Thromb Haemost 2001; 27: 519-22
16. Mismetti P, Laporte-Simitsitis S, Navarro C, et al. Aging and venous thromboembolism influence the pharmacodynamics of the anti-factor Xa and anti-thrombin activities of a low molecular weight heparin (nadroparin). Thromb Haemost 1998; 79: 1162-5
17. Sanderink GJ, Guimart CG, Ozoux ML, et al. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. Thromb Res 2002; 105: 225-31
18. Merli GJ. Treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin in the geriatric patient population. Clin Geriatr Med 2001; 17: 93-106
19. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-42
20. Tinzaparin French summary product characteristics. 76th rev ed. Vidal Dictionary. Paris: Vidal ed, 2000
21. Barrett JS, Hainer JW, Kornhauser DM, et al. Anticoagulant pharmacodynamics of tinzaparin following 175 iu/kg subcutaneous administration to healthy volunteers. Thromb Res 2001; 101 (4): 243-54
22. Cambus JP, Saivin S, Heilmann JJ, et al. The pharmacodynamics of tinzaparin in healthy volunteers. Br J Haematol 2002; 116: 649-52
23. Barrett JS, Gibiansky E, Hull RD, et al. Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. Int J Clin Pharmacol Ther 2001; 39: 431-46
24. Siguret V, Pautas E, Février M, et al. Elderly patients treated with tinzaparin (Innohep®) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days. Thromb Haemost 2000; 84: 800-4
25. Elalamy I, Lecrubier C, Potevin F, et al. Absence of *in vitro* cross-reaction of pentasaccharide with the plasma heparin dependant factor of 25 patients with heparin-associated thrombocytopenia. Thromb Haemost 1995; 74: 1379-87
26. Manckoundia P, Zarouala B, Lalu-Fraisse A, et al. Muscle hematoma in the very elderly receiving low-molecular weight heparins [letter in French]. Presse Med 2000; 29: 702
27. Dear Doctor Letter. LMWHs [in French]. French Drug Agency, 2001 Sep 1
28. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992; 326: 975-82
29. Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin for acute pulmonary embolism. N Engl J Med 1997; 337: 663-9
30. Tardy-Poncet B, Tardy B. Heparin induced thrombocytopenia: minimising the risks in the elderly patient. Drugs Aging 2000; 16: 351-4
31. Warkentin TE. Heparin-induced thrombocytopenia: a clinicopathologic syndrome. Thromb Haemost 1999; 82: 439-47
32. Palareti G, Hish J, Legnani C, et al. Oral anticoagulation in the elderly. Arch Intern Med 2000; 160: 470-8
33. Veiga F, Escriba A, Maluenda MP, et al. Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. Thromb Haemost 2000; 84: 559-64
34. Hull RD, Pineo GF, Mah AF, et al. Home-LITE: safety and efficacy results for a study investigating the long-term out-of-hospital treatment of patients with proximal venous thrombosis using subcutaneous low molecular weight heparin versus warfarin [abstract no. 1647]. Thromb Haemost 2001; 86 Suppl.
35. Breddin HK, Hach-Wunderle V, Nakov R, et al. Effects of a low molecular weight heparin on thrombus regression and recurrent thromboembolism in patients with deep vein thrombosis. N Engl J Med 2001; 344: 626-31
36. Monreal M, Roncales FJ, Ruiz J, et al. Secondary prevention of venous thromboembolism: a role for low molecular weight heparin. Haemostasis 1998; 28: 236-43

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