SHORT COMMUNICATION

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Modifications of Low-Molecular Weight Heparin Use in a French University Hospital after Implementation of New Guidelines

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Abstract

Background: Previous studies performed in 1999 and 2000 showed frequent misuse of low-molecular weight heparins (LMWHs) in France, leading to an increasing risk of bleeding. In 2002, the French Medicine Agency (Agence Française de Sécurité Sanitaire des Produits de Santé) released guidelines on the prescription and monitoring of LMWH. This study assesses LMWH use before and after the implementation of these guidelines.

Methods: We performed a 'pre and post' survey comparing data collected in 1999 (before guidelines) and in 2003 (1 year after guidelines) at a French university hospital. The same design and the same medical wards were used for both data-collection periods, and the data collected included patient characteristics, LWMH prescription information (daily dose, indication) and adverse drug reactions (ADRs). The main outcome was the frequency of prescription of LMWHs for curative treatment in patients with severe renal insufficiency, defined as having a creatinine clearance of ≤30 mL/min, estimated using the Cockroft formula.

Results: The analysis was performed in 332 patients in 1999 and 566 in 2003. Despite a similar frequency of prescription of LMWHs as curative treatments, the frequency with which patients with severe renal insufficiency were exposed to a LMWH as a curative treatment decreased significantly from 3.0% in 1999 to 1.0% in 2003 ($p = 0.03$). Compared with patients treated in 1999, those treated in 2003 were younger, more likely to be men, with a higher bodyweight and a shorter duration of hospitalisation. The incidence of haemorrhagic ADRs significantly decreased, with an odds ratio of 0.26 (95% CI 0.09, 0.73) according to the results of a multiple logistic regression analysis.

Conclusions: Our results show a better agreement of prescribing practice with contraindications and cautions about LMWH prescription in patients at risk following the introduction of guidelines on LWMHs. However, these data only reflect LMWH utilisation in a French university hospital. In order to assess the impact of the guidelines more widely, other studies should be performed, including studies in ambulatory care settings.

1. Background

Deep venous thrombosis and pulmonary embolism have a high prevalence among inpatients and are significant causes of morbidity and mortality.[1-6] For curative or prophylactic treatment,[7] low-molecular weight heparins (LMWHs) have been shown to be as safe and effective as unfractionated heparin (UFH); however, when used in ambulatory care for deep vein thrombosis they are more convenient for nurses and patients.[8] Thus, LMWHs have completely replaced UFH for thromboprophylaxis and are about to do the same in the field of curative treatments.

In the late 1990s, an unexpectedly high number of serious haemorrhagic adverse drug reactions (ADRs) were observed in France. In a previous study carried out in the Toulouse University Hospital, we found that these ADRs were related to the misuse of LMWHs.[9,10] Following results of a national benefit-risk evaluation of LMWHs,[11] the French Medicine Agency (Agence Française de Sécurité Sanitaire des Produits de Santé [AFSSAPS]) released guidelines about LMWH prescription and monitoring in October 2002.[12] The guidelines state that curative use of LMWHs is absolutely contraindicated in patients with a recent intracerebral haemorrhage or severe renal insufficiency (defined as having a creatinine clearance ≤30 mL/min estimated by the Cockroft formula). The use of LMWHs is also not recommended as a preventive treatment in patients with severe renal insufficiency, or as curative treatment in patients with mild-to-moderate renal insufficiency (30–60 mL/min), those with cachexia and those with unexplained bleeding. Special cautions are also outlined regarding the duration of use (maximum 10 days, 8 days for unstable angina and non-Q-wave myocardial infarction and 14 days for preventive use in medical conditions) and with regards to co-prescription of several drugs, which are not recommended (aspirin [acetylsalicylic acid], NSAIDs, oral anticoagulants and platelet aggregation antagonists). These precautions on LMWH use are especially important when treating elderly patients.

This study was undertaken to compare patterns of prescription of LMWHs and related haemorrhagic ADRs in our University Hospital before and after the introduction of these guidelines on LWMH use.

2. Methods

The study was a pre-post comparison using data collected in 1999 (previously published[9]) and in 2003. We applied the same design for the second data collection as was used for the first. All inpatients who received at least one prescription for a LMWH were included in the study and followed up until discharge from the hospital. To observe an expected decrease of at least 33% (relative risk of 0.66) in the use of LMWHs in situations in which their use is contraindicated, with a value for α of 5% and a value β of 20%, we calculated that we needed to include at least 554 patients in the 2003 study. Thus, the second study was carried out over a longer period, from January to March 2003 (1.5 months vs 1 month in 1999).

2.1 Medical Wards

Both studies were carried out in the same clinical context; that is, in the cardiology (three medical wards), geriatrics (three medical wards: cardiology, internal medicine and rehabilitation), vascular medicine and infectious diseases departments, where LMWH are principally prescribed as preventive treatment for deep vein thrombosis.

2.2 Available Low-Molecular Weight Heparins (LMWH)

At the Toulouse University Hospital, enoxaparin sodium and tinzaparin sodium were available in 1999 and 2003 and nadroparin calcium was introduced in 2003. Enoxaparin sodium was frequently used off-label for the prevention of thrombosis in certain medical conditions in 1999;[9] however, it was secondarily approved for use in this indication in France in 2000. Also in 2000, once-daily tinzaparin sodium was approved for the treatment of pulmonary embolism.

2.3 Outcomes

We defined the main outcome in this study as the frequency of absolute contraindicated use of LMWHs for curative treatment in patients with severe renal insufficiency. The secondary outcome was the frequency of at least one haemorrhagic adverse reaction. We also investigated the frequency of the use of LMWHs in patients with relative contraindications or other situations cautioned against in the AFSSAPS recommendations:

- Curative treatment in patients with mild-to-moderate renal insufficiency (30–60 mL/min);
- Thromboprophylaxis in elderly patients (aged >65 years according to our definition), patients with cachexia (weight <40kg) and having a duration of treatment of over 10 days;
- Co-prescription with drugs that increase the risk of bleeding, whatever the type of treatment.

2.4 Statistical Analysis

Data were analysed with SPSS® 11 statistical software. Comparisons between 1999 and 2003 data were performed using the Student's t-test or the Kruskall-Wallis nonparametric ANOVA for quantitative variables (presented as mean ± SD), and with Chi-squared (χ^2) test with continuity correction, or exact Fisher's test when necessary for qualitative variables.

In a second step, a multivariate analysis was performed using two models of backward stepwise logistic regression. In the first model, the dependent variable was the frequency of the primary outcome, i.e. the absolute contraindicated use of LMWHs (curative treatment in patients with severe renal impairment). Independent variables were the study period, patient characteristics (age, sex, WHO scale for autonomy),[13] the medical departments in which the patients were treated and the characteristics of LMWH treatment (indication, duration of use). In the second model, the dependent variable was the frequency of haemorrhagic adverse reactions, while the independent variables were patient characteristics, the medical departments in which the patients were treated, the characteristics of LMWH treatment and creatinine clearance. Variables retained in the final models were those with a level of significance <0.10. The change in the frequency of LMWH use in contraindicated situations and haemorrhagic ADRs between 1999 and 2003 was estimated using an odds ratio (OR) and its 95% confidence interval (CI), obtained from the results of the logistic regression.

3. Results

Characteristics of the 332 patients included in the 1999 study and of the 566 included in 2003 are presented in table I (two patients recruited in 1999 were not included in the comparative analysis due to a lack of data for the comparison). The prevalence of

Table I. Characteristics of patients included in the 1999 and 2003 studies

Characteristic	1999 study	2003 study	p-Value
Number of patients included (% of all inpatients in the period)	332 (38.0)	566 (25.4)	<0.0001
Medical wards (% of patients on ward who were exposed to LMWHs)			
vascular medicine and infectious disease	62 (25.4)	70 (16.9)	<0.0001[a]
cardiology	145 (39.9)	405 (29.0)	
geriatrics and internal medicine	125 (47.2)	91 (18.9)	
Sex (% female)	44.0	36.5	0.03
Age (years; mean ± SD)	72.5 ± 16.3	67.5 ± 15.3	<0.0001
Bodyweight (kg; mean ± SD)	67.7 ± 15.2	72.0 ± 14.5	<0.001
WHO scale for autonomy [n (%)]			
0–1	146 (44.0)	368 (65.0)	<0.0001[b]
2	63 (19.0)	110 (19.5)	
3–4	123 (37.0)	88 (15.5)	
Duration of hospitalisation (days; mean ± SD)	14.0 ± 21.3	8.8 ± 9.6	0.01
≤10 days (% patients)	211 (63.6)	427 (75.4)	<0.001[c]
11–29 days [n (%)]	91 (27.4)	111 (19.6)	
≥30 days [n (%)]	30 (9.0)	28 (5.0)	
Creatinine clearance (mL/min; mean ± SD)	61.0 ± 30.8	75.7 ± 31.8	<0.0001
Severe renal insufficiency[d] [n (%)]	48 (14.5)	31 (5.5)	<0.001
Duration of LMWH use (days; mean ± SD)	12.5 ± 19.0	7.8 ± 8.2	<0.0001

a For change in the distribution of patients across the wards.

b For change in the distribution of patients across scores on the WHO scale for autonomy.

c For change in the distribution of patients across duration of hospitalisation strata.

d Defined as having a creatinine clearance of ≤30 mL/min.

LMWH = low-molecular weight heparins.

LMWH exposure in inpatients decreased from 1999 to 2003 in all departments, the greatest decline being in the geriatrics department (−28.3%). The characteristics of the patients who were treated changed between 1999 and 2003; in 2003, patients were younger and more likely to be men, with a higher bodyweight and a shorter duration of hospitalisation. In 2003, the frequency of disabled patients (WHO scale for autonomy >2) who were treated with LMWH decreased and treated patients had a higher mean value for creatinine clearance (table I). The characteristics of medical care and of the population of inpatients in these wards did not significantly change between the two periods.

3.1 LMWH Use, Indications and Adherence to Guidelines

The median duration of exposure to LMWHs decreased from 7 days in 1999 (with one patient treated >100 days) to 5 days in 2003. This trend was observed for curative (8.0 ± 7.1 days in 2003 vs 15.7 ± 23.5 days in 1999, $p < 0.0001$) and preventive treatment (7.6 ± 8.8 days in 2003 vs 10.7 ± 15.8 days in 1999, $p = 0.003$). The characteristics of LMWH use are presented in table II. The proportion

Table II. Characteristics of use of low-molecular weight heparins (LMWHs) and co-prescribed drugs

Characteristic (n [%] patients)	1999 study (n = 332)	2003 study (n = 566)	p-Value
LMWH			
enoxaparin sodium	197 (59.3)	545 (96.3)	<0.0001[a]
tinzaparin sodium	135 (40.7)	12 (2.1)	
nadroparin calcium[b]		9 (1.6)	
Duration of use			
≤10 days (% patients)	237 (71.4)	459 (81.1)	<0.001[c]
11–29 days (% patients)	70 (21.1)	88 (15.5)	
≥30 days (% patients)	25 (7.5)	19 (3.4)	
Type of treatment[d]			
preventive treatment	256 (77.1)	443 (78.3)	0.48[e]
curative treatment	118 (35.5)	216 (38.2)	
curative treatment in patients with severe renal impairment	10 (3.0)	6 (1.1)	0.03
Indications[d]			
thrombosis (deep venous thrombosis, pulmonary embolism)	48 (14.4)	40 (7.0)	0.0001[f]
cardiologic (unstable angina, myocardial infarction)	53 (15.9)	140 (24.7)	
other (atrial fibrillation)	17 (5.1)	38 (6.7)	
Co-prescribed drugs known to increase bleeding risk (ATC codes)			
cephalosporin (J01DA)	23 (6.9)	28 (4.9)	NS
antiplatelets, oral anticoagulants (B01A)	200 (60.2)	395 (69.8)	0.004
NSAID (M01A)	7 (2.1)	14 (2.5)	NS
antiepileptic drugs (N03A)	17 (5.1)	15 (2.7)	NS
SSRI (N06AB)	18 (5.4)	22 (3.9)	NS

a For change in the distribution of LMWH used between 1999 and 2003.

b Nadroparin calcium was introduced at Toulouse University Hospital in 2003.

c For change in the distribution of duration of use between 1999 and 2003.

d Total exceeded 100% because some patients were treated for more than one indication.

e For change in the distribution of preventive vs curative use between 1999 and 2003.

f For change in the distribution of indications between 1999 and 2003.

ATC = Anatomical Therapeutic and Chemical classification (WHO); **NS** = not statistically significant; **SSRI** = selective serotonin reuptake inhibitor.

of patients receiving LMWH for curative treatment was similar in both time periods (38.2% in 2003 and 35.5% in 1999, NS; see table II), but a greater proportion of patients were receiving treatment for cardiologic indications in 2003. We observed a significant decrease in the use of LMWHs as a curative treatment in patients with severe renal insufficiency in 2003 compared with 1999, and this decrease remained significant (OR 0.3, 95% CI 0.17, 0.52) after adjustment for confounding variables related to differences between the treated populations in 1999 and 2003 (age, sex, WHO scale for autonomy, medical wards, indication, duration of use).

3.2 Co-Prescribed Drugs

Most patients were exposed to between six and nine other drugs (52% in 1999 and 62% in 2003). The proportion of patients exposed to drugs associated with a high risk of bleeding, i.e. aspirin, antiplatelet agents or oral anticoagulants, was significantly higher in 2003 (table II).

3.3 Adverse Drug Reactions (ADR)

In 1999, 36 of 332 patients experienced an ADR (10.8%) versus 17 of 566 in 2003 (3.0%, $p < 0.0001$). The frequency of haemorrhagic adverse reactions was lower in 2003 than 1999 (1.1% vs 4.5% of patients; $p = 0.004$). All six haemorrhagic ADRs that occurred in 2003 were serious (two men, four women; age range 43–93 years; one case resulted in death [cerebral haemorrhage in a 75-year old woman who had a creatinine clearance of 45 mL/min and was treated for 4 days for medical prophylaxis]). Treatment was curative in three cases, but none of the patients had severe renal insufficiency.

Table III shows the results of the model of the multiple logistic regression analysis that investigated the factors associated with haemorrhagic ADRs. We observed a significant decrease in these ADRs in 2003 compared with 1999. The only factor other than the study period that remained significantly associated with these ADRs in the multivariate analysis was the creatinine clearance rate.

Table III. Results of the multiple logistic regression model for the incidence of haemorrhagic adverse reactions

Variables	Odds ratio	95% CI
Study period (2003 vs 1999)	0.26	0.09, 0.73
Creatinine clearance (per mL/min decrease)	0.96	0.94, 0.99
Age (per year increase)	1.02	0.96, 1.08
Sex (female vs male)	0.89	0.32, 2.46
Autonomy according to WHO scale		
0–1	1	
2	8.55	1.76, 41.43
3–4	5.79	1.47, 22.77
Curative vs preventive treatment	1.35	0.53, 3.43
Duration of treatment (per day increase)	1.00	0.97, 1.03
Wards		
geriatrics and internal medicine	1	1
vascular medicine and infectious disease	0.89	0.15, 5.36
cardiology	0.53	0.13, 2.07

4. Discussion

Our study found a significant decreased of use of LMWHs in contraindicated indications between 1999 and 2003. In parallel, we observed a significant decrease in haemorrhagic ADRs in exposed patients. These differences could be due to differences between the two populations of patients treated in the hospital during these two time periods, but could also be due to the impact of the guidelines introduced in 2002.

In 2003, patients who were treated with LMWHs were younger and healthier than those included in the 1999 study. This could suggest that fewer patients in the hospital in 2003 required LMWHs, but the data do not suggest that the number of patients treated in our hospital and their characteristics have changed from 1999 to 2003. The medical wards involved in the study (vascular medicine and infectious disease, cardiology, geriatrics and internal medicine) were the same in the two periods and they were chosen because a high proportion of patients in

these wards need treatment with LMWH. The population of patients hospitalised in these wards is generally elderly, have several comorbidities and are exposed to many medications, especially drugs known to increase the risk of bleeding.[14] Despite the stability of the hospital activity, we observed a widening of the medical indications of the LMWHs in 2003. In the cardiology department, the prescription of LMWHs to patients with cardiac arrhythmia increased. By contrast, fewer patients from geriatric wards were exposed to LMWHs in 2003 compared with 1999. Since the total number of inpatients in geriatric wards was similar in 1999 and 2003, two hypotheses could explain this decrease. Firstly, elderly patients hospitalised in 2003 needed less frequent thrombosis prevention or were less frequently affected by pulmonary embolism or cardiac indications for LMWHs; however, this was not confirmed by hospital medical databases. On the other hand, hospital doctors may prefer to use UFH in patients with renal insufficiency (even of mild or moderate severity), although use has not been evaluated in elderly patients.[15,16] The analysis of the evolution of anticoagulation prescription using data from the computerised system of individual prescriptions of the geriatric department may support this second hypothesis. Between December 2000 and December 2002, prescription of UFH dramatically increased (+ 295.3%), whereas LMWH utilisation decreased by 22.6% during the same period. Examination of changes in the use of UFH and the occurrence of haemorrhagic complications of UFH use would have been interesting, but this was not possible because such an analysis was not planned in 1999. However, no increase was observed in the frequency of haemorrhagic reactions related to UFH use in the elderly that were reported to the regional pharmacovigilance centre. We could hypothesise that, despite the constraints of monitoring, especially in elderly patients, physicians chose to use UFH instead of LMWHs because of the high risk for bleeding in this particular population that frequently has renal impairment.[17,18]

To test the potential impact of the French guidelines of the AFSSAPS, a 'pre- and post-' comparative design was the most appropriate for this study, which was performed in the context of one university hospital.[19] We already had data concerning the use of LMWHs in our hospital before the national pharmacovigilance study[11] and the implementation of guidelines.[9] In order to minimise bias due to the nonrandom comparison, we applied, as strictly as possible, the same method for the data collection, and recruitment was performed in the same medical wards in order to provide similar populations of patients. Because of the limits of nonexperimental observational studies, it is not possible to determine if the observed differences are partially due to the effects of guidelines or to spontaneous evolution. The differences could also be due to differences in the medical use of LMWHs or in the population treated in this tertiary hospital. In order to minimise bias due to these last points, we tried to take into account most of factors related to modifications of prescription (changes in the indications for LMWHs, changes in the characteristics of patients) in a multivariate analysis. In fact, the logistic regression found that the prescription of LMWHs in contraindicated situations remained independently and significantly associated with the time period, after adjustment for these confounding factors.

This study outlines changes in doctors' attitudes towards prescribing LMWHs in our hospital. Almost all prescriptions were in agreement with the new guidelines in 2003. The significant decrease of haemorrhagic ADRs was probably related to these changes in use. In most cases (5 of 6) that occurred in 2003, the patient was aged >70 years; however, for all these patients, the dose of LMWH had been previously adjusted in accordance with renal function. No ADRs were observed in patients with severe renal impairment. This suggests that doctors

had probably estimated creatinine clearance in patients with a high risk of haemorrhagic ADRs before prescribing and had chosen to use UFH in combination with careful monitoring instead of LMWHs. There is no absolutely safe anticoagulation treatment with regards to the risk of bleeding in elderly patients or patients with impaired renal function. Thorevska et al.[20] found no statistically significant difference in the incidence of major bleeding between patients who received twice-daily administration of enoxaparin sodium and those who received UFH, whatever their renal function. In a large randomised trial comparing enoxaparin sodium with UFH in high-risk patients with non-ST segment-elevation coronary syndromes, the LMWH was found to be a safe and effective alternative to UFH.[21] However, the authors emphasised that the greater convenience with enoxaparin sodium should be balanced with the excess of major bleeding.

5. Conclusion

In 2003 compared with 1999, this study found a significant decrease in the frequency of use of LMWHs in contraindicated conditions in the Toulouse University Hospital. In parallel, the frequency of haemorrhagic ADRs decreased. These differences could be due, in part, to the effects of the national French guidelines published in 2002. The decrease in LMWH use was mainly in elderly people, whereas the number of patients treated with unfractionated heparin in geriatric wards has increased, without an apparent increase of the number of reported haemorrhagic ADRs. However, because of the 'pre-post' design of this study, it is not possible to definitively conclude that these changes are related to the implementation of guidelines. Despite these limits, this study shows rational use of drugs has a positive impact on medical practice, at least by improving the safety of the use of drugs.

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