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Severe bleeding secondary to misuse of fondaparinux: a case report

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Abstract Venous thromboembolism (VTE) remains a great challenge because of its frequency and of its potential severity. However, VTE treatment can also lead to iatrogenic complications. We report a case of thigh haematoma by a 83-year-old woman under fondaparinux for a solear thrombosis. Then we discuss the indications of Unfractionated Heparin (UFH), Low-Molecular-Weight Heparins (LMWH) and Fondaparinux, which are the three classes of rapidly acting anticoagulant treatments nowadays available. As their efficacy is comparable, the choice between these classes relies on the risk of adverse effects, which depends on some patient's characteristics. LMWH and fondaparinux are contra-indicated by the patients with a renal clearance under 30 ml/min. Only UFH are authorised during the whole pregnancy even though LMWH are more and more used. Fondaparinux has proven its safety by patients over 100 kg. UFH requires a daily biological management whereas it is optional for LMWH and fondaparinux, as long as their contra-indications are taken into account. No Heparin-induced-thrombocytopenia Syndrome (HIT-Sd) has been proven yet under fondaparinux so that platelets management seems not necessary, contrary to UFH and LMWH which require a twice-weekly platelets count. The accuracy of the therapeutic indication should result in the best benefit/risk assessment.

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Introduction

The treatment of venous thromboembolism (VTE) still remains a major challenge, since venous thrombosis and pulmonary embolism are common [1] and account for life-threatening diseases [2]. Anticoagulant therapy is particularly tricky for elderly patients [3] and for patients with renal impairment [4]. For these patients the therapeutic margin is narrow. The prevention of the bleeding adverse effects such as haematoma or severe haemorrhage requires acute monitoring of the anticoagulation level. Until recently, patients were firstly administered for a few days heparin (usually low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) in case of renal impairment), which allows vitamin K antagonists (VKA) to reach an adequate level of anticoagulation within usually four days; VKA were then administered *per os* for 3–6 months according to the presence of pulmonary embolism. In the late 90s, fondaparinux, a new anticoagulant, has been evaluated in several studies: this synthetic pentasaccharide improves the ability of antithrombin to inactivate specifically the factor Xa, and therefore limits the coagulation process [5]. One of the foresights of fondaparinux is the probable absence of heparin immuno-induced thrombocytopenia. Nevertheless, as every anticoagulant, fondaparinux can induce major bleeding. We report the case of an 83-year-old woman who underwent a thigh major haematoma with neurological complications, due to a treatment by fondaparinux, prescribed to cure a deep venous thrombosis, whereas she presented renal impairment.

Case report

An 83-year-old woman consulted her general practitioner because of persistent pain in the left calf, 3 weeks after an accidental fall in the stairs. Her previous diseases were chronic renal impairment, arterial hypertension, hypercholesterolemia and bilateral total hip-replacement. Her treatment comprised piribedil (TRIVASTAL®) 20 mg a day, bromazepam (LEXOMIL®) 3 mg a day, and furosemide (LASILIX®) 20 mg a day.

Phlebitis was suspected and eventually confirmed by a venous echo-Doppler of the inferior limbs (day 1); the radiologist concluded "high suspicion of sural venous thrombosis concerning the solear veins at the superior third of the left calf".

Therefore, the general practitioner prescribed fondaparinux 7.5 mg/day subcutaneously. After the third injection, the patient noticed an augmentation of the volume of her left thigh (day 3). She consulted at the emergency ward of our hospital on the following day (day 4).

There was no fever; pulse was at 97/min and arterial pressure at 152/85 mmHg. Physical examination showed a haematoma from the medium third of the left thigh to popliteal fossa, and an increase of the perimeter of the whole left inferior limb. The foot was warm showing an adequate perfusion of the limb. Pain was acute, but there was no argument toward acute compartment syndrome. There was a hyposensitivity in the external sciatic-popliteal territory. Motility was hard to evaluate initially because of the pain, but a paresis of the elevator and extensor of the left foot was confirmed on the following days.

There was no argument toward pulmonary embolism complicating the thrombosis: the patient showed no dyspnoea and lung auscultation was normal. There was no argument toward a neoplasia explaining the thrombosis (in particular no breast nodule, no adenopathy).

She presented anaemia at 6.7 g/dl, and anti-Xa activity was at 2 UI/l. Creatininemia was at 133 µmol/l, with a clearance calculated at 24 ml/min, using the Cockroft & Gault formula. There was also an inflammatory syndrome (C reactive protein at 87 mg/l) with rise of the neutrophils at 19,000/mm^3 and a hypokaliema at 2.6 mmol/l.

A tomography found neither vascular compression by the haematoma nor tumourous process.

She received at the emergency ward three 250 ml red blood cell units.

As no surgical indication was established, she was admitted in a cardiology ward, and fondaparinux was immediately stopped, despite the confirmation of the thrombosis by a new venous echo-Doppler. Fortunately, she presented no pulmonary embolism during this thrombosis event. She benefited from a foot splint and could walk again with a crutch.

An echo-Doppler four days later (day 8) found no intraluminal thrombus in the superficial venous network.

Two weeks later (day 22), another echo-Doppler revealed the persistence of an isolated thrombus at the superior third of an internal left twin vein; moreover, a voluminous blood collection was still present at the posterior side of the thigh, measured 15 cm by 3 cm. She was treated by UFH with careful monitoring.

Eventually, she was discharged to stay in a convalescence hospital where she underwent rehabilitation. Three months later, only partial recovery of the paresis was revealed by an electromyogram. Three more months of rehabilitation were decided; she could undergo arthrodesis in case of lack of improvement.

Finally, the outcome of this haematoma due to misuse of fondaparinux resulted in a blood red cell transfusion, a one-month-long hospitalisation, (including Christmas and New Year's Day), followed by a six-month-long rehabilitation. This case report was notified to the French pharmacovigilance center.

Discussion

In this case, indication of anticoagulant treatment was indisputable but fondaparinux was not the right choice. Adequate prescription of anticoagulant drug must include proven-efficacy therapeutics but must also consider individual patients' characteristics. Elderly patients need special attention because of age-related renal impairment, drug associations which may increase the interaction probability and the occurrence of adverse drug event, and patient isolation which may stand in the way of medical consultation. In the topic of anticoagulation by the elderly, balance and falls are too a major outcome in the treatment decision. Benefit-risk assessment must therefore be systematic and patient-adjusted, and the different factors must be organized into a hierarchy so that the best compromise is reached. The efficacy of heparins (LMWH or UFH) and fondaparinux has been proven for the treatment of phlebitis by well-designed studies [6–8]. They are the three types of drugs available for this indication in France. As these drugs have comparable efficacy, we examined their side effects (considering also their gravity and frequency), their acceptability by the patient and eventually their price in a medico-economic perspective. We did not examine danaparoid nor hirudin as they are not first-intention treatments.

Main features of UFH, LMWH and fondaparinux are compared in Table 1.

This table underlines that a creatinine clearance under 30 ml/min is a contra-indication for LMWH and fondaparinux; patients with clearance between 30 and 60 ml/min

Table 1 Comparison of unfractionated heparins (UFH), low-molecular-weight heparins (LMWH) and fondaparinux

	UFH	LMWH	Fondaparinux
Common contra-indications	Haemorrhagic events including haemorrhagic stroke and gastric or duodenal ulcer, recent neurosurgery or ocular urgery (a period of 3 weeks is usually admitted), bacterial endocarditis, pericardial effusion, severe arterial hypertension		
	Drug hypersensitivity		
	Intra-muscular injection, intra-articular or intra-arterial puncture or injection, sympathetic infiltration		
Specific contra-indications	Previous heparin-induced thrombopenia		
		Renal failure (creatinine clearance <60 ml/min for curative treatment)	Renal failure (contra-indicated if creatinine clearance is under 30 ml/min, cautious use if between 30 and 50 ml/min)
		Pregnancy and breastfeeding	
Inadvisable associations	Non-steroidal anti inflammatory drug, acetyl-salicylic acid and related drugs, ticlopidin		
Cautious associations	VKA, corticosteroids, dextrans, thrombolytics		
Common Adverse effects[a,b]	Haemorrhagic events in case of overdose or in case of bleeding lesion		
	1.1% of the patients	1.2% of the patients	1.2% of the patients
Specific adverse effects[c,d]	Heparin-induced Thrombocytopenia (3% of the patients)	Heparin-induced Thrombocytopenia (0,3% of the patients)	No immunologic thrombocytopenia[e]
	Haematoma or cutaneous necrosis at the injection site, urticarial lesions, rash, transaminases elevation, hypereosinophilia, hyperkaliemia, hypoaldosteronism	Haematoma or cutaneous necrosis at the injection site, allergic reaction, thrombocytosis	Anaemia, non-immunologic thrombocytopenia, headache, vertigo, nausea, vomiting, liver function disorder, rash or reaction at the injection site, urea elevation
	Alopecia, osteopenia in case of long lasting treatment (more than one month)	Osteopenia in case of long lasting treatment (more than one month)	
Administration	Slow intravenous injection	Subcutaneously once or twice a day	Subcutaneously once a day
	or		
	Subcutaneously twice or three times a day		
Efficacy Monitoring	Activated partial thromboplastin time daily and 4 hours after every change of dosage	Anti-Xa activity (non systematic; when indicated: no recommended frequency)	None
Tolerance Monitoring	Platelets twice weekly for 3 weeks then once weekly		None
Antidote	Protamine sulfate	Protamine sulfate	No specific antidote
Half-life[f,g,h,i,j]	About 1.5 h	3–4 h (enoxaparin) 4 h (dalteparin) 3.5 h (nadreparin) and 2 h (tinzaparin)	17–21 h

Table 1 continued

	UFH	LMWH	Fondaparinux
Hindsight	About 60 years[k]	About 20 years[l]	About 13 years[m]
Origin	Porcine gut (not cow because of the risk of bovine spongiform encephalopathy)	UFH, so porcine gut	Synthetic thus no contamination from pathogenic animal agent

[a] The Matisse Investigators [8]
[b] The Matisse investigators [36]
[c] Warkentin et al. [37]
[d] Dinwoodey and Ansell [38]
[e] Duchaussoy et al. [39]
[f] ARIXTRA [18]
[g] FRAGMINE [package insert]. Pfizer Inc. 1996
[h] FRAXIPARINE [package insert]. GlaxoSmithKline Inc. 2005
[i] INNOHEP [package insert]. Leo pharma Inc. 2005
[j] LOVENOX [package insert]. Sanofi Synthelabo Inc. 2005
[k] Hyers [35]
[l] Hirsh et al. [40]
[m] Boneu et al. [5]

for LMWH, 30 and 50 ml/min for fondaparinux, can receive only a prophylactic antithrombotic treatment by LMWH or fondaparinux. As the creatinine clearance decreases by 1 ml/min/year after 20, it is very important to consider that patients older than 80 are *systematically* exposed to excessive doses. Some authors have therefore argued that only UFH should be used by the elderly, or that the LMWH dosages should be lowered for this population, although no study evaluated this assessment. Systematic anti-Xa activity monitoring has also been proposed [9]. UFH requires either a continuous intravenous injection or a twice to three times daily subcutaneous injection, and at least a once daily biological control. LMWH requires a twice daily injection subcutaneously, except tinzaparin and nadroparin administered once daily, and do not expressly necessitate biological control. When it is needed, anti-Xa activity reflects the anticoagulation level. Fondaparinux requires a once daily subcutaneous injection. It does not have a reference parameter yet, but interestingly in one study fondaparinux blood concentration was measured by 333 patients by inhibition assay and expressed by the area under the curve in mg h/l after 4 days of treatment [7]. The reference values were, respectively, 15.1, 19.7 and 22.9 mg h/l for dosages of 5, 7.5 and 10 mg per day. More recently a new system called Sonoclot has been evaluated in this purpose [10]. Lastly, some authors propose to use an anti-Xa activity assay calibrated with fondaparinux instead of LMWH [11].

Regarding the adverse effects, the major one remains bleeding, because of its frequency and its gravity with possible life threat [12, 13]. A recent prospective study on renal insufficient patients presenting a deep venous thrombosis and treated with anticoagulants (UFH, LMWH and/or VKA) showed that the main cause of death among them in the first three months of treatment was bleeding and not pulmonary embolism [14]. In studies comparing UFH and enoxaparin to fondaparinux, major bleeding was occurring in 1.1% of the patients treated by UFH (*versus* 1.3% for fondaparinux) [8], and 1.2% by the patients treated by enoxaparin (*versus* 1.1% for fondaparinux) [15].

Three major studies evaluated fondaparinux in the treatment of deep venous thrombosis and pulmonary embolism, including altogether 3,764 patients [7, 8, 15].

In the Rembrandt study, several doses of fondaparinux were compared to dalteparin (Table 2). Only patients with a weight between 50 and 100 kg and without known renal insufficiency were included [7]. Groups of treatment comprised between 103 and 119 patients. Interestingly, the authors reported major bleedings in two periods: the first from the initiation of the treatment to two days after the end of the studied drug administration, the second from the end of the first period until the end of follow-up. Regarding the pharmacokinetic characteristics of fondaparinux

Table 2 Overview of studies about fondaparinux

Study	Aim	Population	Efficacy	Adverse events	Mortality
The Rembrandt Investigators *Circulation* 2000	Fondaparinux *versus* dalteparin in the treatment of deep vein-thrombosis	396 patients Meanage 61	*Recurrent venous thromboembolism*: Fondaparinux: 2.4% Dalteparin: 5.0%	*Major bleeding*: fondaparinux 1.8% dalteparin: no event *Non-immunological thrombocytemia*: data not provided *HIT*: data not provided	Fondaparinux 4.5% Dalteparin: 7.6%
The MATISSE Investigators *New EnglandJournal of Medicine* 2003	Fondaparinux *versus* unfractionated heparin in the treatment of pulmonary-embolism	2213 patients Meanage 62	*Recurrent venous thromboembolism*: Fondaparinux: 3.8% Unfractionated heparin: 5.0%	*Major bleeding*: fondaparinux 1.3% unfractionated heparin 1.7% *Non-immunological thrombocytemia*: fondaparinux 0.9% unfractionatedheparin: 1.2% *HIT*: no anti-PF4 antibodies	Fondaparinux 5.2% Unfractionated heparin: 4.4%
The MATISSE Investigators *Ann Intern Med* 2004	Fondaparinux *versus* enoxaparin in the treatment of deep vein-thrombosis	2,205 patients Meanage 61	*Recurrent venous thromboembolism*: Fondaparinux: 3.9% Enoxaparin: 4.1%	*Major bleeding*: fondaparinux 1.1% enoxaparin 1.2% *Non-immunological thrombocytemia*: fondaparinux 0.6% enoxaparin: 0.6% *HIT*: no event	Fondaparinux 3.8% Enoxaparin: 3.0%

HIT Heparin induced thrombocytopenia

All the results are not statistically different as presented in the table

(half-life of about 17 h [16]) and the characteristics of the studied population (no renal insufficiency), it seems to us more logical that one should consider only the first period because the adverse effect occurring during the second period do not result from fondaparinux or dalteparin treatment, but rather from VKA treatment. Shorr [17] subscribes moreover to this point of view. Although incidence of "all bleeding" was in favour of fondaparinux (incidence rate calculated from the article data: 1.2% patient-day for 5 mg/day, 1.2% patient-day for 7.5 mg/day, paradoxically 0.7% patient-day for 10 mg/day, 1.6% patient-day for dalteparin), major bleeding occurred exclusively by patients under fondaparinux during the first period (incidence rate calculated from the article data: 0.4% patient-day for 5 mg/day, 0.3% patient-day for 7.5 mg/day, 0.1% patient-day for 10 mg/day; no major bleeding for dalteparin). The authors nevertheless detailed the causes of these major bleedings: four occurred at the site of malignant lesions, one was related to an INR of 4.7 and the latter was a large muscular haematoma at an injection site in a patient placed in the fondaparinux 10 mg/day group. This case seems very similar to ours, if we assume that injecting a renal insufficient patient 7.5 mg/day of fondaparinux equals to a 10 mg/day (or more) treatment. Even though the incidences are too few to conclude to a statistical relevance, the occurrence of major bleeding only under fondaparinux cannot let us incurious.

In another study [15], fondaparinux was compared to enoxaparin in deep venous thrombosis treatment. The weight range of the 2,205 included patients was larger but only 22 patients treated by fondaparinux weighted less than 50 kg. One of the exclusion criteria was creatininemia over 177 µmol/l, without clearance calculation. On the other hand, creatinine clearance was calculated by included patients, and it is interesting to note that it was missing in 18 patients treated by fondaparinux and 12 patients treated by enoxaparin; this shows that even in the controlled studies we are facing "real life" concerns. Fondaparinux and enoxaparin dosages were adapted to the patients' weight (fondaparinux: 5.0 mg/day if weight <50 kg, 7.5 mg/day if 50 kg < weight <100 kg, 10.0 mg/day if weight >100 kg; enoxaparin: 1 mg/kg twice-daily). Only 25 patients with clearance under 30 ml/min were treated by fondaparinux. Defined observation periods of major bleeding were adapted to creatinine clearance. The results showed no difference between fondaparinux and enoxaparin in terms of global mortality, but we can note that two deaths (with supra-therapeutic INR) were related to major bleeding during the initial period of treatment by fondaparinux, whereas no death related to major bleeding occurred in the enoxaparin group; the number of deaths related to pulmonary embolism was the same in the two groups. There was no difference in terms of major bleeding between the two groups, when we consider the whole population of each group. The mean duration of treatment was provided for the two groups of treatment; if we extrapolate this duration to sub-groups of patients determined upon their creatinine clearance, the incidence of major bleeding is, respectively, 1.1% patient-day (clearance <30 ml/min, fondaparinux), 0.8% patient-day (clearance <30 ml/min, enoxaparin), 0.1% patient-day (clearance >30 ml/min, fondaparinux), 0.2% patient-day (clearance >30 ml/min, enoxaparin). The difference between <30 ml/min and >30 ml/min groups of fondaparinux treated patients in terms of major bleeding is statistically relevant ($P < 0.01$, χ^2 test). Unfortunately, data provided in the article cannot allow us to calculate the specific incidence of patients with a creatinine clearance between 30 and 50.4 ml/min (0.84 ml/s). The same calculation is possible with groups determined upon the patient's weight; incidence of major bleeding is, respectively, 0.5% patient-day (weight <50 kg, fondaparinux), 0.2% patient-day (50 kg < weight <100 kg, fondaparinux), 0 for >100 kg patients under fondaparinux, 0 for <50 kg patients under enoxaparin, 0.2% patient-day (50 kg < weight <100 kg, enoxaparin), 0.1% patient-day (weight >100 kg, enoxaparin). It seems therefore that low weight is not a statistically established bleeding risk factor.

A third study compared fondaparinux to UFH in the treatment of pulmonary embolism [8]. A total of 2,213 patients with a creatininemia under 177 µmol/l were included; again only 22 patients treated by fondaparinux weighted less than 50 kg. With the same limits as above, we can calculate the incidence of major bleeding during the initial treatment; they are, respectively, 1.2% patient-day (clearance <30 ml/min, fondaparinux), 0.5% patient-day (clearance <30 ml/min, UFH), 0.2% patient-day (clearance >30 ml/min, fondaparinux), 0.1% patient-day (clearance >30 ml/min, UFH). The difference between <30 and >30 ml/min groups of fondaparinux treated patients in terms of major bleeding is statistically relevant ($P < 0.01$, χ^2 test).

It seems therefore that

1. only creatinine clearance is a risk factor for major bleeding,
2. incidence of major bleeding under fondaparinux by patients with creatinine clearance <30 ml/min is about 1.1% patient-day,
3. incidence of major bleeding under fondaparinux by patients with creatinine clearance >30 ml/min is about 0.1% patient-day.

Age appears not to be an independent risk factor of bleeding according to the data of the monograph given by the manufacturer [18]; it seems implicated only via the renal function impairment related to age, already

considered in the Cockroft–Gault formula (although the extrapolation of this formula by patients over 70 can be discussed [19]). Even if it does not stand for a risk factor, the fact remains that the elderly are more fragile patients, prone to fall and to present adverse drug events.

Recently the French Health Products Safety Agency has recorded between 1 January 2005 and 31 January 2007, 122 haemorrhagic incidents with use of fondaparinux. Most of these adverse drug events involved more-than-75-year-aged patients or patients with renal insufficiency [20]. Unfortunately precise data are not yet available so that we cannot evaluate the prevalence per patient-day of exposure in "real life" neither check the absence of renal failure by over-75-year-old patients.

No specific antidote is available for fondaparinux, even though some authors suggest the use of recombinant activated factor seven [21, 22], which does not play the same role as protamine sulfate does for heparins. The experts from the 7th ACCP conference [23] recommend to inactivate 100 UI of LMWH with 1 mg of protamine sulfate, and to add half this dosage if the bleeding goes on. Smaller doses are required if the LMWH injection lasts from more than 8 h. On the contrary recombinant factor seven does not bind to the fondaparinux and is not a specific antidote.

Heparin-induced thrombocytopenia (HIT), the second most endangering adverse effect, occurs more often by the patients treated with UFH (3%) than by the ones treated with LMWH (0.3%) [24]. Its reality is discussed by the patients treated by fondaparinux. Pathophysiological studies have increased our knowledge of what can be called HIT-syndrome (HIT-Sd); we must distinguish non-immunological type 1 thrombocytopenia—benign and related to a direct pro-aggregating effect of the heparins on the platelets, the presence in the serum of anti heparin-platelet-factor-four antibodies, and finally a clinically expressed HIT-Sd related to a type 2 immunological thrombocytopenia [25]. It seems much more interesting to evaluate the incidence of clinically expressed HIT-Sd, than only the incidence of thrombocytopenia even associated with anti-heparin-platelet-factor-four antibodies. UFH are usually described to cause more HIT than LMWH [26], although this point is sometimes discussed. A prospective study noticed HIT by 0.8% of 1,754 patients under LMWH (principally nadroparin and dalteparin) [27]. The same author conducted a similar designed prospective study by patients under UFH; HIT-prevalence was 0.84%, associated with a 60% risk of clinical expressed thromboembolic complications [28]. The minimal size required to induce anti-heparin-platelet-factor-four antibodies has been identified as a tetrasaccharide [29]; however, a 10–12 saccharides length is necessary to obtain a strong reactivity with anti-heparin-platelet-factor-four antibodies. Therefore, the pentasaccharide fondaparinux was expected not to create HIT-Sd, and few anti-heparin-platelet-factor-four antibodies, contrary to LMWH which median size is 15 saccharides [23]. Warkentin found an identical rate of presence of anti-heparin-platelet-factor-four antibodies by patients in surgical ward previously treated by fondaparinux or LMWH, but none of the fondaparinux-treated patients presented HIT-Sd [30]. Only one case of thrombosis related to an immunological thrombocytopenia by a patient under fondaparinux has been recently published [31]. It was a 48-year-old woman who underwent bilateral knee replacement. On day 7, she was diagnosed deep venous thrombosis with bilateral adrenal infarction. She presented also thrombocytopenia and anti-heparin-platelet-factor-four antibodies. However, the causal relationship between fondaparinux and the thrombosis complications in this case is still strongly discussed. Moreover, fondaparinux has even been proposed as a treatment in HIT-Sd [32]. No case of thrombocytopenia was reported in the Rembrandt study; 7 cases were described in each group of treatment in the deep venous thrombosis study of the Matisse investigators, with no anti-heparin-platelet-factor-four antibodies. In the Matisse investigators pulmonary embolism study, ten patients amongst 1,103 presented a thrombocytopenia, but no patient had anti-platelet antibodies. Considering the current state of knowledge, we can argue that platelets count is not necessary in case of fondaparinux treatment because even if thrombocytopenia was found, treatment would not be changed, because of the absence—or negligible incidence—of the risk of HIT-Sd. This represents the main foresight of fondaparinux.

UFH and LMWH may lead to other adverse drug events such as osteoporosis, which is a real concern in the elderly. Data about the other adverse drug events of fondaparinux are poor.

Concerning the upper weights, contrary to enoxaparin, fondaparinux has proven a safe efficacy by patients with a Body Mass Index over 27 kg/m^2 [33].

Once efficacy and safety are well demonstrated, pharmacoeconomic concerns are also a major point, because of the prevalence of thromboembolic phenomena and because of the length of the treatment. Bénard and his colleagues evaluated the worldwide annual incidence of deep venous thrombosis between 60 and 100 per 100,000, and the worldwide annual incidence of pulmonary embolism between 23 and 107 per 100,000 [1]. LMWH had already proven their cost-effectiveness versus UFH [34]. Fondaparinux has been evaluated to be cost-effective versus enoxaparin [21]. Towards a whole home treatment, on the one hand fondaparinux provides a simply using syringe, which simple use has been assessed in studies [15], on the other hand, it is more comprehensible to calculate a dose per kg as it is done for the LMWH, than to prescribe the same dosage for patients from 50 to 99 kg, all the more so

as no follow-up is required. However, given that this dosage setting has been assessed in well-designed studies, this range of only three dosages leads to less product spoiling and represents an economic foresight.

In this context, pharmacists play a key role in the follow up of the recommendations of the French Health Products Safety Agency and in the supervision of the renal function in biochemistry. They must notify any event within the framework of pharmacovigilance.

Moreover, pharmacists help practitioner in his prescription providing him some informations about new therapeutics. Rivaroxaban is a new anticoagulant drugs put in the market in France but they will be manipulated with caution when creatinine clearance is between 15 and 30 ml/min. Finally, a monitoring of age and clearance are necessary to optimise treatment.

Conclusion

In our case, fondaparinux as well as LMWH were contra-indicated and should not have been prescribed, as UFH are effective and can be used by renal-insufficient patients. Risks must be organized into a hierarchy according to their gravity and incidence by every single patient; considering the bleeding risk is much more important than considering the risk of HIT-Sd, or the pharmacoeconomic issues. In this case, the costs resulting from the complications were in the end much higher than the ones saved by the absence of initial hospitalization. As the use of UFH implies usually a hospitalization, patients with renal impairment presenting a deep venous thrombosis should all be hospitalized. This statement is obviously valid for patients presenting a pulmonary embolism. Lastly, practitioners should keep acute attention to patients with renal impairment and systematically check the absence of contra-indication, all the more when a choice between several treatments is available. We are still waiting for the ideal anticoagulant which characteristics have been described by Thomas M. Hyers in 2003 [35].

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