Safety and efficacy of thromboprophylaxis with fondaparinux in elderly acutely ill medical patients with renal impairment: a retrospective single center study

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ABSTRACT

The majority of acutely ill medical patients are elderly with some degree of renal impairment. In this setting, venous thromboembolism (VTE) is one of the leading causes of morbidity and mortality and, to reduce this risk, a correct thromboprophylaxis is needed. The aim of this single center retrospective study was to assess the safety and efficacy of fondaparinux in elderly acutely ill medical patients with renal impairment. All patients aged 60 years or over, bedridden for at least four days, with a creatinine clearance (CrCl) of 50 mL/min or under, and who had received fondaparinux during hospitalization were evaluated and followed for up to 90 days after discharge. A total of 125 patients were evaluated (34.4% males); median age was 83.0 years. Median duration of thromboprophylaxis was 9.0 days. Forty-one (32.8%) patients were treated with fondaparinux 1.5 mg daily, 84 (67.2%) with 2.5 mg daily. Inappropriately high doses of fondaparinux were used in 77 patients with CrCl 20-50 mL/min, in 12 patients with CrCl below 20 mL/min, in 14 patients with prothrombin time (PT) ratio over 1.2, in 8 patients with PT ratio over 1.5, and in 3 patients with thrombocytopenia. No episodes of VTE or of major bleeding were recorded while there were 6 episodes (2.4%) of minor bleeding. Both dosages of fondaparinux showed similar safety and efficacy. Twenty-six patients (20.8%) died; no cause of death was related to fondaparinux. In conclusion, in elderly acutely ill hospitalized medical patients with renal impairment, prophylaxis with fondaparinux 2.5 or 1.5 mg daily is safe and effective in preventing VTE without increasing bleeding risk.

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Introduction

Back in 1991, Anderson *et al.*[1] demonstrated that the annual incidence of venous thromboembolism (VTE) among adults progressively increases with age, reaching 500-600 cases per 100,000 of the population over the age of 80 years, which is the median age of the population of most divisions of Internal Medicine in Western countries.

Furthermore, VTE is one of the leading causes of morbidity and mortality in acutely ill medical patients. In fact, the incidence of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) has been reported to range between 10% and 30% in hospitalized medical patients, a figure similar to that of surgical patients,[2] and PE is thought to be associated with 5-10% of deaths of hospitalized patients, most of whom are medical patients.[3] Large randomized controlled trials have demonstrated that prophylaxis with anticoagulant drugs reduces the risk of VTE,[4-6] and in 2012 the American College of Chest Physicians (ACCP) recommended anticoagulant thromboprophylaxis with low molecular weight heparin (LMWH), low-dose unfractionated heparin, b.i.d., t.i.d., or fondaparinux (all Grade 1B) for high-risk hospitalized acutely ill medical patients.[7]

Several reports have shown that up to 40% of individuals hospitalized in Internal Medicine wards are carriers of some degree of renal impairment.[8-9] As a consequence, they are at increased risk of both VTE and bleeding complications,[10-13] particularly because they are older and have more co-morbidities than patients with normal renal function. Moreover, they frequently need thromboprophylaxis with anticoagulant drugs, such as LMWHs or fondaparinux, at predominant renal excretion and this is, therefore, potentially harmful since their bioaccumulation may result in excessive anticoagulant effect.

However, in general, there is little clinical information on safety and efficacy of fondaparinux in renal impaired patients and so far this been addressed in only one recent paper (the FONDAIR study).[14]

The aim of the present study was to evaluate safety and efficacy of fondaparinux in a 'real-life' context in a population of elderly hospitalized acutely ill medical patients with renal impairment.

Materials and Methods

We retrospectively reviewed the charts of all consecutive acutely ill medical patients over the age of 60 years admitted to the Internal Medicine Division of the Latisana Hospital, Italy, from January to June 2011 and given thromboprophylaxis with fondaparinux. Those with a creatinine clearance (CrCl) below 50 mL/min (part of a larger group of treated patients) were then evaluated for this retrospective single center study and make up this study cohort. Based on a local protocol, at hospital admission all patients received thromboprophylaxis if they were expected to remain in bed for at least four days and were affected by one of the following: congestive heart failure New York Heart Association (NYHA) class III or IV, acute respiratory failure, acute infection or inflammatory disorder, active cancer. Thromboprophylaxis was not administered if patients had active bleeding, bleeding events in the previous three months, known bleeding diathesis, ongoing oral anticoagulant treatment, known brain metastases, eye surgery, neurosurgery, spinal surgery, acute bacterial endocarditis or stroke within the previous 30 days.

At hospital admission, CrCl (calculated with the Cockroft-Gault formula[15]), platelet count (Plt) and prothrombin time (PT) ratio were evaluated before starting treatment.

According to the manufacturer's indications, fondaparinux (Arixtra®, GlaxoSmithKline, Brentford, UK) 2.5 mg s.c. daily should be given to patients with CrCl over 50 mL/min, Plt over 100×10^9/L and PT ratio below 1.2; and fondaparinux 1.5 mg s.c. daily to patients with CrCl 20-50 mL/min, or Plt $50\text{-}100\times10^9$/L or PT ratio 1.2-1.5. Patients with CrCl below 20 mL/min, or Plt below 50×10^9/L or PT ratio over 1.5 should be excluded from thromboprophylactic treatment.

According to the local protocol, all patients were treated until hospital discharge, and they were subsequently followed-up after 90 days by means of a visit or a phone interview. Information on their health status, including the occurrence of symptomatic VTE or hemorrhagic events, was collected.

Major bleeding was defined according to the International Society of Thrombosis and Hemostasis guidelines:[16] fatal bleeding, and/or symptomatic bleeding in a critical area/organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of 2 or more units of whole blood or red cells. Clinically relevant non-major bleeding (CRNMB) was defined as any overt bleeding requiring medical intervention and/or treatment discontinuation and not meeting the criteria for major bleeding. Symptomatic DVT had to be confirmed by Doppler ultrasound; symptomatic PE by helical computed tomography. Both bleeding events and DVT episodes were respectively considered as side effects or lack of efficacy of fondaparinux if they occurred during administration of the drug or in the 48 h following suspension.

Statistical analysis

Continuous variables were expressed as a mean plus or minus the standard deviation (SD) or as a median with range. Univariate analysis of base-line characteristics and prevalence of potential risk factors in patients with CrCl over or below 50 mL/min was performed by t-test in case of continuous variables, and by χ^2 test or Fisher's exact test in case of categorical variables. Data were analyzed using R (version 2.15.0) software. $P<0.05$ was considered significant.

Results

Patients

Over the 6-month study period, 210 consecutive patients admitted to the Internal Medicine division who met inclusion criteria for thromboprophylaxis, received treatment with fondaparinux. For the purpose of this study, only the 125 patients with a CrCl below 50 mL/min are reported. Base-line characteristics of this population are summarized in Table 1.

Briefly, 43 (34.4%) patients were male, mean age was 83.2±7.3 years and median age 83.0 (64-98) years. Creatinine clearance was 20-50 mL/min in 113 (90.4%) patients and below 20 mL/min in 12 patients (9.6%). Table 1 also shows the main diseases for

which patients were admitted to the hospital and given thromboprophylaxis, and main concomitant disorders.

Of 125 patients, 77 (61.6%) were receiving concomitant anti-platelet agents; the majority of these patients (n=65, 84.4%) were on aspirin, 7 were receiving ticlopidine (9.1%) and 5 were receiving dual antiplatelet therapy with aspirin and clopidogrel (6.5%).

Overall, fondaparinux was used at the dose of 1.5 mg daily in 41 (32.8%) patients, and at 2.5 mg daily in 84 (67.2%).

Mean duration of hospitalization was 13.7±10.9 days and mean duration of thromboprophylaxis with fondaparinux was 12.3±11.9 days (range 5-69). In particular, fondaparinux was administered for up to 14 days, according to current guidelines, in 96 patients (75.6%) and for over 14 days in the remaining patients.

Table 2 shows the relationship between CrCl, PT ratio, platelet count and the actual dose of fondaparinux used: a high dose of fondaparinux (2.5 mg

Table 1. Patients' characteristics.

Total no. patients		125	
Male, no. (%)		43 (34.4%)	
Age (years), mean±SD; median (range)		83.2±7.3; 83.0 (64-98)	
Creatinine clearance	20-50 mL/min, no. (%) <20 mL/min, no. (%)	113 (90.4%) 12 (9.6%)	
Inclusion criteria, no. (%)		Acute infection* Congestive heart failure° Active cancer# Acute respiratory failure Inflammatory diseases Miscellaneous	45 (36.0%) 26 (20.8%) 22 (17.6%) 21 (16.8%) 5 (4.0%) 6 (4.8%)
Concomitant disorders, no. (%)		Congestive heart failure Hypertension Type 2 diabetes mellitus COPD§ + chronic respiratory failure Atrial fibrillation Chronic cerebrovascular diseases Ischemic heart disease Obesity^ Ischemic stroke Infection	32 (25.6%) 30 (24.0%) 23 (18.4%) 23 (18.4%) 22 (17.6%) 21 (16.8%) 18 (14.4%) 16 (12.8%) 6 (4.8%) 5 (4.0%)
Concomitant antiplatelet treatment, no. (%)		77 (61.6%) ASA 65 (84.4%) Ticlopidine 7 (9.1%) ASA/clopidogrel 5 (6.5%)	
Daily dose of fondaparinux	1.5 mg, no. (%) 2.5 mg, no. (%)	41 (32.8) 84 (67.2)	
Duration of hospitalization (days), mean±SD; median (range)		13.7±10.9; 10.0 (5-69)	
Duration of treatment with fondaparinux (days), mean±SD; median (range)		12.3±11.9; 9.0 (5-69)	
Duration of follow up (days)		90	

*Including lung infections (pneumonia, bronchitis and exacerbated chronic obstructive pulmonary disease) and other infections (*i.e.* sepsis, cholecystitis, urinary tract infection and erysipelas); °NYHA class III-IV; #on chemotherapy or in progression on supportive care; §chronic obstructive pulmonary disease; ^BMI ≥30 for males and ≥28.6 for females.

Table 2. Relationship between creatinine clearance, prothrombin time ratio, platelet count and fondaparinux dose used.

		All patients (no. 125)	Fondaparinux 1.5 mg/die (no. 41)	Fondaparinux 2.5 mg/die (no. 84)
CrCl mL/min	20-50 < 20	113 (90.4%) 12 (9.6%)	36 (87.8%) 5 (12.2%)	77 (91.7%) 7 (8.3%)
PT ratio	<1.2 1.2-1.5 >1.5	90 (72.0%) 27 (21.6%) 8 (6.4%)	24 (58.5%) 13 (31.7%) 4 (9.7%)	66 (78.6%) 14 (16.7%) 4 (4.7%)
Platelets×10^9/L	≥100 <100 <50	121 (96.8%) 3 (2.4%) 1 (0.8%)	40 (97.6%) 1 (2.4%) 0	81 (96.4%) 2 (2.4%) 1 (1.2%)

CrCl, creatinine clearance; PT, prothrombin time.

daily) was inappropriately used in 84 patients with CrCl below 50 mL/min (7 of whom with CrCl <20 mL/min). Of these, 18 patients showed also a PT ratio over 1.2 and 3 patients a Plt count below 100×10^9/L; no bleeding was observed in this group of patients. Fondaparinux at 1.5 mg daily was also inappropriately used in 5 patients with CrCl below 20 mL/min (4 of whom showed also a PT ratio >1.2) and in 4 patients with a PT ratio over 1.5; again no bleeding was observed also in this group of patients.

Safety

Study outcomes are described in Table 3. No major bleedings were observed.

Three CRNMB episodes (2.4%) were registered: one (melena) in a patient with lung cancer and liver cirrhosis receiving fondaparinux 1.5 mg daily plus ASA and a PT ratio of 1.27; one (melena) in an 86-year old female with diabetes mellitus and chronic cerebrovascular disease, receiving fondaparinux 1.5 mg daily; and one (epistaxis and gum bleeding) in a patient with pharyngeal cancer programmed for chemo- and radiotherapy, receiving fondaparinux 1.5 mg daily. In all these cases, fondaparinux was continued. Another episode of CRNMB (hematuria) occurred after discharge in a patient receiving aspirin. The event occurred 17 days after fondaparinux had been stopped and is, therefore, not counted as being related to thromboprophylaxis.

When comparing the base-line characteristics of patients with CrCl below or above 50 mL/min at univariate analysis (Table 4), bleeding events were equally distributed among the two groups, even though the group with renal impairment was significantly older, and with more patients aged over 80 years and on antiplatelet therapy.

Efficacy

While no DVT episodes were registered during administration of fondaparinux, only one case was registered during follow up (upper arm, catheter-related), but this must not be included in the study outcomes since it occurred at Day 67 after discharge and discontinuation of fondaparinux in a patient with urothelial cancer of bladder.

Mortality

During the observation period, 26 of 125 patients (20.8%) died. Only 5 (19.2%) of these died during hospitalization while on thromboprophylaxis (2 multi-organ failures, 2 cancers and one infection); the others died either during follow up or off therapy. Causes of death are summarized in Table 5; no cause of death was related to fondaparinux.

Table 3. Study outcomes.

Outcome	No. events	%
Major bleeding	0	-
CRNMB	3	2.4
Symptomatic VTE	0	-

CRNMB, clinically relevant non-major bleeding; VTE, venous thromboembolism.

Table 4. Comparison of characteristics of patients with creatinine clearance < or ≥50 mL/min.

Characteristics	CrCl <50 mL/min no. 125	CrCl ≥50 mL/min no. 85	P
Male, no. (%)	43 (34.4%)	48 (56.5%)	<0.05
Age (years), mean ±SD (range)	83.2±7.3 (64-98)	75.1±7.7 (64-88)	<0.05
Age ≥80 years, no. (%)	86 (68.8)	27 (32.1)	<0.05
Bleeding events, no. (%)	3 (2.4%)	4 (4.7%)	0.352
Antiplatelet therapy, no. (%)	77 (61.6%)	40 (47.0%)	<0.05
Fondaparinux dose 2.5, no. (%)	84 (67.2)	56 (65.9)	0.936
PT ratio >1.2, no. (%)	34 (27.2)	21 (24.7)	0.698
Platelets $<100\times10^9$/L, no. (%)	4 (3.2)	6 (7.1)	0.190
Active cancer, no. (%)	22 (17.6)	17 (20.0)	0.631
Obesity	16 (12.8)	29 (34.1)	<0.05
Symptomatic VTE	0	1 (1.2)	0.405

CrCl, creatinine clearance; PT, prothrombin time; VTE, venous thromboembolism.

Table 5. Causes of death.

Causes of death	No. patients (%)
Died	26 (20.8%)
Cancer	9 (34.6%)*
Multiorgan failure	8 (30.8%)
Chronic heart failure	5 (19.2%)
Infection	2 (7.7%)
Complications of AMI	1 (3.8%)
Unknown	1 (3.8%)

*Percentage of total number of patients who died (n=26). AMI, acute myocardial infarction.

Discussion

As compared to the usual 2.5 mg daily-dose of fondaparinux, a lower dose (1.5 mg daily) was recently approved for the prevention of VTE in patients with renal impairment, after data had been obtained in patients undergoing major orthopedic surgery.[17] This lower dose has been prospectively tested in only one recently published multicenter study on patients affected by renal impairment (creatinine clearance between 20 and 50 mL/min) (the FONDAIR study).[14] The characteristics of the patient population in this study were similar to those in ours. In fact, these included 206 patients with a mean age of 82.1 years, with multiple co-morbidities, with a high percentage of patients being affected by cancer (21.8%) and receiving antiplatelet medication (62.1%). The observed incidence of major bleeding (0.49%), of CRNMB (3.88%), and of symptomatic VTE (1.46%) prompted the authors of the study to indicate fondaparinux at 1.5 mg daily as safe and effective for the prevention of VTE in acutely ill medical patients with renal impairment.

In our study, the dose of fondaparinux should have been used according to the manufacturer's instructions (after evaluating creatinine clearance, Plt count and PT ratio). However, when retrospectively analyzing hospital charts, we realized that many daily doses administered to patients were higher (2.5 mg daily) than those advised. Nevertheless, when comparing our safety data with those of the FONDAIR study and of the three large randomized studies on VTE prophylaxis with fondaparinux, enoxaparin and deltaparin,[4-6] we noted that, in our population, the incidence of bleeding episodes (major and non-major) was even lower than that reported by those trials, even among patients in whom non-appropriate doses of fondaparinux were used, *i.e.* 2.5 mg daily in patients with a CrCl 20-50 mL/min or PT ratio over 1.2 or Plt below 100×10^9/L or 1.5 mg daily in patients with a CrCl below 20 mL/min or PT ratio over 1.5.

These safety issues appear to be of particular importance considering the population studied, *i.e.* a very old population, older than that of the three randomized studies mentioned above (83.0 *vs* 75.0, 73.1 and 68.5, respectively), with a greater percentage of patients affected by cancer (17.6 *vs* 14.5, 12.3 and 4.6, respectively) and a higher number of deaths (20.8 *vs* 3.3, 11.4 and 6.1, respectively). In other words, a population with no base-line selection of patients and poorly represented in those randomized studies, *i.e.* the *real-life* elderly acutely ill patients admitted onto medical wards. This is also confirmed by the unsurprisingly high fatality rate reported in our study (20.8%), as compared to the 4.3% of a meta-analysis of randomized studies in patients receiving active treatment[18] and to the 4.9% of the Lifenox study,[19] given the mean age of the population and, most of all, the severity of co-morbidities (Table 1).

As far as efficacy is concerned, no VTE episodes were observed in our study among patients receiving thromboprophylaxis, while the incidence of symptomatic VTE was higher (0.38% DVT and 0.20% PE) in the meta-analysis of Dentali,[18] and even higher again (1.46%) in the FONDAIR study.[14] In their conclusions, the authors of this last study questioned whether a higher dose of fondaparinux (*i.e.* 2.5 mg) would have been more effective and whether it would have been able to reduce this rate. Our data on the safety of the 2.5 mg daily dose in a population with renal impairment might in some way answer this question, suggesting the need for a direct comparison between the higher and the lower dose of the drug to provide concrete evidence as to which approach is associated with the most favorable clinical benefit in this population.

Our study has a number of limitations: i) its retrospective nature; ii) it was carried out in a single center; iii) only a small number of patients were enrolled; iv) asymptomatic deep vein thrombosis was not routinely screened and some events could have been missed; and v) the method used to estimate renal function might not have been the most appro-

priate. Nevertheless, it opens up some interesting points for debate since it shows that the use of fondaparinux is a safe and effective strategy to prevent VTE in elderly acutely ill medical patients with renal impairment, with a very low incidence of bleeding complications.

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