Low-dose fondaparinux in suspected heparin-induced thrombocytopenia in the critically ill


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ABSTRACT

Background: In critically ill patients, heparin-induced thrombocytopenia (HIT) is estimated to account for approximately 1 to 10% of all causes of thrombocytopenia. HIT exerts a strong procoagulant state. In case of suspected HIT, it is an important clinical decision to stop heparin and start treatment with alternative nonheparin anticoagulation, awaiting the results of laboratory testing for the final diagnosis of HIT (bridging therapy). Fondaparinux acts by factor Xa inhibition and expresses no cross-reactivity with HIT antibodies. Excretion of fondaparinux is mainly renal. We describe our early experience with fixed low-dose fondaparinux bridging therapy and monitoring of anticoagulant activity for safety reasons.

Methods: This retrospective cohort study was conducted in a closed format general intensive care unit in a teaching hospital. Consecutive critically ill patients suspected of HIT were treated with fondaparinux after discontinuation of unfractionated heparin or nadroparin. Anti-Xa levels were determined afterwards.

Results: Seven patients were treated with fondaparinux 2.5 mg/day for 1.8 to 6.5 days. Anti-Xa levels varied from 0.1 to 0.6 U/ml. A negative correlation was found between creatinine clearance and mean and maximum anti-Xa levels. No thromboembolic complications occurred. Bleeding complications were only minor during fondaparinux treatment. Transfusion requirements did not differ significantly between treatment episodes with fondaparinux or with heparin anticoagulants.

Conclusion: In this small sample of critically ill patients suspected of HIT, bridging therapy with fixed low-dose fondaparinux resulted in prophylactic and therapeutic anti-Xa levels. Monitoring of anticoagulant activity is advised in patients with renal insufficiency.

KEYWORDS

Critically ill, fondaparinux sodium, heparin-induced thrombocytopenia, pentasaccharide

INTRODUCTION

In critically ill patients, a decrease in the platelet count is frequently observed. Heparin-induced thrombocytopenia (HIT) is estimated to account for approximately 1 to 10% of all causes of thrombocytopenia. When HIT is suspected an important clinical process of diagnostic and therapeutic strategies starts. Diagnostic laboratory testing needs to be performed to support the diagnosis. Due to the strong procoagulant character of HIT, it may be necessary to stop heparin-like drugs promptly and to start treatment with alternative nonheparin anticoagulation. We call the pre-emptive treatment of suspected HIT, awaiting the test results for the final diagnosis of HIT, bridging therapy. The diagnosis of HIT is based upon the combination of clinical criteria and laboratory test results according to the diagnostic classification systems as developed by the International Society on Thrombosis and Haemostasis (ISTH). Continuation of the alternative nonheparin anticoagulation depends on the final diagnosis of HIT. For treatment of HIT, danaparoid, lepirudin and argatroban are to date the most widely used nonheparin anticoagulants. All three drugs have their advantages and disadvantages (table 1). In 5 to 10% of cases, Danaparoid, with an anti-Xa:anti-IIa ratio of 28:1, exerts cross-reactivity with antibodies against the heparin/platelet factor 4 (PF4) complex, known as HIT antibodies. Lepirudin can induce antilepirudin antibodies, which may lead to a strong increase of lepirudin activity and anaphylaxis at re-exposure. Excretion of danaparoid and
lepirudin is mainly renal, which may lead to accumulation of anticoagulant activity in case of renal impairment. Argatroban has a short half-life and is metabolised hepatically. In critically ill patients with the multiple organ dysfunction syndrome, the dose has to be adjusted to prevent anticoagulant accumulation due to an apparent degree of hepatic dysfunction. Argatroban is not available in the Netherlands. Neutralising agents are lacking for all three drugs. Each of these drugs can lead to an increased risk of bleeding, especially in critically ill patients who are already prone to bleeding complications due to thrombocytopenia, other coagulopathies, recent surgery and the necessity of frequent invasive procedures. In this complex situation a balance should be found between the prevention of HIT-induced thromboembolic complications and nonheparin anticoagulant-induced bleeding complications. In search of a more favourable nonheparin anticoagulant for the treatment of HIT, fondaparinux has emerged as a suitable alternative with possibly a more favourable benefit/harm profile.

**Table 1. Alternative nonheparin anticoagulant strategies in patients with heparin-induced thrombocytopenia (HIT)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of anticoagulation</th>
<th>Monitoring</th>
<th>Pro</th>
<th>Con</th>
<th>Clearance</th>
<th>T½</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danaparoid</td>
<td>Anti-Xa/anti-IIa</td>
<td>Anti-Xa</td>
<td>• 5-10% cross-reactivity to anti-H/ PF4</td>
<td>Mainly renal</td>
<td>Normal: 25 h</td>
<td>In renal failure</td>
<td></td>
</tr>
<tr>
<td>Heparinoid from pig/intestinal mucosa</td>
<td>28:1</td>
<td></td>
<td></td>
<td>Anuria: increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Anti-Xa antithrombin-mediated</td>
<td>Anti-Xa</td>
<td>• Very low cross-reactivity to anti-H/ PF4</td>
<td>Accumulation in ARF</td>
<td>Renal</td>
<td>Normal: 15-20 h</td>
<td></td>
</tr>
<tr>
<td>Synthetic pentasaccharide</td>
<td></td>
<td></td>
<td>rFVIIa is potential partial antagonist</td>
<td></td>
<td>Anuria: increased</td>
<td>In renal failure</td>
<td></td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Anti-IIa direct irreversible</td>
<td>ECT</td>
<td>• No cross-reactivity to anti-H/ PF4</td>
<td>Accumulation in ARF</td>
<td>Renal</td>
<td>Normal: 60-100 min</td>
<td></td>
</tr>
<tr>
<td>(Recombinant-hirudin) direct thrombin inhibitor</td>
<td></td>
<td>APTT is unreliable</td>
<td></td>
<td>Anuria: 1.5-15 h</td>
<td></td>
<td>In renal failure</td>
<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td>Anti-IIa direct reversible</td>
<td>APTT</td>
<td>• No cross-reactivity to anti-H/ PF4</td>
<td></td>
<td></td>
<td>39-51 min</td>
<td>In hepatic failure</td>
</tr>
<tr>
<td>Synthetic direct thrombin inhibitor</td>
<td></td>
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</tbody>
</table>

Anti-H/PF4 = antiheparin/platelet factor 4 antibodies; ECT = ecarin clotting time; rFVIIa = recombinant factor VIIa. * Anti-Xa is not a reliable predictor of bleeding. ** Unknown whether anti-Xa is a reliable predictor of bleeding. † Dose-dependent prolongation of APTT in the low-dose range, at higher doses APTT increase is relatively smaller; a higher degree of anticoagulation is therefore easily missed.

Based upon the possibly favourable characteristics we decided to use fondaparinux for the treatment of critically ill patients with suspected HIT awaiting the definite diagnostic classification. Arbitrarily we chose a fixed prophylactic dose of 2.5 mg/day anticipating a possible accumulation of anticoagulant activity in critically ill patients with a certain degree of kidney dysfunction. The
anticoagulant activity of fondaparinux was measured by anti-Xa levels. In this article, we describe our early clinical experience with low-dose fondaparinux bridging therapy, with a focus on monitoring of the anticoagulant activity for safety reasons.

MATERIALS AND METHODS

Study design
This assessment was performed as a retrospective cohort study. On 28 November 2002, the Institutional Drug Committee of our hospital approved the use of fondaparinux sodium (Arixtra, the Netherlands; 2.5 mg/0.5 ml) for the treatment of suspected HIT in the critically ill. This indication concerns off-label use. Fondaparinux is licensed for venous thromboprophylaxis in orthopaedic surgery. To monitor the safety of this novel therapy we determined anticoagulant activities in relationship to calculated endogenous creatinine clearances in the first series of patients for six months. The protocol for the start of fondaparinux treatment was not submitted to the Institutional Medical Ethics Committee. No informed consent was asked of the patients or their legal representatives.

For patients with suspected HIT, a strict diagnostic and therapeutic strategy was followed during the observation period. We used the ISTH classification system to estimate the pretest probability of HIT. If the pretest probability was intermediate or high, unfractionated heparin (UFH) or nadroparin was stopped, a blood sample for HIT antibody testing was drawn and, awaiting the test results, fondaparinux 2.5 mg/day was administered as a once-daily subcutaneous injection at 06.00 hours or as a continuous intravenous infusion without loading dose at the discretion of the treating intensivist. The ISTH diagnostic classification system was used for the final diagnosis of HIT. If HIT was classified as unlikely or possible, fondaparinux was stopped and UFH or nadroparin restarted. If HIT was classified as probable or definite, fondaparinux was continued.

Blood samples were drawn for monitoring the anticoagulant activity of fondaparinux by measurement of anti-Xa levels. Anti-Xa levels were measured before the start of anticoagulation with fondaparinux and every treatment day at 08.00 and 18.00 hours. The endogenous creatinine clearance was calculated from the serum creatinine level in the 06.00 hour routine blood sample and a six-hour urine sample collected between 06.00 and 12.00 hours according to the formula: creatinine clearance (ml/min) = [urine creatinine (mmol/l) x urine volume (ml)/serum creatinine (µmol/l) x urine collection time (min)].

Thromboembolic complications, bleeding complications and the amount of transfusion products administered were documented during the three episodes of anticoagulation, which we distinguished in the natural course of suspicion of HIT: 1) UFH or nadroparin before start of fondaparinux; 2) fondaparinux bridging therapy; and 3) UFH or nadroparin after fondaparinux bridging therapy. An intensive care information system (MetaVision, IMD Soft, Tel Aviv, Israel) was used for prospective data collection.

Patients and setting
Consecutive patients with suspicion of HIT were treated with fondaparinux in an 18-bed tertiary referral closed format general ICU in a university-affiliated teaching hospital. A team of intensivists takes responsibility for the intensive treatment including antithrombotic treatment, a restrictive transfusion strategy and high volume continuous venovenous haemofiltration. All patients and their legal representatives were informed that clinical and biochemical data concerning disease and treatment were being collected in an electronic database to be available for evaluation of treatment.

Anticoagulant management
During the observation period of fondaparinux bridging therapy, the anticoagulant management was standardised in our department. Unfractionated heparin sodium (UFH) (manufactured at the Department of Clinical Pharmacy of our hospital; 5000 IU/ml) was used for continuous intravenous administration in a fixed dose (10,000 IU/day) not targeted at a prolongation of the aPTT for heart valve prosthesis thromboprophylaxis. Nadroparin calcium (Fraxiparine) was used for subcutaneous administration for venous thromboprophylaxis: 2850 IU anti-Xa/0.3 ml once daily for a body weight of <100 kg or 3800 IU anti-Xa/0.4 ml once daily for a body weight of >100 kg. Nadroparin was used for anticoagulation of the extracorporeal circuit of CVVH by an intravenous bolus of 2850 IU anti-Xa followed by continuous intravenous administration of 380 IU anti-Xa/h (9120 IU anti-Xa/day). Nadroparin was used for treatment of disseminated intravascular coagulation by continuous intravenous administration of a fixed dose of 3800 IU anti-Xa/day. Coagulation parameters were measured for safety monitoring, but not for targeting of therapy. Trisodium citrate was used for regional anticoagulation of the extracorporeal circuit of CVVH in patients with an increased risk of bleeding.

Heparin-induced thrombocytopenia, thrombosis and haemorrhage
We defined thrombocytopenia as a platelet count <100 x 10⁹/l measured at least twice and lasting for more than 24 hours with exclusion of pseudothrombocytopenia induced by the EDTA phenomenon. A HIT plot depicting the relationship between use of heparin and nonheparin anticoagulants and platelet count against time was made for all patients.
The diagnostic criteria for HIT, as developed by Warkentin and Chong on behalf of the Subcommittee on Platelet Immunology of the Scientific and Standardisation Committee of the ISTH, were used to support our clinical suspicion of HIT and for diagnostic classification.3,4

The four-item scoring system (the 4 T’s) according to Warkentin was used for the estimation of pretest probability of HIT and consists of: 1) Thrombocytopenia; 2) Timing of onset of thrombocytopenia; 3) Thrombosis (or other sequelae of HIT); and 4) Other cause for thrombocytopenia apparent. Each item can score 0, 1, or 2 points; a total score of 6 to 8 points is classified as a high pretest probability for HIT, 4 to 5 points as an intermediate pretest probability for HIT, and 0 to 3 points as a low pretest probability for HIT.4

The scoring system was recently validated in the intensive care setting.5

The diagnostic classification system for HIT according to Chong consists of clinical criteria and laboratory tests. The clinical criteria are: thrombocytopenia between 5 to 10 days after starting heparin treatment (3 points), thrombocytopenia between 1 to 4 days or >11 days (1 point), exclusion of other causes of thrombocytopenia (2 points), resolution of thrombocytopenia after cessation of heparin (1 point), reoccurrence of thrombocytopenia after rechallenge with heparin (1 point), and thrombosis (1 point). The laboratory tests are: immunoassay positive (2 points), functional assays: two-point system (i.e. measurement of aggregation in the presence of two heparin concentrations) positive (3 points), non-two-point system positive (2 points). If more than one diagnostic test is used, the test with the maximum score is taken for calculation of the total score. A total score of 0 to 2 points classifies HIT as unlikely, 3 to 4 points as possible, 5 to 6 points as probable, and ≥7 points as definite.3

**Laboratory testing**

Testing of HIT was performed in all patients by the direct antibody assay (Asserachrom HPIA Heparin/PF4 antibody ELISA, Stago, Asnière, France) to confirm the presence of antibodies against the heparin-platelet factor 4 complex. To detect possible accumulation of anticoagulant activity, anti-Xa levels (IU/ml) were determined by a chromogenic factor Xa inhibition assay (Coamatic Heparin, Chromogenics, Milan, Italy) calibrated for fondaparinux. Samples for measurement of anti-Xa levels were collected before the start of anticoagulation with fondaparinux and on every treatment day at 08.00 and 18.00 hours. All anti-Xa levels were determined after the observation period of fondaparinux bridging therapy. The prophylactic range was considered to be reflected by anti-Xa levels of 0.2 to 0.4 IU/ml and the therapeutic range by anti-Xa levels of 0.5 to 0.8 IU/ml.

The detection of thromboembolic complications (TEC) was based on regular clinical practice; when symptomatic venous or arterial TEC was suspected, TEC had to be proven by standard diagnostic imaging techniques such as duplex scanning and spiral CT scanning or by pathological anatomical examination. Remarkably early and/or frequent clotting of extracorporeal circuits and haemofilters, defined as two or more circuit survival times of <12 hours in the presence of a normal functioning central venous access catheter, was regarded as a manifestation of a procoagulant state.

Bleeding complications were classified as clinically important major and clinically important minor bleeds according to Landefeld’s Bleeding Severity Index.4 Occult minor bleeding was not analysed separately because this clinical situation often does not represent clinically important bleed. Occult bleeding usually reflects a decrease in the haemoglobin level below a certain trigger level for transfusion upon which erythrocyte concentrates are administered.

Our strategy of transfusion of blood products is restrictive.4-6 For erythrocyte concentrate, the transfusion trigger was determined at a haemoglobin level of 4.0 mmol/l for patients <40 years with good cardiopulmonary function, at 4.5 mmol/l for patients 40 to 60 years, at 5.0 mmol/l for patients >60 years and at 5.5 mmol/l for patients >60 years with critical coronary atherosclerosis or severe pulmonary disease. A transfusion trigger of 5.5 mmol/l was used in case of overt bleeding for all patients. For platelet concentrate, the transfusion trigger was set at <10 x 10⁹/µl without overt bleeding and at <50 x 10⁹/µl in case of a planned percutaneous or surgical intervention. In case of overt bleeding a platelet count of >50 x 10⁹/µl was targeted.

**Statistical analysis**

Descriptive statistics were used. Variables with a normal distribution were expressed as mean and standard deviation and variables with a nonparametric distribution were expressed as median and range. For comparison between variables, Fisher’s exact test, repeated measures analysis of variance (ANOVA) and linear regression and correlation were used when appropriate. The level of significance was 0.05. The statistical software packages Epi Info version 5.00 and Primer Biostatistics version 3.0 were used.25,15

**RESULTS**

From March to August 2003, we treated seven critically ill patients suspected of HIT with fondaparinux. The baseline characteristics are shown in table 2. According to the diagnostic classification system, six patients were classified as having an intermediate pretest probability and one patient as having a high pretest probability of HIT with scores between 4 and 7 points. The samples for HIT-antibody testing were taken between day 2 and day 7 after the start of UFH or nadroparin. HIT...
antibodies appeared to be absent in all patients. Five patients were classified as being unlikely of having HIT and two patients as having possible HIT. Thus, none of the patients needed continuation of treatment for proven HIT. Fondaparinux was stopped and replaced again by UFH or nadroparin.

The platelet count recovered in five patients and did not recover in two patients, both of whom died. One patient died in the ICU due to refractory septic shock with multiple organ failure. The other patient died of postanoxic encephalopathy after readmission to the ICU because of late postoperative right haematothorax during UFH therapy following re-CABG and mitral valve annuloplasty. The maximal platelet count in the ICU during UFH or nadroparin therapy before fondaparinux bridging therapy was 146 ± 151 x 10^9/l (mean ± standard deviation), the platelet count decreased to a nadir of 42 ± 35 x 10^9/l in 2 to 5 days, and recovered during fondaparinux bridging therapy followed by UFH or nadroparin to 151 ± 91 x 10^9/l in 2 to 9 days (repeated measures ANOVA: p=0.078).

The duration of treatment with fondaparinux was 1.8 to 6.5 days. In one patient treated with a lower dose of fondaparinux of 1.25 mg/day, ordered by the responsible intensivist because of earlier postoperative bleeding complications, anti-Xa levels were undetectable. In the other six patients receiving 2.5 mg/day, anti-Xa levels varied from 0.1 to 0.6 IU/ml. Anti-Xa activities showed an initial peak followed by a decrease suggesting that accumulation of anticoagulant activity did not occur (figure 1). We found negative correlations between creatinine clearance and mean anti-Xa-levels (r=-0.86, p=0.028) and between creatinine clearance and maximum anti-Xa-levels (r=-0.77, p=0.072). No TEC occurred. In two patients overt minor bleeding occurred with anti-Xa levels of 0.4 IU/ml in both. A total of 17 units of erythrocyte concentrate, two units of plasma and two units of platelet concentrate were administered in 21 fondaparinux treatment days.

The duration of treatment with UFH and nadroparin per patient varied from 2.0 to 26.9 days with in total 56.8 treatment days. No TEC occurred. In four patients,
five episodes of major bleeding occurred during the treatment episode before fondaparinux bridging therapy. In two patients, two episodes of major bleeding occurred during the treatment episode after fondaparinux bridging therapy. A total of 61 units of erythrocyte concentrate, 36 units of plasma and 11 units of platelet concentrate were administered in the treatment episode before fondaparinux bridging therapy. A total of ten units of erythrocyte concentrate, one unit of plasma and no units of platelet concentrate were administered in the treatment episode after fondaparinux bridging therapy.

There was a significant difference in number and severity of bleeding complications between the episode of anticoagulation with UFH or nadroparin before the start of fondaparinux bridging therapy and the episode of anticoagulation with fondaparinux (5 major and 0 minor bleeds vs 0 major and 2 minor bleeds: Fisher’s exact test p=0.048). No significant difference was found between the episode of anticoagulation with fondaparinux and the episode of anticoagulation with UFH or nadroparin after fondaparinux bridging therapy. Transfusion requirements during the three different episodes of anticoagulation did not differ significantly for erythrocyte concentrates, fresh frozen plasma and platelet concentrates (repeated measures ANOVA: p=0.16, p=0.24 and p=0.16, respectively).

**DISCUSSION**

Heparin-induced thrombocytopenia is a rare disease and is characterised by the development of thrombocytopenia during treatment with heparin coagulants. The low platelet count is the result of immune-mediated platelet activation and aggregation caused by antibodies directed at the heparin-platelet factor 4 complex. The HIT antibodies are also directed against the heparan sulphate-platelet factor 4 complex in the endothelial glycocalyx resulting in the release of subendothelial tissue factor, which strongly activates the coagulation cascade. So HIT exerts a strong procoagulant state with a high risk of life-threatening venous and arterial thromboembolism. When HIT is seriously suspected, all heparin anticoagulants should be stopped and treatment with nonheparin anticoagulants should be started.

In this small cohort of critically ill patients with thrombocytopenia suspected of HIT, awaiting the laboratory test results to make a final diagnosis of HIT, short-term bridging therapy with fixed low-dose fondaparinux (2.5 mg/day) resulted in anticoagulant activities in the prophylactic and therapeutic range as measured by anti-Xa levels. Although impairment of endogenous creatinine clearance was associated with higher mean and maximum anti-Xa levels, no accumulation of anticoagulant activity was
detected. Dose reduction of the initial treatment to 1.25 mg/day resulted in undetectable anti-Xa levels in one patient. No TEC occurred during treatment with fondaparinux and treatment with UFH or nadroparin before and after fondaparinux bridging therapy. Despite low platelet counts, overt bleeding was only minor during fondaparinux treatment. We found a significant difference in the number and severity of bleeding complications during treatment with UFH or nadroparin before the start of fondaparinux bridging therapy, but this may well reflect surgery-related bleeding complications. Transfusion requirements did not differ substantially between the different anticoagulation episodes.

Our observation has limitations. Firstly, the small sample of patients limits firm conclusions on the clinical efficacy and safety of bridging therapy with fondaparinux. Large prospective investigations have to elucidate the clinical efficacy and safety of short-term fixed low-dose fondaparinux bridging therapy. Secondly, all patients tested negative for the presence of HIT antibodies and thus HIT was an unlikely cause of the development of thrombocytopenia. The blood samples for HIT antibody testing may have been drawn too early to detect the development of HIT antibodies and repeat testing was not performed. Clearly, other explanations for the low platelet count were present as well, such as loss of platelets due to massive haemorrhage and consumption of platelets due to disseminated intravascular coagulation and treatment with extracorporeal and intravascular devices.29,31 Sustained treatment with fondaparinux in critically ill patients with proven HIT deserves to be investigated and its anticoagulant activities and clinical efficacy and safety need to be determined. Thirdly, the optimal target for therapeutic anti-Xa levels is unknown. Ideally, target anti-Xa levels should reflect levels of anticoagulation for adequate prevention or treatment of TEC due to HIT at the lower level balanced by a safe treatment with nonheparin alternative anticoagulants without increased bleeding risk at the higher level. Anti-Xa levels between 0.30 and 0.50 IU/ml may be adequate therapeutic target values.

In conclusion, fixed low-dose fondaparinux bridging therapy in critically ill patients suspected of HIT, awaiting definite diagnostic classification, can lead to therapeutic anticoagulant activity. To reduce the risk of bleeding, we ideally advocate determination of anti-Xa levels to detect possible accumulation of anticoagulant activity, especially in patients with renal insufficiency. In daily clinical practice in the ICU, suspicion of HIT occurs regularly leading to the need to make important diagnostic and therapeutic decisions. A possible role for bridging therapy with low-dose fondaparinux in this complex clinical context remains to be elucidated in future investigations.

PRESENTATION
The content of this article was presented at the 17th Annual Congress of the European Society of Intensive Care Medicine, 10 to 13 October 2004, Berlin, Germany and was published as an abstract in Intensive Care Medicine (Koole MA, Wester JP, Bosman RJ, et al. Efficacy and safety of fondaparinux sodium in the critically ill. Intensive Care Med 2004; 30(Suppl): S88,P332).

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