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ORIGINAL ARTICLE
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Heparin-induced thrombocytopenia treated with fondaparinux: single center experience

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ABSTRACT

Background: Heparin-induced thrombocytopenia (HIT) is the most frequent drug-induced, immune-mediated thrombocytopenia. It is associated with significant morbidity and mortality. Anticoagulation with heparin must be stopped immediately and replaced by some suggested alternative — lepirudin, danaparoid or argatroban. Fondaparinux has been also successfully used in HIT.

Methods: We present a cohort of 10 patients diagnosed with HIT and treated in a university hospital in a period of four years. Diagnosis was based on Keeling´s scoring system, screening immunologic test for HIT (STic EXPERT® HIT) and sandwich ELISA (detection of IgG/heparin-PF4 antibodies). While other alternative anticoagulants are not readily available in our hospital, we used fondaparinux in all cases.

Results: From 2014 to 2018, eight males and two females (mean age 67 years, range 46-86 years) were diagnosed with HIT in our hospital. This complication developed in 9 cases after low-molecular-weight heparin and in one after heparin flushes in hemodialysis. A drop-in platelet count developed in all patients, thrombotic complications in 7 and skin necrosis in 2 cases. Fondaparinux was used in all patients, including two cases with severe renal impairment, the dose was chosen individually. We observed complete platelet recovery in all cases. One patient died because of advanced malignancy, others did not have any complication. In 6 cases we switched to oral anticoagulation after platelet recovery.

Conclusions: In our group of 10 HIT patients fondaparinux was shown to be both safe and effective, even in those with severe renal impairment. Additional studies are warranted to confirm this observation.

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Key words: Thrombocytopenia; Fondaparinux; Skin; Necrosis; Anticoagulants.

Heparin-induced thrombocytopenia (HIT) is the most frequent drug-induced, immune-mediated type of thrombocytopenia. It is caused by the formation of antibodies (Ab) to complexes of platelet factor 4 (PF4) and heparin. HIT can occur after exposure to any form or amount of heparin products. Paradoxically, HIT is a hypercoagulable state and the patients with HIT may develop thromboembolic complications (both arterial and venous) that are associated with significant morbidity and mortality. The heparin-induced immune reaction is common (8% to 50%),[1-3] fortunately thrombosis is far less frequent (0.2% to 3%).[4, 5] The awareness of HIT is very important in clinical practice because the rapid laboratory work-up and immediate therapy are crucial for the management of patients. Heparin must be stopped and replaced by an alternative anticoagulant. Lepirudin, danaparoid or argatroban are suggested anticoagulant drugs for patients with HIT.[6] Unfortunately, none of these medications are readily available in the vast majority of Czech hospitals. Therefore, fondaparinux remains the therapy of choice in this scenario.

The aim of this paper was to retrospectively evaluate the management of HIT patients in a tertiary hospital setting. We have taken into considerations two main points in the treatment of HIT patients in the Czech hospital setting: 1) while most Czech hospitals do not have any available test for HIT, we tried to assess the usefulness of our diagnostic algorithm for clinical practice; 2) an alternative anticoagulant recommended for HIT patients is not routinely accessible in our practice. Moreover, the treatment should be provided by a team that is experienced in diagnosis and treatment of HIT. Therefore, we have evaluated the efficacy and safety of fondaparinux in this indication in our hospital setting.

Materials and methods

In our center we use Keeling's scoring system[7] and an immunologic screening test for HIT (STic EXPERT® HIT).[8] In the case of positive results we confirm the diagnosis by classic sandwich ELISA for the detection of IgG/heparin-PF4 (ZYMUTEST HIA MonoStrip IgG).[9] If this test is also positive, we stop heparin and continue anticoagulation with fondaparinux at a dose chosen individually in every case.

Clinical suspicion of HIT

All patients exposed to either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) with clinical suspicion of HIT were assessed with Keeling´s scoring system.[10] HIT was suspected if at least one of the following potential manifestations occurred:

- thrombosis (in any vascular bed) + thrombocytopenia;
- thrombocytopenia, *i.e.* the absolute drop in platelet count (with the onset 5-10 days after heparin exposure);
- a relative decline of >50% from baseline platelet counts (with the onset 5-10 days after heparin exposure);
- skin necrosis;
- systemic reaction (fever, chills, hypertension, tachycardia, chest pain, dyspnea).

The 4T score (a pretest scoring system for HIT) was calculated as outlined in Table I.[10] Patients with a score of ≤3 points were not tested for HIT. Patients with a score of 4 to 5 were considered to have an intermediate probability and a score of 6 to 8 a high probability of HIT. All patients with a score ≥4 were tested for HIT. Heparin was immediately stopped and fondaparinux was administered. We have not used any other scoring system but we are aware that HIT Expert Probability (HEP) is also useful for clinical practice, mainly in Intensive Care Units (ICU) and among less experienced clinicians.

Laboratory work-up

After probability calculation, the laboratory work-up of HIT used in our hospital was initiated. The first step included the screening test for HIT (STic EXPERT® HIT). This test is a nanoparticle-based lateral-flow immunoassay with high sensitivity for the detection of Ab/heparin-PF4. If positive, the

TABLE I.—*4Ts score for HIT.*[10]

	2 points	1 point	0 points
Thrombocytopenia	>50% drop, or 20-100x10⁹/L	30-50% drop or 10-19x10⁹/L	<30% drop or <10x10⁹/L
Timing	Drop of platelets after 5-10 days of therapy, in case of heparin use within previous 100 days	Thrombocytopenia after 10 days or later	Drop of platelets without presence of heparin
Thrombosis or skin lesion	New thrombosis, skin necrosis, systemic reaction to IV heparin	Progression or recurrence of thrombosis, redness of skin	None
Other cause of thrombocytopenia	Any other obvious cause	Possibility of other cause	Clear other cause
Probability	6-8 high	4-5 moderate	0-3 small

confirmation test (ZYMUTEST HIA MonoStrip IgG) was performed. This assay is a classic sandwich ELISA detecting IgG/ heparin-PF4 complex. If the diagnosis of HIT was confirmed using this ELISA based assay then fondaparinux was administered to the patient. The dosage of fondaparinux was driven by clinical and laboratory characteristics of the patients, *i.e.* primary indication of heparin (prohylactic or therapeutic use), clinical manifestation of HIT and renal function was taken into account in individual cases.

This work-up was performed in all patients and, moreover, in 3 of these cases, the diagnosis was also additionally confirmed by the gold standard test (serotonin release test, *i.e.* a functional test). This assay is available only in one laboratory in the Czech Republic.

If considered necessary, monitoring anti-Xa activity was performed by a chromogenic anti-Xa method (BIOPHEN™ Heparin LRT), using BIOPHEN™ Arixtra® Calibrator for calibration and BIOPHEN™ Arixtra® Control for the quality control of the measurements.

Treatment

As mentioned above, lepirudin, danaparoid and argatroban are not readily and routinely available in our hospital. The cost of these drugs, limited utility (for HIT patients only) and a lack of experience (monitoring etc.) resulted in limited accessibility. This is the reason why fondaparinux remains the therapy of choice in our country. Fondaparinux is a synthetic pentasaccharide administered as a once-daily subcutaneous injection. It is a selective indirect inhibitor of FXa with 100% bioavailability, and is eliminated renally as unchanged compound. According to the summary of product characteristics, the elimination half-life is 17 hours in healthy young individuals and 21 hours in healthy elderly subjects. The effect of fondaparinux persists for 24 hours. More recently, fondaparinux has been increasingly used off-label for the management of HIT.[11, 12] While fondaparinux is an option for the management of patients with suspected or confirmed HIT, it has been rarely implicated as a cause of HIT in case reports.[12, 13]

Results

This study included 10 patients with confirmed HIT who had been successfully treated with fondaparinux in our hospital from 2014 to 2018. Our cohort consists of 8 males and 2 females, with the mean age of 67 years (range 46-86 years). The rough estimate of the frequency of HIT among the patients receiving therapeutic or prophylactic heparin or LMWH in our hospital is 0.05-0.1%. Individual cases are summarized in Table II.

TABLE II.—*The individual cases with HIT.*

Age (y)	Initial diagnosis	LMWH dose	Time to HIT onset (days) Drop of Plt (10^9/L)	HIT manifestation	Fondaparinux dose and duration (days)	Time to platelet recovery (days)	Following anticoagulation
66	Colorectal cancer + acute proximal DVT	Therapeutic	6 260/86	Rethrombosis	Therapeutic 7.5 mg, 5 days	5	Dabigatran
66	Adenocarcinoma of the lungs	Prophylactic	9 270/110	DVT	2.5 mg every other day	26 (till death)	-
56	Femoral DVT	Therapeutic	6 188/62	Re- thrombosis	Therapeutic 7.5 mg, 7 days	7	Dabigatran
46	Femoral DVT	Therapeutic	6 175/52	Re- thrombosis	Therapeutic 7.5 mg, 5 days	5	Apixaban
68	AF, valve replacement	Therapeutic	8 225/31	DVT	Therapeutic 7.5 mg, 6 days	6	Warfarin
77	Colon cancer + femoral DVT	Therapeutic	13 185/44	Re- thrombosis	Therapeutic 10 mg, 6 days	6	Rivaroxaban
86	Erysipelas	Prophylactic	14 371/45	Skin necrosis	Prophylactic 2.5 mg, 21 days	7	None
64	TKR	Prophylactic	5 176/76	Skin necrosis	Prophylactic 2,5 mg for 3 days, then 10 mg for 3 days	6	Rivaroxaban
71	Acute glomerulonephritis	UFH flush (dialysis)	9 224/27	DVT	Prophylactic 2.5 mg every other day	16*	None
68	Head injury	Prophylactic	14 225/57	Thrombo-cytopenia	Prophylactic 2.5 mg 6 days	6	None

LMWH: low molecular weight heparin; HIT: heparin-induced thrombocytopenia; Plt: platelets; DVT: deep vein thrombosis; AF: atrial fibrillation; TKR: total knee replacement; UFH: unfractionated heparin.
*Other cause of thrombocytopenia.

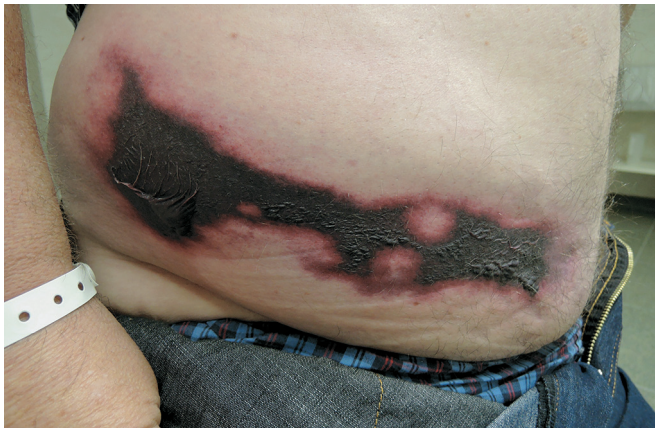

Figure 1.—Heparin induced skin necrosis in a 64-year-old male.

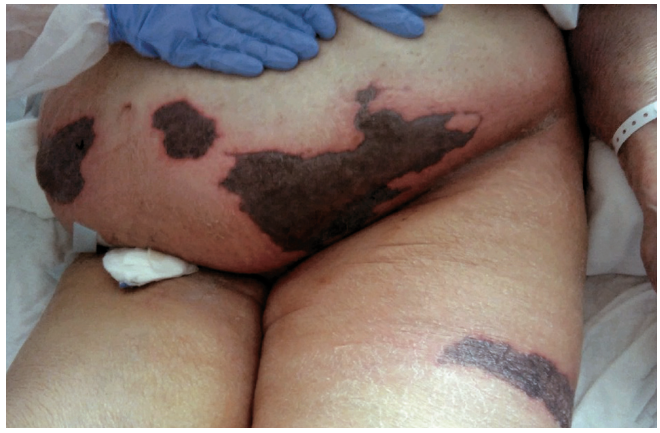

Figure 2.—Heparin induced skin necrosis in an 86-year-old female.

In summary, HIT developed in 5 cases after therapeutic dosage of LMWH, in 4 patients after prophylactic dose of LMWH and in one after UFH flushes used in hemodialysis. The mean duration of heparin administration to HIT onset was 9 days (range 6-14). Three of the patients had a malignancy. A drop-in platelet count was observed in all patients, the minimal platelet count was $27x10^9$/L in one case. Thrombotic complications developed in 7 cases (in 4 of them as a rethrombosis and in 3 as a new onset of deep vein thrombosis). In 2 cases, clinical manifestation of HIT was skin necrosis, as shown in Figure 1 (64-year-old male) and Figure 2 (86-year-old female). In one case, thrombocytopenia was the only sign of HIT. Fondaparinux was successfully used in all patients, with complete platelet recovery (mostly after 5-7 days). As mentioned above, the dose of pentasaccharide was chosen individually, with respect to the primary indication of anticoagulation and according to the clinical manifestation of HIT. In 2 cases with severe renal impairment we were extremely cautious and used prophylactic dose of fondaparinux every other day. We were fully aware of the risk associated with impaired renal elimination of the drug, but we did not have any alternative option. We monitored anti-Xa activity twice daily and did not observe any adverse effects. One patient died because of advanced malignancy. In 6 patients we switched to oral anticoagulation after platelet recovery. This therapy consisted of direct oral anticoagulants (DOACs) in 5 cases (dabigatran in 2 patients, apixaban in one and rivaroxaban in 2 cases) and warfarin in 1 case. DOACs seem to be an option in HIT patients but due to our limited experience in this indication we did not use them in the acute phase of HIT.

Discussion

HIT is a rare but potentially fatal antibody-mediated reaction to heparin. The treatment of HIT should start as soon as a 4T score of ≥4 is determined.

Functional laboratory diagnostic tests are more specific than enzyme immunoassays (are better at detecting the clinically significant HIT antibodies, respectively).

However, the mentioned "gold standard" test is available only in one laboratory in the Czech Republic and the delay in receiving results makes this diagnostic approach unacceptable in a real-world clinical practice.

If HIT is suspected, the first step is the discontinuation of heparin and the initiation of the treatment with an alternative anticoagulant. The anticoagulant of choice in patients with acute HIT is argatroban, a direct thrombin inhibitor (DTI) that does not interact with PF4 or heparin-induced antibodies. This drug is not routinely available in most Czech hospitals and the same is true for bivalirudin (a synthetic DTI) and danaparoid (a low-molecular-weight heparinoid). The mentioned alternative anticoagulants have apparent limitations. Danaparoid has been subject to world-wide shortages repeatedly. The use of argatroban is limited in patients with hepatic insufficiency and aPTT- and INR-confounding may occur in various clinical settings, *e.g.* disseminated intravascular coagulation, transition to vitamin K antagonist treatment, during heparin therapy etc. Outpatient use of argatroban and bivalirudin is not possible because these drugs require continuous intravenous infusion and laboratory monitoring. All those compounds (argatroban, bivalirudin, danaparoid) are expensive. Finally yet importantly, lepirudin (recombinant hirudin) which we have also used has not been available on the market since 2012.

In the acute phase of HIT, the use of UFH, LMWH, warfarin and platelet transfusions is absolutely contraindicated. Unlike UFH or LMWH, fondaparinux contains only 5 sugar units and therefore the drug binds less to plasma proteins and does not interact with PF4 or heparin-induced antibodies. This compound does not seem to induce HIT, and can be safely used in patients with a history of HIT[14, 15] and potentially in the treatment of acute HIT[16-18] However, fondaparinux has never been evaluated in methodologically rigorous clinical trial and it is not FDA-approved for this indication. The data about fondaparinux use in HIT patients are available in the form of case reports, case series, and retrospective cohort studies. One small retrospective review of hospital-admitted patients with suspected HIT (N.=47) found fondaparinux to be similarly efficacious and safe in the prevention of new, recurrent or progressive thromboembolic events compared to DTIs.[19] In a retrospective study of 133 patients receiving fondaparinux for HIT, the incidence of thrombosis and/or bleeding complications did not significantly differ from propensity matched controls treated with DTIs.[20] Some case reports, however, document increased bleeding rates (10% to 22%, respectively) in fondaparinux treated HIT patients, especially in those with renal insufficiency[21, 22] Therefore, its use must be carefully monitored in these situations.

Fondaparinux is mentioned as an option in the treatment of HIT by the American Society of Hematology (ASH) but not by the American College of Chest Physicians (ACCP).[23] ASH recommends the discontinuation of all heparin agents for patients with the diagnosis of HIT or with moderate to high suspicion of developing HIT. Concerning therapy, ASH recommends argatroban, danaparoid, bivalirudin, and fondaparinux.[6] There is a statement in the ASH recommendations noting the difference from the ACCP recommendations: "Other experts believe that fondaparinux is an important treatment option, especially in stable, non-critically ill patients." Fondaparinux is being used more often as an off-label treatment for HIT.[24] Clinical experience with fondaparinux has been systematically reviewed recently.[25] The review evaluated the efficacy and safety of fondaparinux in the treatment of confirmed and probable HIT. Nine studies with 154 consecutive adult patients were included. HIT diagnosis was performed by laboratory tests (serologic-release assay or heparin-induced platelet activation assay or ELISA) in conjunction with clinical criteria (mainly 4Ts score). Fondaparinux was used as the primary anticoagulant for acute HIT in doses varying from prophylactic to therapeutic. The included studies were retrospective registries or cohorts and all of them comprised information about important clinical outcomes, *i.e.* thrombotic and hemorrhagic events. Taken together, thrombotic complications during fondaparinux therapy occurred in 10 cases (6.5%) and major bleeding in 26 patients (16.9%). The authors conclude that the rate of thrombotic and bleeding complications on fondaparinux were similar to drugs approved for HIT treatment, and, therefore fondaparinux appears to be effective and safe in acute HIT despite the absence of randomized trials. They also stress the need to be cautious in the patients with renal insufficiency.

Our own experience from the presented HIT case series encouraged us in our approach, which had been developed due to limited access to diagnostic tests and alternative anticoagulants in clinical practice. Fondaparinux was efficacious and safe in the acute phase, even in two risky situations with severe renal impairment.

DOACs may also represent potential alternatives in the treatment of some patients with HIT,[26, 27] but we used them only after platelet recovery in 5 cases with an ongoing indication for anticoagulation. DOACs will probably never completely replace parenteral agents such as fondaparinux because oral drug administration is not always possible (for various reasons, *e.g.* GI intolerance, vomiting, ileus, mucositis, non-cooperative patients etc.).

Duration of anticoagulation therapy for HIT depends on the presence or absence of concurrent thrombosis. American and British guidelines recommend therapeutic doses of anticoagulation for 4 weeks in patients with isolated HIT and for 3 months in HIT patients with thrombosis.[23, 28]

Conclusions

While heparin and its derivatives are commonly used in hospitalized patients, physicians should be aware of the risk of HIT. However, the current options of laboratory testing and treatment of HIT are not fully satisfactory in a routine clinical practice. Fondaparinux is widely used off-label for suspected HIT, but the efficacy and safety require further evaluation. We used fondaparinux successfully in a heterogeneous cohort of 10 patients, and, with extreme caution even in those with severe renal impairment. Fondaparinux and DOACs are emerging as major HIT treatment options, in spite of the absence of regulatory approval for the treatment of HIT. Larger clinical studies are required to validate this observation in patients with HIT.[29, 30]

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