Srp Arh Celok Lek. 2016 Nov-Dec;144(11-12):654-656
ПРИКАЗ БОЛЕСНИКА / CASE REPORT
DOI: 10.2298/SARH1612654K
UDC: 615.273.065; 616.61-78-06

Fondaparinux monitoring in a patient with heparin-induced thrombocytopenia on hemodialysis

Jovana Kušić[1], Andrijana Kulić[2], Veselinka Djurković[1], Rodoljub Marković[1], Velja Milačić[3], Ljiljana Surić-Lambić[1], Gordana Peković[1]

[1]Clinical Hospital Center Zemun, Department of Nephrology, Belgrade, Serbia;
[2]Clinical Hospital Center Zemun, Blood Bank Department, Belgrade, Serbia;
[3]Clinical Hospital Center Zemun, Department of Surgery, Belgrade, Serbia

SUMMARY

Introduction Heparin-induced thrombocytopenia associated to hemodialysis is rare. In case when citrate dialysis and/or non-heparin anticoagulants are not available, only possible medication to use for anticoagulation during hemodialysis is fondaparinux. However, laboratory monitoring of fondaparinux based on anti-Xa activity in dialysis patients has not been sufficiently documented yet.

Case Outline We created a local anti-factor Xa assay for measuring fondaparinux plasma concentration and efficacy in a patient with heparin-induced thrombocytopenia during hemodialysis. Fondaparinux given subcutaneously increases risk of adverse events due to its extended release and prolonged maintenance of toxic levels. When used intravenously fondaparinux remains safe, with reached steady-state level within dialysis and low risk of toxicity afterwards.

Conclusion Fondaparinux may be used as an alternative anticoagulant medication during hemodialysis in patients who develop heparin-induced thrombocytopenia. Adequate dose must be adjusted to patients' dry weight (0.03 mg/kg intravenously) and fondaparinux anti-coagulation monitoring must be provided.

Keywords: heparin-induced thrombocytopenia; fondaparinux specific monitoring; hemodialysis

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a serious, potentially fatal, decline in platelet number due to use of unfractionated heparin, low-molecular weight heparin, and/or other polyanions [1–4]. It may present as a non-immune or immune-mediated form, with immune complexes formed between heparin and platelet factor 4 (PF4) [5, 6]. This form of thrombocytopenia may be followed by life-threatening thromboembolic events, such as deep vein thrombosis and pulmonary embolism [7, 8]. HIT associated with hemodialysis is rare, but even small amounts of heparin used for anticoagulation during hemodialysis treatment may provoke HIT [3, 4, 8]. In chronic dialysis patients, HIT frequency is low (3.9% in the literature) in newly diagnosed patients [4, 8]. Application of non-heparin anticoagulant preparations, including the specific anti-Xa inhibitor fondaparinux, is necessary [9]. Therefore, clinical management of HIT in patients on hemodialysis is difficult, in some countries often limited by the lack of drug supplies. Laboratory monitoring of fondaparinux based on anti-Xa activity in dialysis patients has not been sufficiently documented. This case report presents the application and dose adjustment of fondaparinux in dialysis patients with type II HIT.

Correspondence to:
Jovana KUŠIĆ
Department of Nephrology
Clinical Hospital Center Zemun
9 Vukova Street, 11080 Belgrade
Serbia
jovanakusic@yahoo.com

CASE REPORT

A 56-year-old patient was admitted to our hospital with terminal stage of chronic kidney failure secondary to polycystic kidney disease. During the hospitalization, he was started on the chronic program of hemodialysis, through central venous catheter. Arteriovenous fistula was created three days after his first (urgent) hemodialysis, as he previously refused it. Fifteen days after hemodialysis was started, the patient developed a significant decline in the platelets count from 286×10^9/L to 41×10^9/L. Clinical suspicion for HIT II was confirmed by a highly positive result for HIT-Ab (20.6 IU/mL). The presence of HIT antibodies was detected with immunoturbidimetric assay (HIT-AbPF4-H HemosIL, IL ACL 300, Instrumentation Laboratory Company, Milan, Italy).

When diagnosis was confirmed, heparin was discontinued. As citrate dialysis is not available in Serbia, and non-heparin anticoagulants are not proposed by the healthcare system for the diagnosis of HIT, the only possible medication to use was fondaparinux (fondaparinux sodium; GlaxoSmithKline, Brentford, UK). However, official data for fondaparinux used in patients on hemodialysis was limited. Thus, after consultation with transfusion medicine specialist, it was decided to establish a local fondaparinux-specific anti-Xa assay for the fondaparinux monitoring. Anti-Xa assay was created with fondaparinux calibrator and performed with anti-Xa heparin chromogenic

method (anti-Xa heparin assay IL on ELITE PRO® IL, Instrumentation Laboratory Company, Milan, Italy).

Fondaparinux plasma level was measured at the beginning of dialysis, every hour during the dialysis and 24 hours after every dialysis treatment. The known mean steady state plasma concentration is in the range of 0.46 to 0.62 mg/l, which is regularly applied to patients with symptomatic deep vein thrombosis and pulmonary embolism undergoing treatment with fondaparinux [10]. As hemodialysis session itself requires effective dosage of anticoagulant to prevent potential thrombotic complications in blood and extracorporeal circuit, and as HIT additionally favors thrombosis, we have used the same steady state for coagulation monitoring in our patient [10].

In our patient, 0.03 mg/kg (of patient's estimated dry-weight) of fondaparinux was firstly administered subcutaneously at the beginning of dialysis treatment. During the third hour of dialysis, plasma level of fondaparinux reached toxic values (0.71 mg/L). Two days afterwards, at the second dialysis course, twice-reduced dose (0.015 mg/kg) was administered subcutaneously at the beginning of dialysis, when fondaparinux plasma level was within steady-state levels. However, toxic levels were reached during dialysis: 0.89 mg/L, 0.77 mg/L, and 0.84 mg/L at the first, second and third hour, respectively. At the start of the third hemodialysis, 0.03 mg/kg of fondaparinux was applied intravenously. During the entire aforementioned treatment, fondaparinux plasma levels were within the optimal range, with maximum of 0.61 mg/L at the third hour of hemodialysis (Table 1).

Comparing pharmacokinetics between the dialyses, while fondaparinux was administered subcutaneously, its plasma levels were reaching toxic values, 1.13 mg/L and 0.69 mg/L even 12 hours after first and second dialysis, respectively. However, when fondaparinux was administered intravenously, its plasma level remained within the reference interval during the follow-up (Table 2). Therefore, 0.03 mg/kg of fondaparinux was continued intravenously during further hemodialysis treatments of this patient. Coagulation monitoring was checked after every hemodialysis session, and remained within the effective and safe range.

Nevertheless, type of dialysis was changed during the hospitalization. Both low-flux bicarbonate hemodialysis and postdilutional hemodiafiltration were inappropriate. Postdilutional hemodiafiltration was effective for fondaparinux elimination and prevention of its accumulation, but in the arteriovenous system it produced high hemoconcentration, which led to coagulation in the dialysis set. However, high-flux bicarbonate hemodialysis showed the best performance for both dialysis effectiveness and low fondaparinux accumulation.

Soon after heparin discontinuation, platelet number returned within reference levels. After four months, heparin was re-introduced to hemodialysis in the same patients, and no thrombocytopenia occurred.

Table 1. Fondaparinux serum levels during hemodialysis (HD)

Fondaparinux (mg/L)	HD I	HD II	HD III
Before HD	0.51	0.40	0.24
1 hour of HD	0.74	0.89	0.59
2 hours of HD	0.65	0.77	0.57
3 hours of HD	0.71	0.84	0.61

Table 2. Fondaparinux levels within hemodialysis

Time (h)	Fondaparinux (mg/L)
12 h after 1st HD	1.13
12 h after 2nd HD	0.69
12 h after 3rd HD	0.16
12 h after 4th HD	0.28
12 h after 5th HD	0.36
12 h after 6th HD	0.39

DISCUSSION

This case illustrates the main obstacles in treatment management of HIT in hemodialysis. Current guidelines recommend immediate discontinuation of heparin and use of non-heparin anticoagulants, such as anti-Xa and direct thrombin inhibitors. Danaparoid and lepirudin are usually recommended, together with new oral anticoagulants [7, 11, 12, 13]. However, Serbia has limited access to these anticoagulants. Citrate-based dialysis, which is recommended in case of HIT development, is also unavailable in Serbia. When guideline-suggested non-heparin medications and anticoagulants are not available for treatment of this serious condition, especially in the resource-limited settings, fondaparinux may present as a possible alternative.

Although fondaparinux, as a coagulation factor Xa inhibitor, is noted to be used in several cases of HIT until now, there are still no officially established protocols for fondaparinux use [10, 14, 15]. This is particularly an inconvenience in a population which develops HIT during hemodialysis, because of its mainly renal route of excretion [9, 10]. Additionally, fondaparinux monitoring assays are not commercially available, which thoroughly disables its routine use [16].

The assay methodology for measuring fondaparinux plasma concentration and efficacy is very similar to the standard anti-factor Xa assay for low-molecular-weight heparin or unfractionated heparin, but still not equivalent [14, 15]. Thus, in our case, we created a fondaparinux-specific assay using fondaparinux calibrator with an anti-factor Xa heparin assay method (anti-factor Xa heparin IL).

As our case showed, fondaparinux had given subcutaneously increases risk of adverse events due to its extended-release and prolonged maintenance of toxic levels, even 12 hours after dialysis. However, when used intravenously, fondaparinux remains safe, with reached steady-state level within dialysis and low risk of toxicity afterwards.

Potential cross-reactivity of fondaparinux to previous use of heparin is acknowledged and may be provoked, but it nonetheless has lesser extent of immunogenicity than heparin [7]. Furthermore, dosage of fondaparinux must be adjusted to the rate of glomerular filtration due to its increased risk of accumulation in patients with renal failure [10, 14, 17]. When used in patients on hemodialysis, it is necessary to apply fondaparinux adjusted to patients' estimated dry weight. If possible, it is advisable to perform high-flux bicarbonate dialysis. Therefore, when fondaparinux is used in specific groups, such as patients with renal failure and/

or patients on chronic dialysis, a specific fondaparinux anti-coagulation assay must be developed.

In conclusion, fondaparinux may be used as an alternative anticoagulation during hemodialysis in patients who develop HIT. Adequate dose must be adjusted to patients' dry weight, and fondaparinux anti-coagulation monitoring must be provided.

REFERENCES

1. Baroletti SA, Goldhaber SZ. Heparin-induced thrombocytopenia. Circulation. 2006; 114(8):355–6. [DOI: 10.1161/circulationaha.106.632653] [PMID: 16923760]
2. Dutt T, Schulz M. Heparin-induced thrombocytopenia (HIT) – an overview: what does the nephrologist need to know and do? Clin Kidney J. 2013; 6(6):563–7. [DOI: 10.1093/ckj/sft139] [PMID: 26069824]
3. Davenport A. Heparin-induced thrombocytopenia during renal replacement therapy. Hemodial Int. 2004; 8(3):295–303. [DOI: 10.1111/j.1492-7535.2004.01108.x] [PMID: 19379430]
4. Hutchinson CA, Dasgupta I. National survey of heparin-induced thrombocytopenia in the hemodialysis population of the UK population. Nephro Dial Transplant. 2007; 22(6):1680–4. [DOI: 10.1093/ndt/gfm055] [PMID: 17371779]
5. Arepally GM, Ortel TL. Clinical practice. Heparin-induced thrombocytopenia. N Engl J Med. 2006; 335(8):809–17. [DOI: 10.1056/NEJMcp052967] [PMID: 16928996]
6. Greinacher A, Warkentin TE. Recognition, treatment, and prevention of heparin-induced thrombocytopenia: review and update. Thromb Res. 2006; 118(2):65–76. [DOI: 10.1016/j.thromres.2005.07.012] [PMID: 16139874]
7. Bakchoul T, Greinacher A. Recent advances in the diagnosis and treatment of heparin-induced thrombocytopenia. Ther Adv Hematol. 2012; 3(4):237–51. [DOI: 10.1177/2040620712443537] [PMID: 23606934]
8. Matsuo T, Wanaka K, Miyasita K, Perched M, Walenga JM. Clinical evaluation of acute systemic reaction and detection of IgG antibodies against PF4/heparin complexes in hemodialysis patients. Thromb Res. 2012; 129(4):474–8. [DOI: 10.1016/j.thromres.2011.10.012] [PMID: 22088491]
9. Ortel TL. Heparin-induced thrombocytopenia: when a low platelet count is a mandate for anticoagulation. Hematology Am Soc Hematol Educ Program. 2009; 225–32. [DOI: 10.1182/asheducation-2009.1.225] [PMID: 20008202]
10. Arixtra Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline; 2011. p. 6.
11. Esposito P, Libetta C, Borettaz I, Barone M, Canevari M, Martinelli C, et al. Heparin-induced trombocytopenia: pathogenesis, clinical manifestations and management in hemodialysis. G Ital Nefrol. 2014; 31(3). [PMID: 25030007]
12. Davenport A. Antibodies to heparin-platelet factor 4 complex: pathogenesis, epidemiology, and management of heparin-induced thrombocytopenia in hemodialysis. Am J Kidney Dis. 2009; 54(2):361–74. [DOI: 10.1053/j.ajkd.2009.03.012] [PMID: 19481318]
13. Kang M, Sawh S, Kovacs MJ, Lazo-Langner A. Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia a propensity score matched study. Blood. 2015; 125(6):924–9. [DOI: 10.1182/blood-2014-09-599498] [PMID: 25515959]
14. Cope J, Bushwitz J, An G, Antigua A, Patel A, Zumberg M. Clinical experience with prophylactic fondaparinux in critically ill patients with moderate to severe renal impairment or renal failure requiring renal replacement therapy. Ann Pharmacother. 2015; 49(3):270–7. [DOI: 10.1177/1060028014563325] [PMID: 25515864]
15. Haase M, Bellomo R, Rocktaeschel J, Ziemer S, Kieswetter H, Morgera S, et al. Use of fondaparinux (ARIXTRA®) in a dialysis patient with symptomatic heparin-induced thrombocytopaenia type II. Nephrol Dial Transplant. 2005; 20(2):444–6. [DOI: 10.1093/ndt/gfh544] [PMID: 15673695]
16. Johnson PN, Benefield EC, Bui PYN, Gausman JN, Marlar RA, Gessouroun MR. Fondaparinux monitoring: need for a local fondaparinux-calibrated anti–factor Xa assay. J Pediatr Pharmacol Ther. 2013; 18(4):318–9. [DOI: 10.5863/1551-6776-18.4.318] [PMID: 24719594]
17. Antonijević N, Kanjuh V, Živković I, Jovanović Lj, Vukčević M, Apostolović M. Contribution of novel anticoagulants fondaparinux and dabigatran to venous thromboembolism prevention. Srp Arh Celok Lek. 2015; 143(3-4):230–6. [DOI: 10.2298/SARH1504230A] [PMID: 26012138]

Коагулациони мониторинг фондапарина код болесника са хепарином индукованом тромбоцитопенијом на хемодијализи

Јована Кушић[1], Андријана Кулић[2], Веселинка Ђурковић[1], Родољуб Марковић[1], Вања Милачић[3], Љиљана Сурић-Ламбић[1], Гордана Пековић[1]

[1]Клиничко-болнички центар „Земун", Служба нефрологије, Београд, Србија;
[2]Клиничко-болнички центар „Земун", Служба за трансфузију крви, Београд, Србија;
[3]Клиничко-болнички центар „Земун", Служба хирургије, Београд, Србија

КРАТАК САДРЖАЈ

Увод Хепарином индукована тромбоцитопенија је нежељена реакција на примену хепарина, а код болесника на хемодијази је ретка компликација. Код особа које развију хепарином индуковану тромбоцитопенију током хемодијализног третмана контраиндикована је примена хепарина за антикоагулацију, те се у свету у оваквим случајевима примењује цитратна дијализа и/или нехепаринска антикоагулантна терапија. Уколико су цитратна дијализа и/или нехепаринска антикоагулантна терапија недоступне, потенцијални начин антикоагулације током хемодијализе је примена фондапарина (инхибитор фактора коагулације *Xa*). Ипак, до сада није креиран рутински коагулациони мониторинг за процену ефикасности и безбедности примене фондапарина код болесника на хемодијализи.

Приказ болесника За потребе нашег болесника са хепарином индукованом тромбоцитопенијом који је на хроничном програму хемодијализе креирали смо локални специфични мониторинг анти-*Xa* активности за одређивање концентрације фондапарина у плазми и праћење његове ефикасности и безбедности. Како је наш приказ случаја доказао, примена фондапарина субкутано повећава ризик од нежељених ефеката због продуженог времена ослобађања и одржавања токсичних вредности. Када се фондапарин примењује интравенски (0,03 *mg/kg* суве телесне тежине), његова примена је безбедна, са малим ризиком од нежељених реакција.

Закључак Фондапарин се може применити као алтернативни антикоагуланс за болеснике на хроничном програму хемодијализе који су развили хепарином индуковану тромбоцитопенију. Адекватна доза се одређује према сувој телесној тежини болесника (0,03 *mg/kg* интравенски) уз примену специфичног антикоагулационог мониторинга.

Кључне речи: хепарином индукована тромбоцитопенија; специфични коагулациони мониторинг фондапарина; хемодијализа

Примљен • Received: 28/12/2015 **Ревизија • Revision:** 06/03/2016 **Прихваћен • Accepted:** 09/03/2016

doi: 10.2298/SARH1612654K