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Letter to the Editors-in-Chief

Danaparoid use for haemodialysis in a morbidly obese patient with heparin-induced thrombocytopenia – Need for a higher than recommended weight-based dosing

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SUMMARY

What is known and objective: Heparin is widely used to prevent clotting of the extracorporeal circuit during haemodialysis (HD). Heparin-induced thrombocytopenia (HIT) is a potentially devastating immune mediated adverse drug reaction caused by the emergence of antibodies that activate platelets in the presence of heparin, leading to a pro-thrombotic state. Danaparoid is an alternative anticoagulant used in patients on HD with HIT but its dosing recommendations in obese patients on HD are relatively scarce.

Case summary: We report a case of a 48-year-old morbidly obese patient who received weight-based dosing of danaparoid for HD with monitoring of anti-Xa activity. However, despite the patient's anti-Xa level being within the therapeutic range at various time points, the circuit lines kept clotting during HD.

What is new and conclusion: The report provides evidence that the manufacturer's recommendations on dosing danaparoid based on body weight may lead to sub-optimal therapeutic benefit and highlight the need for higher than recommended weight-based dosing in obese individuals on dialysis.

1. What Is known and objective

Exposure of blood to extracorporeal circuits results in activation of the coagulation pathway, in addition to other cascade systems. Anticoagulation with unfractionated heparin (heparin) is widely used during haemodialysis (HD) to prevent clotting of the circuit and the dialyzer [1]. However, it is well-known that rarely heparin can cause immune-mediated thrombocytopenia due to autoantibody formation against endogenous platelet factor 4 (PF4) in complex with heparin (HIT antibodies) and lead to platelet activation and a pro-coagulant state [2]. Heparin may by itself contribute to HD associated platelet activation, thrombocytopenia, and increased PF4 release from platelets during a dialysis session [3]. If HIT is suspected then all applications of heparin should be stopped regardless of indication, dose, dosing schedule or route of administration [2]. Low-molecular weight heparins (LMWH) can also induce HIT antibodies, albeit less frequently than heparin but because of high rates of cross-reactivity, once heparin has induced HIT antibody formation, LMWH should also be avoided [2].

Danaparoid is an alternative anticoagulant that can be used in patients on HD with HIT [2,4–7].It is a heparinoid of low molecular weight (5.5 kDa) consisting of heparan (~84%), dermatan sulphates (~12%) and glycosaminoglycans (4%), with < 10% cross reactivity with heparin. It inhibits thrombin generation and has a minor indirect effect on thrombin activity [6,7]. The inhibition of thrombin generation and factor Xa is much more selective than LMWH with an activity ratio for factor Xa to thrombin inhibition of 22:1 versus 3:1 for LMWH - as a result plasma anti-Xa activity is used for monitoring its efficacy [8]. Elimination of danaparoid is predominantly renal and in patients with normal renal functions, it has an elimination half-life of 25 h. In patients with end stage kidney disease (ESKD), the half-life of danaparoid can be prolonged between 31 h to 4 days [9,10]. Hence in patients receiving dialysis, monitoring and adjustment of bolus dose is often based on the anti-Xa activity before the start of subsequent dialysis session [11]. In practice, the recommended dosing schedule is weight-based with 3750 units as IV bolus for first and second dialysis and 3000 units for subsequent dialysis in patients weighing > 55Kgs and 2500 units for first two dialysis sessions followed by 2000 units for subsequent HDs in patients weighing < 55Kgs [11]. However, information on dosing of danaparoid in obese patients on HD in relatively scarce. Although a pharmacokinetic study in patients with normal renal functions concluded that anti-Xa activity following danaparoid administration is relatively insensitive of body weight [12], this cannot be extrapolated in patients on dialysis as well as in obese individuals, since it is well known that the physiological changes in obesity influence pharmacokinetic characteristics of several drugs, including distribution, protein binding, metabolism and renal excretion [13]. We report a morbidly obese patient with HIT on HD who received danaparoid with monitoring of anti-Xa activity and highlight the need for higher than recommended weight-based dosing in these individuals.

2. Case description

A 48-year-old morbidly obese woman (143 kg, BMI 53.82 kg/m^2) with ESKD secondary to diabetic nephropathy was on thrice weekly HDs through a tunnelled internal jugular vascath using the Revaclear 400 dialyzer. Her other co-morbidities included pulmonary embolus (on warfarin therapy), hypertension, congestive cardiac failure, obstructive sleep apnoea on CPAP, asthma, peripheral vascular disease, anxiety, depression and history of HIT. She was commenced on danaparoid as an anticoagulant (after an initial period of 'heparin-free' HDs complicated with frequent clotting of the extra-corporeal circuits) with trisodium citrate (Duralock) as the catheter locking solution. Danaparoid was initiated on a reduced dose of 3000 units during HD (administered predilution) - as opposed to the recommended 3750 units for first and second HD sessions, as the patient was on warfarin for the treatment of her pulmonary embolism [11]. Anti-Xa levels were

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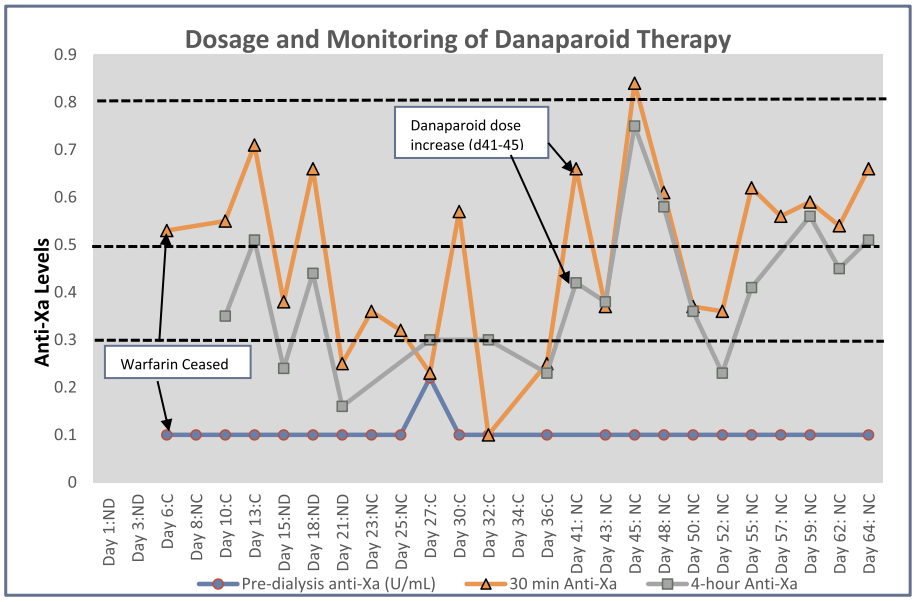

Fig. 1. Monitoring of Anti-Xa levels during danaparoid therapy.
ND: No documentation; C-Clotted lines, NC-No clotting; Target in venous line is ≤ 0.3 units/mL pre-dialysis and up to 0.5 to 0.8 IU/mL during dialysis;

measured using the chromogenic method before dialysis, 30 min after the start of dialysis and after 4 h of dialysis with therapeutic targets of < 0.3 units/mL pre-dialysis and 0.5–0.8 units/mL during dialysis [11].

Danaparoid was continued at the dose of 3000 units (3 times a week) for 30 days despite warfarin being ceased 5 days after the initiation of danaparoid, as the patient had completed recommended duration of anti-coagulation with warfarin for treatment of pulmonary embolism. Despite the patient's anti-Xa level being within the therapeutic range at various time points, the HD circuit lines kept clotting during HD treatments (Fig. 1, Table 1**).** The dose of danaparoid was initially increased to 3750 units without any therapeutic benefit since the HD circuit lines kept clotting and were associated with sub-therapeutic anti-Xa levels. Finally, the dose of danaparoid was up titrated up to 4500 units that resulted in preventing subsequent clotting of HD circuit lines and achievement of therapeutic anti-Xa levels. The patient continued to have dialysis sessions at 4500 units of danaparoid for two more sessions with no further episodes of circuit clotting after which the dose of danaparoid was reduced to 3750 units, still achieving therapeutic anti-Xa levels with no further clotting of lines.

Table 1
Dosage and monitoring of danaparoid therapy.

Day	Danaparoid dose	Pre-dialysis anti-Xa (U/mL)	30 min Anti-Xa	4-hour Anti-Xa	Platelet Count (×10^9/L)
Day 1	3000 IU	Not measured			
Day 3	3000 IU	Not measured			
Day 6	3000 U	< 0.10	0.53		No blood collected
Day 8	3000 U	< 0.10			278
Day 10	3000 U	< 0.10	0.55	0.35	No blood collected
Day 13	3000 U	< 0.10	0.71	0.51	307
Day 15	3000 U	< 0.10	0.38	0.24	279
Day 18	3000 U	< 0.10	0.66	0.44	No blood collected
Day 21	3000 U	< 0.10	0.25	0.16	252
Day 23	3000 U	< 0.10	0.36		283
Day 25	3000 U	< 0.10	0.32		239
Day 27	3000 U	0.22	0.23	0.30	290
Day 30	3000 U	< 0.10	0.57		325
Day 32	3000 U	< 0.10	< 0.10	0.30	306
Day 34	3750 U				335
Day 36	3750 U	< 0.10	0.25	0.23	282
Day 41	4250 U		0.66	0.42	292
Day 43	4250 U	< 0.10	0.37	0.38	310
Day 45	4250 U	< 0.10	0.84	0.75	295
Day 48	3750 U	0.10	0.61	0.58	318
Day 50	3750 U	< 0.10	0.37	0.36	279
Day 52	3750 U	< 0.10	0.36	0.23	338
Day 55	3750 U	< 0.10	0.62	0.41	349
Day 57	3750 U	< 0.10	0.56		288
Day 59	3750 U	< 0.10	0.59	0.56	291
Day 62	3750 U		0.54	0.45	No blood collected
Day 64	3750 U	< 0.10	0.66	0.51	No blood collected

3. What is new and conclusion

The overall incidence of HIT following exposure to heparin is about 1 to 5% [14]. As patients on HD are continuously exposed to heparin they are at a risk of developing PF4-heparin antibodies. The prevalence of HIT antibody in patients undergoing HD has been reported in several studies [15–17] and ranges from 0 to 17.4%, however the risk of HIT complications in the HD population remains unclear. Some studies have reported no clinical sequalae whilst others have reported complications of thrombocytopenia, frequent clotting of the extracorporeal circuit or an increase in the number of failed arteriovenous fistulae [17–19]. In the presence of heparin, these antibodies can become pathogenic leading to life-threatening venous and arterial thromboses. Patients with HITs on HD can receive their HDs without anticoagulating the extra-corporeal circuit with repeated normal saline flushes- 'heparin-free' dialysis, which is not as effective in preventing clotting of the extra-corporeal circuit and carries an inherent risk of fluid overload because of higher ultra-filtration targets during the HD session [20]. Alternatives to 'heparin free' dialysis in patients with HIT include use of danaparoid, fondaparinux, argatroban, bivalirudin and citrate anti-coagulation during an HD session [20–22]. Citrate dialysates for haemodialysis are not available in Australia and amongst the other agents danaparoid is the most cost effective and has the largest experience – the reason why we chose to use this agent in our patient [2].

Several studies have shown that danaparoid has been used successfully in patients with HITs [4,23]. The efficacy of danaparoid has

been established in a prospective randomised controlled trial to treat thrombosis in patients with HITs, but not on dialysis [24]. However, despite its considerable clinical experience danaparoid has several disadvantages; long half-life, no direct antidote, not easily monitored and potential cross reactivity of approximately 10% with heparin [2,4]. Additionally, the dose recommendations for use of danaparoid for intermittent HD provided by the manufacturer are based on body weight [11].

As suggested by our case report, the usually recommended dose of danaparoid may be low for morbidly obese patients with HITs. It is well known that overweight/ obese patients are generally excluded from clinical trials or their participation is significantly limited and pharmacokinetic parameters such as distribution volume, biological half-life and clearance can be significantly altered in these patients. Hence, the use of medications, especially those with a small therapeutic window in obese patients remains a big challenge. Although, danaparoid was initiated cautiously in our case due concomitant warfarin therapy, even after the increase to the recommended dose of 3750 units- the circuit lines clotted. It was only after the dose was increased to 4500 units that the patient attained therapeutic levels with no further clotting of the lines. The maintenance dose of danaparoid was then reduced to 3750 units, with continued achievement of therapeutic anti-Xa levels, a dose that is still higher than the recommended maintenance dose [11]. A potential explanation of 3750 units being able to maintain anticoagulation could be due to the attainment of therapeutic levels following the higher dose (4500 units). A recent analysis of 103 case reports with danaparoid use in patients with HIT and acute renal failure requiring continuous veno-venous renal replacement therapy (CVRRT) reported that plasma anti-Xa levels correlated poorly with bleeding or thrombotic complications but positively with minor bleeding complications [25]. The study suggested danaparoid dosage adaptations is better judged by clinical criteria (bleeding/thrombosis risk balance) than by plasma anti-Xa monitoring [25]. Additionally, anti-Xa assay is poorly standardised between laboratories, not performed in routine coagulation laboratories, and cross laboratory results obtained on the same test sample vary widely in external quality assurance studies [26].

Previous studies [2–4] have also reported persistent or repeated thrombocytopenia with the use of danaparoid. Hence, it is important to monitor platelet count or for new fibrin deposits and clot formation within the extracorporeal circuit after application of danaparoid which may indicate clinically relevant cross-reactivity [2–4]. However, this was unlikely in our case as the platelets were normal and patient kept clotting the circuit lines prior to danaparoid therapy with 'heparin-free' dialysis.

Another potential problem with danaparoid is that renal clearance makes up 40–50% of total plasma clearance and half-life of this drug can range between 31 h to 4 days in patients with ESKD [9,10]. HD patients treated with danaparoid might remain anticoagulated in the interdialytic interval which can be problematic in individuals with high bleeding risk. Furthermore, danaparoid is not removed by high-flux dialysis and plasmapheresis may be the only way to remove the drug in case of severe bleeding [27]. Hence the initial reduced dose of 3000 units due to the presence of concomitant warfarin therapy seems justified. A review of the 102 cases with danaparoid use in CVRRT reported a total of 8 major bleeding events (3 fatal and 5 non-fatal) and despite the poor correlation between plasma anti-Xa and major bleeding or thrombotic events other studies have suggested that the upper level pf the target plasma anti-Xa activity range should be limited to 0.8 U/mL [25,28–30].

4. Conclusion

Although danaparoid has been used safely and effectively for intermittent HD, we report the use of danaparoid dosing in a morbidly obese patient on haemodialysis with HITs. In obese individuals undergoing HD and requiring anticoagulation with danaparoid, higher than recommended weight-based dosing may be considered if standard weight-based dosing recommendations result in extracorporeal haemodialysis circuit thrombotic complications.

Compliance with ethical standards

The manuscript has been prepared and submitted with compliance to the ethical standards

Sources of funding

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Informed consent

Obtained

Declaration of Competing Interest

None

References

[1] K.M.T.P. Thong, A. Khwaja, Management of heparin-induced thrombocytopenia (HIT) in patients with systemic vasculitis and pulmonary haemorrhage, Clin. Kidney J. 6 (2013) 622–625.
[2] S.I. O'Shea, T.L. Ortel, E.C. Kovalik, Alternative methods of anticoagulation for dialysis-dependent patients with heparin-induced thrombocytopenia, Semin. Dial. 16 (2003) 61–67.
[3] T. Matsuo, K. Wanaka, Heparin-induced thrombocytopenia and hemodialysis, Journal of Blood Disorders and Transfusion S2 (2) (2011).
[4] M. Kessler, F. Moureau, P. Nguyen, Anticoagulation in chronic hemodialysis: progress toward an optimal approach, Semin. Dial. 28 (2015) 474–489.
[5] M.I. Wilde, A. Markham, Danaparoid. A review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia, Drugs 54 (1997) 903–924.
[6] F.A. Ofosu, Anticoagulant mechanisms of Orgaran (org 10172) and its fraction with high affinity to antithrombin III (Org 10849), Haemost 22 (1992) 66–72.
[7] H.N. Magnani, A review of 122 published outcomes of danaparoid anticoagulation for intermittent haemodialysis, Thromb. Res. 125 (2010) e171–e176.
[8] B.H. Chong, W.R. Pitney, P.A. Castaldi, Heparin-induced thrombocytopenia: association of thrombotic complications with heparin-dependent IgG antibody that induces thromboxane synthesis in platelet aggregation, Lancet 2 (1982) 1246–1249.
[9] K.G. Fischer, Hemodialysis in heparin-induced thrombocytopenia, in: T.E. Warkentin, A. Greinacher (Eds.), Heparin-Induced Thrombocytopenia, 3rd edn, Marcel Dekker, New York, 2007, pp. 463–485.
[10] U. Frei, M.F. Wilks, S. Boehmer, N. Crisp-Lindgren, R. Schwarzrock, et al., Gastrointestinal blood loss in haemodialysis patients during use of a lowmolecular-weight heparinoid anticoagulant, Nephrol. Dial. Transplant. 3 (1988) 435–439.
[11] K.G. Fischer, Essentials of anticoagulation in hemodialysis, Hemodial 11 (2007) 178–189.
[12] M. Danhof, A. deBoer, H.N. Magnani, J.C.J. Stiekema, Pharmacokinetic considerations on orgaran (Org 10172) therapy, Haemostasis 22 (1992) 73–84.
[13] G. Cheymol, Effects of obesity on pharmacokinetics implications for drug therapy, Clin. Pharmacokinet. 39 (2000) 215–231.
[14] T.E. Warkentin, M.N. Levine, J. Hirsh, et al., Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin, N. Engl. J. Med. 332 (1995) 1330–1335.
[15] S.I. O'Shea, J.J. Sands, S.A. Nudo, T.L. Ortel, Frequency of anti-heparin-platelet factor 4 antibodies in hemodialysis patients and correlation with recurrent vascular access thrombosis, Am. J. Hematol. 69 (2002) 72–73.
[16] T. Sitter, M. Spannagl, B. Banas, H. Schiffl, Prevalence of heparin-induced PF4-heparin antibodies in hemodialysis patients, Nephron 79 (1998) 245–246.
[17] T. Matsuo, H. Kobayashi, M. Matsuo, et al., Frequency of anti-heparin-PF4 complex antibodies (HIT antibodies) in uremic patients on chronic intermittent hemodialysis, Pathophysiol. Haemost. Thromb. 35 (2006) 445–450.
[18] A. Yu, S.H. Jacobson, A. Bygdén, N. Egberg, The presence of heparin-platelet factor 4 antibodies as a marker of hypercoagulability during hemodialysis, Clin. Chem. Lab. Med. 40 (2002).
[19] H. Nakamoto, Y. Shimada, T. Kanno, K. Wanaka, T. Matsuo, H. Suzuki, Role of platelet factor 4-heparin complex antibody (HIT antibody) in the pathogenesis of thrombotic episodes in patients on hemodialysis, Hemodial 9 (Suppl. 1) (2005) S2–S7.
[20] A. Davenport, What are the anticoagulation options for intermittent hemodialysis? Nat Rev Nephrol 7 (2011) 499–508.
[21] H. Watson, S. Davidson, D. Keeling, Haemostasis, Thrombosis Task Force of the British Committee for Standards in H. Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition, Br. J. Haematol. 159 (2012) 528–540.

[22] A. Davenport, What are the options for anticoagulation needs in dialysis for patients with heparin-induced thrombocytopenia? Semin. Dial. 24 (2011) 382–385.
[23] D.T. aSM, Heparin-induced thrombocytopaenia (HIT)—an overview: what does the nephrologist need to know and do? Clin. Kidney J. 6 (2013) 563–567.
[24] B.H. Chong, A.S. Gallus, J.F. Cade, et al., Prospective randomised open-label comparison of danaparoid with dextran 70 in the treatment of heparin-induced thrombocytopaenia with thrombosis: a clinical outcome study, Thromb. Haemost. 86 (2001) 1170–1175.
[25] H.N.W.J. Magnani, Is Danaparoid anticoagulation suitable for patients with HIT and ARF requiring CVVRT? An Analysis of Case Reports. 1 (2012) 423, https://doi.org/10.4172/scientificreports.423.
[26] E.J. Favaloro, G. Lippi, J. Koutts, Laboratory testing of anticoagulants: the present and the future, Pathology 43 (2011) 682–692.
[27] S.A. Schneider, M.S. Nauck, M.A. Nauck, K.-G. Fischer, Only plasmapheresis allows for danaparoid elimination from blood [abstract], Kidney Blood Press Res 27 (2004) a360.
[28] E.W. Massey, J. Biller, J.N. Davis, et al., Large-dose infusions of heparinoid ORG 10172 in ischemic stroke, Stroke 21 (1990) 1289–1292.
[29] J.P. Wester, H.W. de Valk, H.K. Nieuwenhuis, et al., Risk factors for bleeding during treatment of acute venous thromboembolism, Thromb. Haemost. 76 (1996) 682–688.
[30] J.P. Wester, F.J. Haas, D.H. Biesma, J.A. Leusink, G. Veth, Thrombosis and hemorrhage in heparin-induced thrombocytopenia in seriously ill patients, Intensive Care Med. 30 (2004) 1927–1934.

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