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Is Danaparoid Anticoagulation Suitable for Patients with HIT and ARF Requiring CVVRT? An Analysis of Case Reports

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Abstract

Purpose: To assess the efficacy and safety outcomes of case reports of danaparoid anticoagulation in critically ill ICU patients suffering from HIT who require CRRT.

Method: A retrospective analysis of 103 cases.

Results: Based on clinical signs, pre-treatment 4T scores and serological testing, HIT was reasonably 'confirmed' in 67.0% of the cases and 'suspected' in the remainder. The patients, with HIT and ARF received the danaparoid treatment regimen for CRRT for 1–39 (median 7) days. Dose adaptation was necessary in 40.2% of the patients to overcome thrombosis or bleeding (risk). Satisfactory CRRT anticoagulation was provided for 93.6% of 94 cases with information, 53.9% of the patients survived. The hospital mortality of 46.1% was mainly attributed to concomitant morbidity, but 5 deaths were related to thrombosis (n=2) or bleeding (n=3). Maintenance plasma anti-Xa activity correlated poorly with bleeding or thrombotic complications but positively with the minor bleeding frequency, hence advice to restrict the upper limit to 0.8 U/mL or preferably to use evidence of bleeding and systemic thrombosis/circuit clotting to judge the need for dose adaptation. The benefit (no thrombosis)/harm (bleeding induction) ratio and combined inefficacy and major haemorrhagic frequency were 10.5 and 16.6% respectively, showing a generally favourable response to danaparoid.

Conclusions: This case report analysis shows that danaparoid, despite its renal elimination, long half-life and lack of antidote, appears to provide efficacious and safe anticoagulation for the majority of critically ill patients with HIT and ARF who are undergoing CRRT.

Keywords: Acute renal failure; Continuous renal replacement Therapy; Danaparoid sodium; Heparin-induced thrombocytopenia; Intensive care unit; Major bleeding; Thrombo-embolic complication

Abbreviations: AMI: Acute Myocardial Infarction; ARF: Acute Renal Failure; MB: Major Bleeding; CRRT: Continuous Renal Replacement Therapy; CVVRT: Continuous Veno-Venous (Renal) Replacement Therapy; DIC: Disseminated Intravascular Coagulation; ECC: Extracorporeal Circulation; ICU: Intensive Care Unit; LMWH: Low Molecular Weight Heparin; MODS: Multiple Organ Dysfunction Syndrome; PCR: Platelet Count Reduction; TEC: Thrombo-Embolic Complication; UFH: Unfractionated Heparin

Introduction

Acute renal failure and heparin-induced thrombocytopenia

Intensive care unit (ICU) patients who develop acute renal failure (ARF) requiring continuous renal replacement therapy (CRRT) have a high risk of further morbidity and mortality [1]. Up to 50% will develop platelet count reduction (PCR) for various reasons or suffer thrombo-embolic complications (TECs). In those patients recently or currently receiving unfractionated heparin (UFH) or a low molecular weight heparin (LMWH) these events should trigger suspicion of heparin-induced thrombocytopenia (HIT), especially if they occur together, if the PCR worsens whilst continuing heparin or recovers promptly after heparin discontinuation. In this setting clinical confirmation of HIT is provided by: PCR recurrence after heparin re-challenge, multiple TECs especially affecting both venous and arterial circulations, heparin resistance, skin necrosis, white clot syndrome or an acute systemic reaction [2]. Their absence and variations in the timing or extent of the PCR have placed increasing reliance on serological detection of HIT antibodies to heparin:PF-4 complexes to confirm or exclude

the diagnosis by functional methods that detect platelet activation – the PAT (platelet aggregation test), HIPA (heparin-induced platelet activation assay) and SRA (serotonin release assay) or the direct antibody assays by ELISA. The commonest of these, the ELISA and PAT, are insufficiently specific and sensitive respectively [3,4], hence a simple pre-test 4T clinical scoring system [5] was developed to assess HIT probability and improve interpretation of serological testing.

Danaparoid

Danaparoid (danaparoid sodium/Orgaran®, MSD (also known as Merck & Co. Inc.), Oss, The Netherlands) is a low molecular weight, heparin-free, natural mixture of mainly heparan and dermatan sulphates. It inhibits thrombin generation (TGI) [6-8], with a half-life of elimination (predominantly renal) of 7 hours that is prolonged about 50% in renal failure [9], but its effect on plasma anti-Xa activity is used for monitoring purposes. It is well tolerated for either acute or chronic use after intravenous (I.V) or subcutaneous (S.C.) administration [10].

Its advantages are: a favourable benefit (antithrombotic):harm (bleeding) ratio [10], no influence on plasma antithrombin, virtually no effect on platelets [6], a unique ability to disrupt interactions between

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UFH and platelet factor 4 (PF4) [11,12] or platelet receptors [13] and safe transition to vitamin K antagonists. Potential disadvantages for patients with ARF and HIT [9,14] are: clinical cross-reactivity with the HIT antibody, its long terminal half-life that could lead to accumulation and bleeding and lack of antidote (only plasmapheresis has successfully reduced blood levels and haemorrhage [15]. Nevertheless, it is highly recommended for HIT management [4,16].

Aim of the Study

To assess the efficacy and safety outcomes of danaparoid anticoagulation in critically ill ICU patients suffering from both HIT and ARF requiring CRRT.

Materials and Methods

Case report search

Case reports up to October 2011 of ICU patients with HIT and ARF, managed with CRRT and danaparoid anticoagulation, were indentified in the manufacturer's in-house files and by Internet search engines (e.g. Medline, Medscape, Ovid, Scopus, Peer review, Embase, Google). Duplicates were screened to extract the most complete information.

Diagnosis of HIT

All reported diagnoses of HIT were accepted, but after retrospectively calculating pre-test 4T scores [17] cases were stratified into:

Confirmed HIT: with a positive functional HIT test and/or clinical confirmation and/or a pre-danaparoid treatment 4T score of 6-8.

Suspected HIT: all other cases.

Laboratory data

Results of routine blood biochemistry and haematology tests, and amidolytic anti-Xa activity were accepted as described in each report.

Continuous renal replacement therapy

Cases using veno-venous CRRT procedures for haemofiltration, haemodiafiltration, continuous haemodialysis or unspecified CRRT were included, but cases specifically using arterio-venous circuits were excluded. Circuit survival time after danaparoid anticoagulation was considered satisfactory if ³ 24 hours for at least the latter 50% of the procedures performed or stated to be 'no problem/no clotting/supported'.

Danaparoid dosing schedule

The recommended danaparoid dosing schedule for CRRT was a loading i.v. bolus of 2250 U, followed by 400 U/h x4h, then 300 U/h × 4h and finally a maintenance infusion rate of 150-200 U/h for as long as necessary. However, dose adaptation [10] was possible for patients with initial circuit/systemic clotting problems or increased bleeding risk at least until the problem was overcome.

Danaparoid treatment outcome events

Clinical outcomes, reported for up to 32 days after danaparoid discontinuation, were stratified into those with:

No or minor events: any event (including bleeding, systemic TE or circuit clotting) that responded favourably to transient danaparoid treatment interruption or dose adjustment/optimisation.

Thrombotic events: systemic thrombo-embolism (fatal and non-fatal) and/or circuit clotting with survival times <24 hours in more than 50% of CRRT sessions per patient (despite attempted dose optimisation).

Composite inefficacy outcomes: includes thrombotic outcomes and unplanned amputations.

Bleeding events: major bleeding - fatal or clinically relevant non-fatal events that led to transfusion of 2 or more units of blood product or re-operation or a serious consequence, e.g. haemorrhagic shock, heart failure etc., or required permanent danaparoid discontinuation.

Minor bleeding - that did not meet the criterion of a major bleed.

Composite adverse outcomes: include major bleeds and other fatal and non-fatal serious adverse events (excluding composite inefficacy outcomes) that resulted in permanent discontinuation of danaparoid therapy.

Treatment was considered effective if the benefit (no thrombosis)/harm (bleeding induction) balance, i.e. (100%-composite inefficacy outcome)/major bleeding frequency; and the composite inefficacy outcome + major bleeding frequency values were >1 and <50% respectively.

Statistics

Fisher's exact test is used for comparison between variables, the level of significance is <0.05. Otherwise descriptive statistics are used.

Results

One hundred and three unique case reports were identified: 47 in the manufacturer's data base, 55 in 21 independent publications [3,15,18-35] and 1 in a marketing brochure.

Presenting clinical status

The male:female ratio was 2:5. The median platelet count nadir, available for 56 cases, was 30.7 Giga/L (range 4-118 Giga/L), with 16.1% <10 Giga/L and a further 19.6% from 10-19 Giga/L inclusive. The presenting clinical data (Table 1) did not allow calculation of clinical severity scores in sufficient patients for analysis).

HIT diagnosis

The distribution of the 98 pre-test 4T scores for HIT probability that could be calculated was: low (1-3) 9.2%, intermediate (4-5) 50.0%

Clinical problem	(n = 102[2])	
DIC/organ failure[3]	65	63.7%
Sepsis[4]	55	53.9%
Thrombo-embolic event	47	46.1%
Bleeding event/risk[5]	72	70.6%
Other[6]	48	47.1%
≥3 of the above	54	52.9%
Confirmed HIT[7]	69	67.6%
Suspected HIT[8]	33	32.4%

[1]In addition to ARF and HIT
[2]No additional information for 1 case
[3]Including MODS (≥2 organs failed other than the kidneys)
[4]Septicaemia/septic shock, viral/bacterial pneumonia, bacterial endocarditis, peritonitis
[5]Within the previous 7 days
[6]Heart failure, cancer, coma, encephalitis, pancreatitis and diabetes mellitus
[7]Functional test positive and/or re-challenge thrombocytopenia or 4T score 6-8
[8]All other patients.

Table 1: Co-morbid problems[1] at danaparoid treatment initiation.

and high (6-8) 40.8%. Serology for HIT, performed in 89 cases, was positive in 71.9% (43 by functional test ± ELISA, 13 by ELISA only and 8 methods unknown). Overall HIT could be reasonably confirmed in 67.0% (69/103) of the cases, the remainder have been designated suspected HIT. Cases having a functional or direct antibody test (some both) had median 4T scores of 6 and 6.5 respectively for positive test outcomes and 4 for either negative test outcome.

Danaparoid dosing schedules and duration of use

In all but 2 patients with information (88/90) danaparoid was infused continuously for a median of 7 days (range 1-39 days), usually by the recommended i.v. regimen. Filter clotting during early sessions was the usual reason for loading doses >2500 U (n=10) and/or infusion rates of 450-1000 U/h (n=10). An increased bleeding risk or an high UFH/LMWH dose immediately prior to the switch to danaparoid was the usual reason for omission (n=12) or reduction (n=8) of the recommended loading dose and/or maintenance infusion rate, but was associated with failure of PCR recovery (p<0.05) and a trend towards more frequent new clotting/TECs that in 6 reports was managed by increasing the danaparoid dosing intensity. Final maintenance infusions were then adjusted to the lowest rate that provided both circuit patency and adequate systemic anticoagulation (which for 17 patients was <150 U/h).

Plasma anti-Xa activity

Plasma anti-Xa activity levels (available for 57 patients) during the maintenance infusions remained within the target range (0.4-0.8 U/mL) in 63.2% of the cases. Levels consistently above or below this range were reported for 14.0% and 22.8% of the cases respectively.

Treatment outcomes

The 102 available clinical outcomes (Table 2) show that 55 patients (53.9%) survived, of whom 85.5% developed no or minor problems.

The 47 deaths (46.1%), including 13 occurring a median 5 (range

3-30) days after danaparoid treatment cessation, were attributed to sepsis/MODS/DIC: 35 cases (77.8%); major bleeding 3 cases; systemic thrombosis 2 cases; cardiopulmonary arrest without thrombosis at autopsy 2 cases; cancer, heart-failure, encephalopathy 1 case each and 2 were unexplained. The mean ages of survivors and those who died were 61.3 and 60.4 years respectively and mortality was slightly higher in females: 51.7% vs. 42.5%. Figures 1 and 2 shows mortality was related to the number of major clinical problems (DIC/MODS, sepsis/septic shock, systemic thrombosis, active bleeding or recent major surgery, and any other severe clinical problems) at presentation (r=0.9721), but not to the heparin-induced platelet count nadir. The mean platelet counts for survivors (n=46) and non-survivors (n=40) were 39.78 and 38.12 Giga/L respectively.

Correlation coefficient R^2 = 0.945
*5 types:
DIC/MODS.
Sepsis/septic shock.
Thrombotic episode (excluding crrt circuit clotting).
Active bleeding/recent major surgery.
Other, e.g. SLE/APS/LA, cancer, cardiomyopathy, multiple trauma.
The numbers against each point are the patients with relevant data.

Figure 1: Mortality rates in relation to the presenting clinical burden.

Correlation coefficient R^2 = 0.1761
* The points represent the middle of 5 ranges: 0-19 Giga/L, 20-39 Giga/L, 40-59 Giga/L, 60-79 Giga/L,
 and 80-99 Giga/L.
The numbers against the points are the patients with relevant data.

Figure 2: Mortality rates in relation to the platelet count nadir.

General clinical endpoints		(n=102)[1]	
CRRT performed successfully[2]		88	93.6%
Patients with no/minor adverse events		50	49.0%
All thrombosis related events	Systemic non-fatal	2	2.0%
	Circuit clotting	4	3.9%
	Amputation	1	1.0%
	Systemic fatal	2	2.0%
Major bleeding[3]	Non-fatal	5	4.9%
	Fatal	3	2.9%
Persistent/new PCR		31	30.4%
Other non-fatal serious adverse events		8	7.8%
All deaths (during danaparoid use)		34	33.3%
Total hospital mortality		47	46.1%
Composite inefficacy outcome[4]		8	7.8%
Composite adverse outcome[5]		48	47.1%

[1]No overall treatment outcome data for 1 patient,
[2]93 cases with CRRT outcome data,
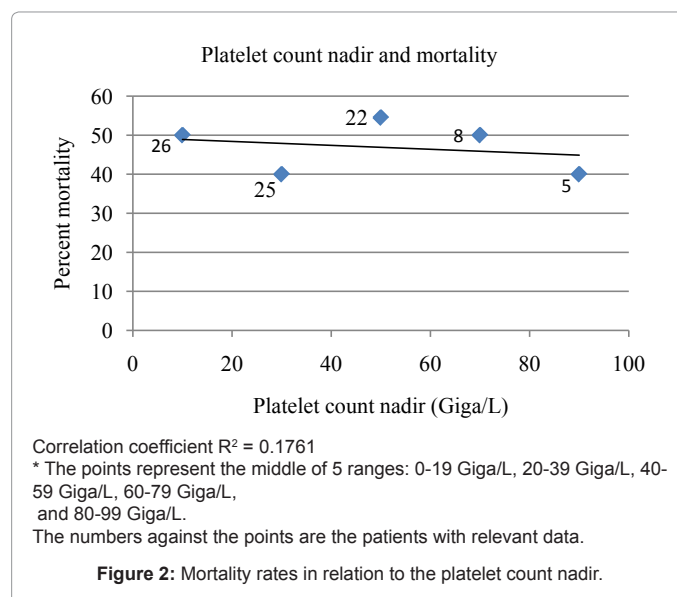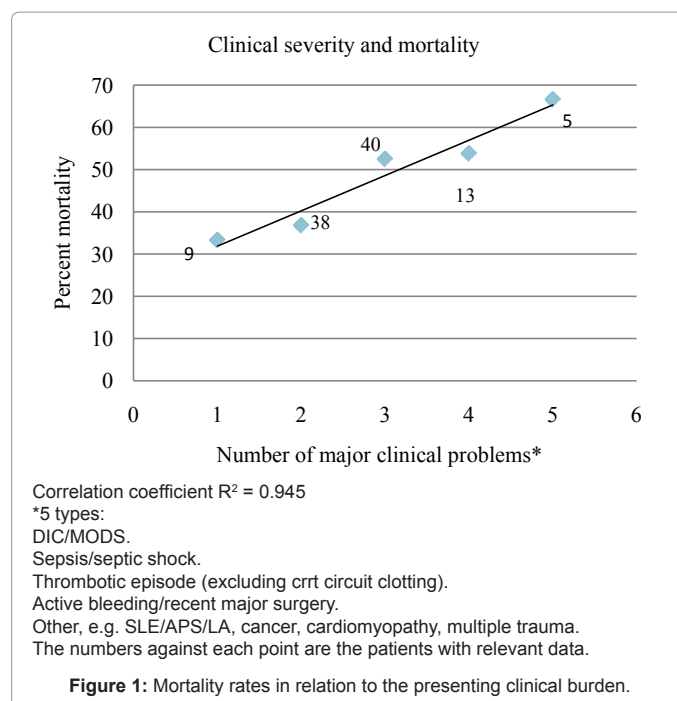[3]Serious events clearly not surgical/procedural errors,
[4]All patients with one or more of the following: fatal or non-fatal thrombo-embolism, unplanned amputation or clotting in the ECC unresponsive to dose adjustment,
[5]All patients with one or more of the following: fatal or non-fatal bleeding, all other deaths (except those due to thrombosis) and other non-fatal SAEs attributed to danaparoid.
CRRT: continuous veno-venous procedures, PCR: platelet count reduction, TEC: thrombo-embolic complication

Table 2: The frequency of clinical outcomes of danaparoid therapy (more than 1 event possible per patient).

Eight cases (7.8%) developed an inefficacy end-point: persistent CRRT circuit/filter clotting (n=4) and/or systemic thrombosis (n=5, two fatal) including an unplanned amputation.

Twelve major bleeding episodes were reported: 4 followed vascular injury (3 lacerated vessels, 1 leaking arterial suture) and were subsequently managed by surgery with perioperative danaparoid; one patient whose supply of danaparoid was used up died 7 days later from a coronary occlusion due to a bleed into an atherosclerotic plaque. In 6 of the 7 remaining episodes danaparoid treatment was discontinued prematurely: one of these patients was switched to lepirudin because of a new DVT and died 3 days later of a pulmonary haemorrhage; one patient in hepatic failure suffered bleeding episodes both before and after danaparoid discontinuation; 3 patients with cancer complicated by fungaemia, DIC and MODS respectively had repeated bleeding at vascular access sites, tracheostomy site and into the urinary tract respectively, that stopped after danaparoid discontinuation; one patient with DIC and hepatic failure had severe bleeding episodes before danaparoid use and subsequently died. The final patient developed tamponade after a re-do cardiac by-pass operation using danaparoid that recovered after aspiration and danaparoid discontinuation but died 8 days later in heart failure. Thus 3 patients died as a direct effect of their major bleeding. Fifty-two cases (51.0%) developed an adverse end-point.

Fourteen minor bleeds (13.7%) were reported: 4 from tracheotomy sites, 3 post-operative, one each due to gastritis, haemothorax aspiration, herpes zoster lesions, haemorrhoids, urinary bladder catheter, retroperitoneal and unknown. All responded to danaparoid dose reduction and/or transient (up to 24h) treatment interruption (4 episodes). Four, of 13 episodes with information on plasma anti-Xa monitoring, occurred at levels >0.8 U/mL.

The benefit/harm balance and the sum of the composite inefficacy + major bleeding frequencies are at best (i.e. excluding surgical/procedural errors) 10.5 and 16.6% respectively and at worst (including all major bleeding and persistent thrombotic events) 5.9 and 23.5% respectively.

During danaparoid administration 32 patients (31.4%) developed new/persistent thrombocytopenia. Twelve of these (including 4 with a diagnosis of sepsis and 1 with an artificial heart) received concomitant platelet transfusions (n=9) or UFH (n=2) or both as possible causes,

16 others had DIC, sepsis, or MODS and the remaining 4 cases had no obvious cause. Four of these 32 patients developed new TECs (12.5%) and 21 died (65.6%). Comparative figures for patients whose PCR recovered are 4/70 (5.7%) and 26/70 (37.1%, p <0.0101) respectively. Mortality in patients with persistent/new PCR who received platelet transfusions was 44.4% compared with 75% for those who did not.

Four patients received concomitant UFH: 3 developed new/persistent PCR and died, (one of widespread thrombosis following 42,000 IU UFH daily up to and including the day treatment was switched to danaparoid just before the patient's demise). The survivor also received platelet transfusions, as did a further 11 patients because of low platelet counts (nadir <33 Giga/L, mean 19.4 Giga/L). Ten of these 11 patients had well documented HIT and a combination of sepsis, DIC or MODS (n=9) or shock syndrome. Comparison of cases receiving platelet transfusions with those receiving neither transfusions nor heparin shows new/persistent thrombocytopenia in 9/11 versus 20/87 (p=0.0002), TECs in 2/11 versus 5/87, major bleeds (2/11 vs. 6/87) and deaths (6/11 vs. 38/87).

CRRT outcomes

The patients underwent 1-23 CRRT sessions (median 3) and circuit survival was satisfactory in 88 of 94 (93.6%) reports with information (Table 2). New/persistent PCR and/or resistant circuit clotting in the remaining 6 cases (in 3 associated with a positive cross-reactivity test (see below) led to premature danaparoid discontinuation and replacement by eprostanol, bivalirudin, argatroban (2) or lepirudin (2). For 9 cases no CRRT outcome data was reported despite danaparoid use for a median of 5 (range 1–27) days.

Serological danaparoid cross-reactivity and/or premature treatment discontinuation

Forty-five patients with a positive functional test for HIT were also tested for danaparoid cross-reactivity. Six (13.3%) were positive (Table 3), 5 before and one within 24h of treatment initiation, leading to premature danaparoid discontinuation in 3 cases. Four of the 6 had satisfactory CRRT patency on danaparoid (despite persistent PCR in 1) and 2 showed early circuit clotting (in one accompanied by systemic thromboses). Two patients died of sepsis and 1 with lung cancer developed fatal pulmonary bleeding 3 days after being switched to lepirudin.

Ref no.[1]	Serologic C-R	PCR	New TEC	Sepsis/MODS	Danaparoid use (d)	Switched to	Outcome
Cup 116	+	+	None	No	2	Eprostanol	Recovered
Ref 32	+	+	Circ/syst	+	4	Lepirudin	Died MB
Ref 34	+	+	Circuit	No	5	Lepirudin	Recovered
Cup 138	+	No	None	+	5		Died sepsis
Cup 280	+	No	None	+	2		Died sepsis
Cup 385	+	no	None	+	12		Recovered
Ref 23	Not done	No	Circuit	+	7		Died
Ref 23	Not done	No	Circuit	+	2		Unknown
Ref 27	Not done	+	Circuit	+	5	Bivalirudin	Died sepsis
Ref 15	Not done	+	No data	+	18	Argatroban	Recovered
Ref 15	Not done	+	None	+	Unknown	Argatroban	Recovered
SAE rpt	Not done	+	No data	No	Unknown		Unknown
SAE rpt	Not done	+	No data	+	2		Unknown

[1]CUP (compassionate-use patients) and SAE rpt (spontaneous adverse event report) in manufacturer's data base
C-R = danaparoid cross reactivity, PCR = (new/persistent) platelet count reduction, TEC = thrombo-embolic complication, MODS = multiple organ dysfunction syndrome, MB = major bleed (during lepirudin administration)

Table 3: Patients with premature danaparoid discontinuation.

Table 3 also includes 7 other premature danaparoid discontinuations after 2-18 (median 5) days of treatment because persistent PCR and/or circuit clotting led to suspected cross-reactivity. Circuit patency was inadequate in 3, satisfactory in 1 and there was no information for 3 cases. Two of these 7 patients died of sepsis (1 after switching to bivalirudin), 2 recovered on argatroban and for 3, information is lacking.

Discussion

Despite limitations (lack of a control group; the variable quality of the information supplied) this case report analysis, showing that 93% of the patients underwent successful CRRT and 53% survived beyond the 30 day follow-up period, provides evidence that danaparoid therapy was beneficial in the majority of these critically ill ICU patients with HIT and ARF. The 46.1% hospital mortality rate compares favourably with rates up to 80% reported for similar patients [1,3,36,37], but this still high mortality appears to be directly related to the number of presenting clinical insults (Figure 1) and not related to the platelet count nadir (Figure 2). The lowest rate of 33.3% in figure 1 compared with 19% and 0% for danaparoid-treated ICU patients with renal failure managed with intermittent haemodialysis and who had concomitant HIT or no HIT respectively [38,39] suggests that the combination of HIT and ARF requiring CRRT seriously reduces survival. The difference may also be related to the frequency of sepsis/DIC and MODS that are more likely to be present in patients requiring CRRT than intermittent haemodialysis and was more frequently cited as the cause of death - 88.4% vs. 24.1% [39] respectively (p<0.0001), but it also suggests that to avoid the risk of HIT development critically ill patients who require CRRT should not be given a heparin.

HIT diagnosis in critically ill patients

Despite a clear difference in median scores between serology positive and negative patients in the current analysis, the severity and/or unusual timing of the thrombocytopenia and/or co-morbidity can undermine the predictive value of the pre-test 4T scoring system in critically ill patients. Coupled with over-diagnosis of HIT by the global ELISA tests [17,40,41], the analysis suggests that use of these diagnostic techniques requires further refinement in this patient setting to minimise errors or delays in HIT diagnosis.

Danaparoid dosing, plasma anti-Xa activity response and safety

The recommended guideline for danaparoid dosing for CRRT was most often followed but 40.2% of the cases required dose adaptation at some time to overcome early circuit and/or systemic clotting [20,21,30] or bleeding (risk) [3]. However, omission of the loading i.v. bolus usually led to new circuit clotting so, unless bleeding is life-threatening, it is better to merely reduce the bolus to minimise delaying antithrombotic protection and to retain danaparoid's unique ability to reduce HIT-induced platelet activation [11-13]. In several reports [3,33], sometimes because of an increased bleeding risk, adequate circuit patency was provided by lower than recommended maintenance rates.

The 12 (11.8%) major bleeds are acceptable for this high risk patient population taking into account that 4 followed surgical errors. It appears that a specific danaparoid antidote would not have mitigated the severity of the bleeding events nor reduced the 2.9% fatality rate (especially since 2 fatal bleeds occurred after danaparoid discontinuation when the influence of danaparoid on plasma anti-Xa levels would have been nil.

Despite poor correlation between plasma anti-Xa levels and major bleeding or thrombosis the current analysis (showing a trend towards increased minor bleeding) and other studies [42-44] suggest that the upper level of the target plasma anti-Xa activity range should be limited to 0.8 U/mL. Nevertheless, the need for danaparoid dosage adaptations in these critically ill patients is better judged by clinical criteria (bleeding/thrombosis risk balance) than by plasma anti-Xa activity monitoring.

Danaparoid cross-reactivity and treatment discontinuation

Table 3 lists cases of premature danaparoid discontinuation due to suspicion of clinical cross-reactivity. Only one case was serologically tested (and found positive). In the current analysis the frequency of positive serological cross-reactivity was greater than that reported for HIT patients without renal failure (6/45 versus 27/587) respectively (p=0.0257) as was failure of PCR recovery (31/102 vs. 57/609, p<0.0001) [10]. However, pre-treatment danaparoid cross-reactivity testing is considered unnecessary [14] because it has seldom been reported to cause clinical complications [4,13,45-47], especially at therapeutic dosing [48]. Thus the net clinical benefit of danaparoid with regard to PCR recovery [49] or efficacy [49-53] is better than or equal to comparative therapies (dextran, ancrod or lepirudin) regardless of possible cross-reactivity. Hence failed PCR recovery and/or thrombotic events, especially within the first 2-3 days of initiating danaparoid therapy, appear most likely to be due to: the natural progression of HIT especially if danaparoid dosing is suboptimal [51,54] (11/36 current cases), clinical manifestation of previously covert TECs (particularly in patients presenting with 'isolated' HIT) [55], co-morbidity [3,55] (26/36 current cases had MODS/DIC/sepsis) impending death [56], continued (LMW) heparin administration or use of heparin bonded catheters and circuits or, more contentiously (see below), platelet transfusions [57-60] (11/36 current cases). However if a new/persistent PCR or TEC cannot be reasonably explained by any of the above reasons then danaparoid should be withdrawn because of possible clinical cross-reactivity [2,12].

Clinical outcomes, platelet count nadirs and platelet transfusion

Critically ill patients develop a high frequency of PCR and have a high mortality [59], but the current analysis shows no relation between mean platelet count nadirs and clinical outcomes. A similar lack of relationship was found for ICU patients with HIT and undergoing intermittent haemodialysis (Magnani, unpublished data). Thus the initial platelet count nadir does not appear to be a reliable marker of impending mortality, even for counts <10 Giga/L, nor for predicting whether or not the PCR will recover. However, persistence or renewed PCR after heparin withdrawal does appear to predict poor outcomes.

Most patients receiving platelet transfusions were severely ill with well documented alternative reasons for their very low platelet counts. The current data does not clarify the influence of these transfusions on the clinical outcomes of patients. In the 11 patients who received them new/persistent PCRs, TECs and deaths occurred more frequently, however, within the 32 patients with persistent/renewed PCR those who received platelet transfusions showed a mortality reduction of 41% compared with those who were not transfused. The current analysis tends to support a casual association between platelet transfusions and adverse outcomes, since the latter appear to be due to the critical clinical status that prompted their administrationin which case they

may be life-saving [61,62], rather than a causal relationship (supporting avoidance of platelet transfusions unless absolutely necessary [14,60]).

Conclusions

Danaparoid can provide safe and effective anticoagulation for critically ill ICU patients with HIT and renal failure requiring CRRT, despite its renal elimination, long effect-half-life, potential clinical cross-reactivity with the HIT antibody and lack of antidote, but dosing may require adaptation to the individual patient's thrombotic: bleeding risk balance.

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