Treating Low-molecular weight heparin-induced thrombocytopenia: a new use for Bivalirudin

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Objective

To explore the use of bivalirudin in a multi-trauma patient suffering from heparin-induced thrombocytopenia (HITT) caused by dalteparin.

Clinical Features

Mr KW, 65 year old male presents to hospital post MBA
PMHx: nil significant, eGFR>90mL/min, regular medication Rabeprazole 20mg
Dx: Multiple fractures including R) fibular # and L) ankle dislocation
D1 of admission: dalteparin 5000 units daily commenced for VTE Prophylaxis
D12 of admission: thrombocytopenia noted; ID Heparin PF4 antibody detected. dalteparin ceased.
D13 of admission: bivalirudin commenced

Features of HITT

- Immune-mediated response caused by IgM or IgG antibodies[1]
- Antibodies are active against complexes of heparin and platelet factor 4[1]
- HITT is associated with an increased risk of thrombus[2]
- Usually develops 7 to 10 days into therapy with heparin / low molecular weight heparin (LMWH)[2]
- HITT occurs more commonly with unfractionated heparin than LMWH[2]

Diagnosis of HITT

Diagnosis is based on clinical picture, HITT antibodies and consultation by haematology[2]
Calculating the pre-test probability of HITT:

Thrombocytopenia: fall in platelets from 167 × 109/L to 78 × 109/L (>50% fall) . 2 points

Timing of platelet count fall or other sequalae: identified on day 10. 2 points

Thrombosis or other sequelae: Nil. 0 points

Other cause for thrombocytopenia not present: on PipTaz (possible other cause). 1 point.

Pre-test probability of HITT = 5 (intermediate)

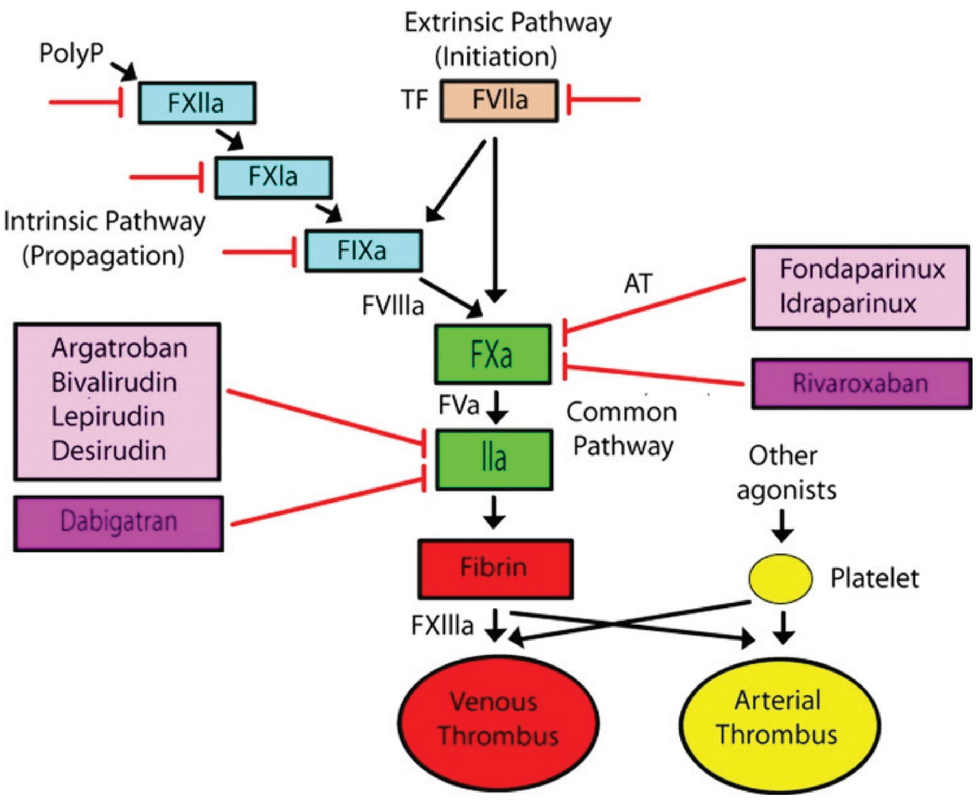
	Points for each of the four categories. Maximum score 8.		
	2	1	0
Thrombocytopenia	>50% fall or platelet nadir 20-10 ×10⁹/L	30-50% fall or platelet nadir 10-19×10⁹/L	Fall <30% or platelet nadir <10×10⁹/L
Timing of platelet count fall or other sequalae	Clear onset between day 5 to 10 or within one day if previous heparin exposure in last 100 days	Consistent with heparin immunisation (heparin exposure within previous 30-100 days) but not clear (eg. Missing platelet counts) OR onset after day 10 of initial heparin exposure	Reduction in platelet count in less than 4 days in those without prior heparin exposure. (This criteria excludes those with heparin exposure in the last 100 days)
Thrombosis or other sequalae	New thrombosis, skin necrosis, post heparin acute systemic reaction	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis not yet proven	None
Other cause for thrombocytopenia not present	No other cause for fall of platelet count	Possible other cause present	Definite other cause present

Pre-test probability score: High = 6-8 points; Intermediate = 4-5 points; Low = 0-3 points

ID-Heparin-PF4 Antibodies detected

Treatment Options

Danaparoid (a selective factor Xa inhibitor LMWH) or Direct Thrombin Inhibitors (bivalirudin and dabigatran) or rivaroxaban (factor Xa inhibitor)[1,2,3]



Bivalirudin

- A direct thrombin inhibitor with a short half-life, making bivalirudin an appropriate choice for Mr KW who still required multiple surgical interventions
- Prevents conversion of fibrinogen to fibrin
- Thrombin-induced platelet aggregation is inhibited
- Indicated in Australia for moderate-high risk unstable angina and non-ST-segment elevation MI[3]
- Has been given "Orphan Status" by the FDA for use in patients with HITT[5]
- There are several studies evaluating the use of bivalirudin in HITT showing it to be an effective treatment option[6,7]

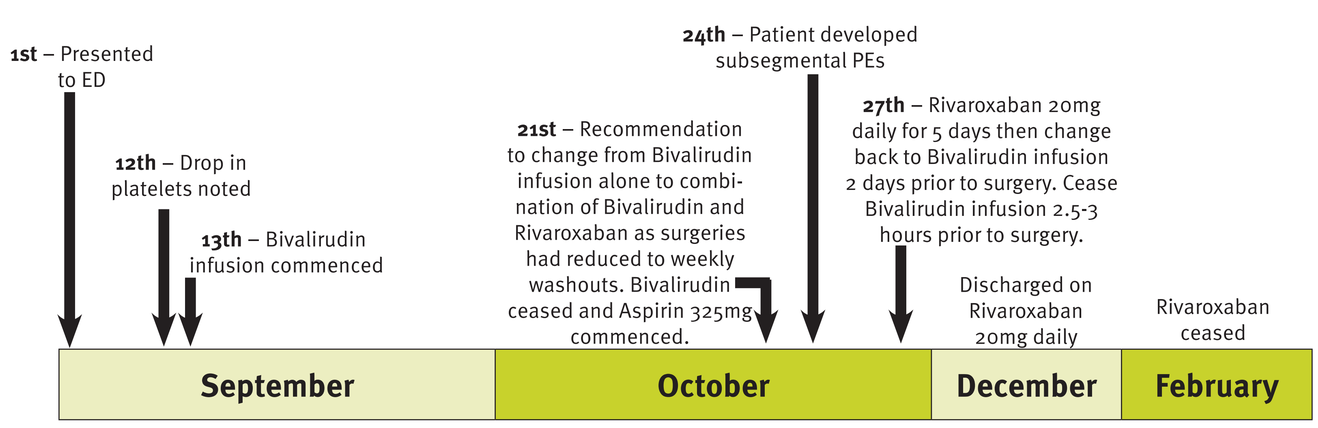
Properties of Bivalirudin	
Absorption and Volume of Distribution	Near instantaneous distribution post IV administration (V_d=volume of plasma + volume of interstitial fluid
Metabolism	Metabolised by plasma proteases and some renal clearance
Half-Life	25 minutes

Dosing information for bivalirudin in the treatment of HITT is limited. Product information and Australian Medicines Handbook suggest dosing guidelines for PCI and NSTEACs[3,8]
One study examining the use of bivalirudin in HITT gives a dosing guide[9]:

Renal Function	Suggested Starting Dose
CrCL>60mL/min	0.15mg/kg/hr
CrCL 30-60mL/min	0.8-0.1mg/kg/hr
CrCL<30mL/min	0.03-0.05mg/kg/hr
APTT Target	1.5-2.5 times higher than baseline[10]

Plan for Mr KW:
Commence infusion at 0.15mg/kg/hr
No boluses (no evidence of thrombus at the point of initiation of bivalirudin)
APTT target ~60 seconds
If APTT<60 increase infusion rate by 20% and repeat APTT in 2 hours
If APTT>90 cease infusion for 1 hour then restart at 50% of previous infusion rate.
Repeat APTT in 2 hours.
Once steady state has been reached, review in 12 hours and once stable for 24 hours and APTT can be reduced to daily reviews.

Outcomes
Bivalirudin continued until surgeries could be reduced to weekly, at which time Mr KW was changed to a combination of rivaroxaban and bivalirudin.



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