1. Introduction

Heparin traditionally has been used in haemodialysis units as an anticoagulant both for the extracorporeal circuit and for locking long term haemodialysis catheters. Both unfractionated and low molecular weight heparin have been used.

In recent years, increasing numbers of patients have been diagnosed with type II heparin-induced thrombocytopenia (HIT). This is a result of antibody formation to the heparin-platelet factor 4 complex which leads to a decline in platelet count and, more importantly, is associated with a risk of venous and arterial thrombosis. A recent survey has demonstrated that the prevalence of HIT in UK dialysis patients is approximately 0.26% (Dasgupta). Because of the widespread use of heparin in haemodialysis both for anti-coagulating the extracorporeal circuit and for locking catheters, it is important to have a clearly defined policy for the diagnosis and management of HIT in haemodialysis patients

For information and advice on diagnosis and treatment of patients with a suspected new diagnosis of HIT please see the separate UHL guideline from Haematology

2. Scope

This guideline is for the use of nephrology medical staff and all suitably qualified registered nurses, who have achieved competency in haemodialysis, or who are working under the direct supervision of a haemodialysis competent nurse.

Clinical guidelines are 'guidelines' only. The interpretation and application of clinical guidelines will remain the responsibility of the individual practitioner. If in doubt consult a senior colleague or expert.

3. Recommendations, Standards and Procedural Statements

3.1 Anticoagulation for haemodialysis for patients diagnosed with HIT

3.2.1 Where patients have been diagnosed with HIT or there is a high or intermediate pre-test probability (pending results of further investigations), heparin should not be used for anticoagulation for haemodialysis. The recommended local policy is to use Fondoparinox – but it is important to note that although widely used this is an 'off-license' use for this drug. Argatroban can also be used but is more complicated to administer and considerably more expensive.

Fondoparinox

Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin (AT) mediated selective inhibition of Factor Xa. By binding selectively to AT, fondaparinux potentiates (about 300 times) the neutralization of Factor Xa by AT. At standard doses, fondaparinux does not affect routine coagulation tests such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalised Ratio (INR) nor bleeding time or fibrinolytic activity. Fondaparinux levels are used to monitor the potential for accumulated effect with fondaparinux.

The use of fondaparinux for anticoagulation of the haemodialysis circuit is an off-label indication. Fondaparinux is 64-77% excreted unchanged in the urine and the half-life is extended up to 72 hours in patients with creatinine clearance less than 30mL/min. Fondaparinux is removed by haemodialysis.

Dosing recommendations

Initial dose

- Consider an initial bolus dose of 0.03 mg/kg (maximum dose of 2.5 mg).
- Withdraw the prescribed dose volume using 1mL syringe and dilute with 20mL of sodium chloride 0.9%
- Administer into the arterial side of the dialyser at the start of dialysis.

Dose adjustment

- For patients who experience clotting of the dialysis circuit on three consecutive dialysis sessions, consider increasing the dose of fondaparinux by 0.01 mg/kg on the next dialysis session.
- If peak fondaparinux levels are greater than 0.4 microgram/mL, dose reduction by 0.01 mg/kg should be considered for the next dialysis session.
- Dose changes should be guided by peak levels only.

Monitoring

- Plasma fondaparinux level monitoring is recommended to guide safe dosing and to reduce the risk of accumulated fondaparinux.
- Caution should be exercised in patients with the following characteristics: low body weight (less than 60kg) or elderly (aged 80 years or over).

Recommended monitoring schedule for fondaparinux on dialysis:

- Weekly monitoring of peak and trough fondaparinux levels for two weeks after treatment initiation
- Weekly monitoring for two weeks after dose adjustment of fondaparinux.
- No routine monitoring required after treatment stabilisation unless there is a fondaparinux dose change, or change in dialysis length or frequency.

Fondaparinux levels should be checked immediately prior to dialysis (trough) and immediately after dialysis (peak). Samples must be sent with a request that indicates that the patient is receiving fondaparinux on haemodialysis. Please inform the haematology laboratory staff in advance.

Post-dialysis fondaparinux levels should be less than 0.4 microgram/mL showing that fondaparinux is not accumulating. Currently, there is limited literature on what trough levels are safe in dialysis patients.

Bleeding complications with fondaparinux

There is no specific antidote for fondaparinux. Fondaparinux treatment should be discontinued immediately in the event of serious bleeding complications. Underlying cause of bleeding complications should also be promptly investigated. Management of bleeding complications must be discussed with a haematologist.

Argatroban

Argatroban is a direct thrombin inhibitor, has a short half-life (45 minutes) and has hepatic clearance. It is therefore the drug of choice if invasive procedures are planned or in patients with renal impairment.

Dosing of Argatroban

- Intermittent Haemodialysis or Haemodiafltration (IHD)

  Start with a bolus of 250 microgram/kg Argatroban and subsequent continuous infusion of 2 microgram/kg/min Argatroban. The maintenance infusion should be stopped one hour before the end of the haemodialysis procedure.

  In patients without any obvious thrombosis, either in the circuit or in their own blood vessels, the

dose may be reduced to 1 microgram/kg/min dose titrated to a lower target APTT ratio of 1.5 -2.5 (instead of the usual 1.5-3.0).

For example: 75kg patient: 250 microgram x 75=18750 microgram (or 18.75mg); 18.75ml of the 1mg/ml infusion bag.

Withdraw required volume from the previously diluted infusion bag (1mg/ml), according to indication and administer over not less than 3minutes.

Monitoring of Argatroban treatment

Aim for systemic APTT ratio of 1.5 – 3.0. Please consult newer UHL haematology guidance (currently in draft) for future use of a direct argatroban assay in the future.

If on continuous therapy, check first APTT 2 hours after starting at a rate of 1 or 2 microgram/kg/min or 4 hours if starting at a rate of 0.5 microgram/kg/min.

Patients on chronic outpatient haemodialysis should have their APTT measured over their first three HD session on Argatroban to establish the maintenance dose. Following this further monitoring should be based on clinical judgement e.g. evidence of bleeding or thrombosis; any change in clinical condition e.g. liver function, acute illness.

3.2 Locking of haemodialysis catheters in patients diagnosed with HIT

Where patients have been diagnosed with HIT or there is a high or intermediate pre-test probability (pending results of further investigations), it is important to remove all sources of heparin to prevent serious thrombotic complications. Heparin either alone or in combination with TauroLock (see protocol) should NOT be used to lock HD catheters (both tunnelled and un-tunnelled catheters). Catheters should be locked with Taurolock alone. Where this is contraindicated or is not maintaining catheter patency, urokinase 12500units or a citrate based solution should be used.

4. Education and Training

This guideline is for the use of nephrology medical staff and all suitably qualified registered nurses, who have achieved competency in haemodialysis, or who are working under the direct supervision of a haemodialysis competent nurse.

5. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
No of patients with kidney disease diagnosed with HIT	Count of positive HIT assays	periodic	

annually			
Argatroban use		periodic	

6. Legal Liability Guideline Statement

See section 6.4 of the UHL Policy for Policies for details of the Trust Legal Liability statement for Guidancedocuments

7. Supporting Documents and Key References

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8. Key Words

Heparin, Haemodialysis, Anticoagulation, Thrombocytopenia, Argatroban

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25Apr2019	3	James Medcalf Patrick Mensah	Minor changes to wording (not substance) of Argatroban dose reduction, and affects on INR.

17Oct2016	2	Graham Warwick James Medcalf Gillian Hartley Patrick Mensah	Lepirudin replaced by Argatroban; updated to new template
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