Children's Hospital of Philadelphia

Effective Date: April 9, 2021

CLINICAL PRACTICE GUIDELINES

Initiation and Maintenance of Bivalirudin Infusion

Disclaimer: ***These clinical practice guidelines are based upon the opinions of staff members of The Children's Hospital of Philadelphia. Treatment should be individualized and based upon the clinical conditions of each patient***

General Information

Bivalirudin is a direct thrombin inhibitor used for the prevention or treatment of thrombosis in patients with suspected or confirmed HIT. It can be considered for patients who require a non-heparin anticoagulant (failed heparin therapy). There is very little evidence regarding the use of this drug in children, 20% is renally cleared, and so doses should be reduced in patients with renal insufficiency.

Baseline Monitoring (To be completed prior (< 48 hrs). Obtaining a baseline PTT for this drug is critical, as it is important for proper dosing.

Baseline labs are to be completed to ensure patient has a normal baseline coagulation state:

- CBC
- PT/PTT
- Basic Metabolic Panel (for SCr)
- Fibrinogen

If the patient has abnormal coagulation studies, or renal impairment, the Hematology team should be consulted prior to initiating bivalirudin.

Administration

- Patients must have a dedicated line for bivalirudin infusions.
- The infusion must **NOT** be stopped or interrupted for other medications.

Dosing

I. Dosing for cardiac catheterization

Bolus dose of bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hr continuous infusion

II. Dosing for continuous infusion anticoagulation (management of DVT, treatment of heparin induced thrombocytopenia, or in patients who require a non-heparin anticoagulant)

Bolus dose of bivalirudin is 0.15-0.3 mg/kg

- **Omission of bolus or lower dose may be used in the following patients:**
  - Stroke
  - Potential increased risk for intracranial bleed
  - Bleeding or high-risk for bleeding
  - Risk factors for hemorrhage include: I.M. injections; peptic ulcer disease; intermittent I.V. injections; increased capillary permeability; menstruation; recent surgery or invasive procedures; severe renal, hepatic, or biliary disease

Maintenance Dose

- Maintenance starting dose is 0.3 mg/kg/hr.
  - Dose adjustment for CrCl < 60 mL/min: decrease by 50%
- Check DTT and PTT in 2 to 3 hours after the start of the infusion

Monitoring

- Bivalirudin increases in a dose-dependent fashion, the PTT, DTT, ACT, PT, and INR.
- Monitoring for therapeutic effect of bivalirudin will be primarily based upon dilute thrombin time (DTT). This can be ordered as a bivalirudin level.
- However, dose titration can also be performed using the PTT (see below).
- For now, we would recommend obtaining both PTT and DTT to monitor when initiating bivalirudin. Since we do not have experience initiating bivalirudin using the DTT, the PTT may be helpful for early dose adjustments.
- Ideally, blood samples for DTT and PTT should be drawn by venipuncture. **Bivalirudin contamination in the central line or IV may affect the level**. In the case where a level is drawn from a line through which bivalirudin has been administered, ensure that an adequate amount of "waste" is withdrawn from the line before drawing the lab [at least twice the volume of the catheter].
  - If waste occurs and DTT is > 200 seconds and/or PTT is > 250 seconds, and there is not significant concern for bleed, please repeat DTT and/or PTT via venipuncture to rule out possible bivalirudin contamination.
- Check DTT and PTT 2-3-hours after initiation of therapy or with any dose change.
- When at least two consecutive DTT values are therapeutic then check DTT daily.

Therapeutic Range

- The recommended therapeutic range using DTT is 60-90 seconds.
- The recommended therapeutic range using the PTT is 1.5 to 2.5 times individual patient's baseline PTT. However, in many patients, the PTT does not increase linearly with bivalirudin dose. Therefore, once a patient reaches the therapeutic DTT range, the PTT should no longer be used to titrate bivalirudin.

Adjustment Dose

Table 1. Dose adjustment of bivalirudin using bivalirudin level (DTT)

DTT (seconds)	Dose Adjustment	Next DTT
< 60	**Increase infusion rate by 20%**	**2 - 3 hours after dose change**
60-90	**NO CHANGE**	**2 - 3 hours after dose change x 1, then daily**
91-100	**Decrease infusion rate by 20%**	**2 - 3 hours after dose change**
> 100	**Hold infusion for 1 hour, then restart at 50% less than previous rate**	**2 – 3 hours after dose change**

Laboratory Information

- Diluted thrombin time (DTT)
  - DTT may be a more sensitive test for bivalirudin, with less interference from other sources.
  - The plasma diluted thrombin time is slightly dependent on fibrinogen level
  - The DTT is prolonged with heparin contamination.
  - Not affected by lupus inhibitors or elevated d-dimers
- Partial thromboplastin time (PTT)
  - Therapeutic PTT is dependent on individual patient's baseline PTT. A plateau effect with PTT is observed with bivalirudin concentrations > 2 mcg/mL. Dose adjustment of bivalirudin should be based upon the goal of 1.5-2.5 x patient's baseline PTT.
  - When baseline PTT is prolonged, accurate monitor of bivalirudin may not be possible.
- International normalized ratio (INR)
  - DTI increases INR with potential for combined effects on INR with the co-administration of bivalirudin and warfarin. See Converting from Bivalirudin to Warfarin section for more information

Safety

- Excessive anticoagulation. Note: Bivalirudin is NOT reversible with protamine or FFP.
  - No bleeding
    - Discontinue or decrease bivalirudin infusion per Table 1.
    - Determine DTT and PTT and other coagulation levels as appropriate
  - Bleed: The major adverse event related to bivalirudin is bleeding. Discontinuing the bivalirudin infusion would generally allow anticoagulation parameters to return to baseline within 3 to 5 hours. Reversal of anticoagulant effect may take longer in patients with renal impairment.
    - Immediately stop bivalirudin administration
    - Consult Hematology
    - Determine DTT and PTT and other coagulation levels as appropriate
- Avoid IM injections and arterial punctures during anticoagulant therapy. When such procedures are clinically necessary, ensure adequate external pressure is applied post-procedure.
- Other invasive procedures that may result in bleeding in a patient who is anticoagulated and should be carefully considered include NG tube insertions, intubation, and rectal temps.
- Avoid drugs that affect platelet function (e.g., aspirin, NSAIDs, dipyridamole, clopidogrel) as they may potentiate the risk of hemorrhage.

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Converting between other anticoagulants:

Converting from Bivalirudin to Warfarin

- There is a potential for combined effects on INR with the co-administration of bivalirudin and warfarin.
- A loading dose of warfarin should NOT be used
- Initiate therapy using the expected daily dose of warfarin. Refer to Clinical Practice Guidelines: Initiation and Maintenance of Warfarin (Coumadin) In Patients Greater Than or Equal to 10 kg.
- Obtain daily INR with co-administration of bivalirudin and warfarin
- Bivalirudin and warfarin therapy should be overlapped for at least 5 days
- Bivalirudin can be discontinued when INR > 3.5 on combined therapy. Repeat INR in 2 to 3 hours after discontinuation. Adjustment of warfarin may be needed if INR > 3.5 during the 5 day overlap period.
- Bivalirudin should be resumed if the repeat INR is below desired therapeutic range. Repeat the procedure daily until the desired therapeutic range is reached.

Converting between Heparin and Bivalirudin

- Bivalirudin may be initiated immediately after discontinuation of heparin and vice versa.

Converting between Bivalirudin and Enoxaparin

- The dose of enoxaparin should be given immediately after discontinuation of the bivalirudin infusion
- Begin the bivalirudin infusion no earlier than 8 hours after the last dose of enoxaparin. If starting within 8-12 hours, do NOT use a bolus dose of bivalirudin. If starting after 12 hours, consider a bolus dose of bivalirudin followed by maintenance dose per protocol.

Elective Procedures

- Hold bivalirudin a minimum of 4 hours prior to scheduled **surgical** procedure or **lumbar puncture**.

Complications

- The attending of record will be responsible for the diagnosis and management of any potential complications (i.e. bleeding, etc.) in consultation with the division of Hematology as deemed appropriate.
- Reporting of complications, including bleeding requiring transfusion, and intracranial hemorrhage, into the electronic reporting system, KAPS, is highly recommended.

Related Policy: Heparin Induced Thrombocytopenia (HIT) Guidelines