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CHAPTER

PARENTERAL DIRECT THROMBIN INHIBITORS

William E. Dager and A. Joshua Roberts

INTRODUCTION

The parenteral direct thrombin inhibitors (DTIs) act independent of antithrombin and are typically used in situations where unfractionated heparin (UFH) is not recommended or contraindicated such as heparin-induced thrombocytopenia, antithrombin deficiency, or in the setting of acute coronary syndromes. This class of agents works differently than other anticoagulants, despite similar laboratory assessments. Further, due to more limited experience with their use, it is important to approach their management and laboratory assay target ranges as independent of observations with other anticoagulants. There are currently two parenteral DTIs available in the United States—bivalirudin and argatroban. Lepirudin and desirudin are no longer available.

PHARMACOLOGY[1-2]

- The activity of thrombin can be inhibited by currently available DTIs that bind directly to either the catalytic (active) site or substrate recognition site (exocite 1). Thrombin also contains a heparin-binding site (exocite 2).
- All commercially available DTIs directly bind to the catalytic (active) site on thrombin responsible for enzymatic activity.
- Binding to the catalytic (active) site on thrombin inhibits several actions of thrombin including cleavage of fibrinogen and platelet activation, both of which are involved in thrombus formation.
- Bivalent DTIs (bivalirudin, desirudin, and lepirudin) also bind to the substrate recognition (exocite 1) on thrombin where fibrinogen can bind.
- DTIs do not bind to exocite 2, and thus are capable of inhibiting the effects of thrombin bound to fibrin (clot bound thrombin).
- DTIs can also block thrombin's ability to activate platelets as well as stimulate granule release, surface receptor expression and aggregation, and a plethora of other factors that mediate vascular integrity.
- Lepirudin and desirudin are able to tightly bind to thrombin and can lead to prolonged inhibition. These agents are no longer available.
- Bivalirudin is enzymatically cleaved by thrombin. This results in loss of activity that is primarily independent of renal or hepatic function. Its effects may not last in stagnant

blood. Increased elimination can occur with hemofiltration.

- The onset of bivalirudin on activated clotting time (ACT) values occurs within 5–10 minutes after a bolus.
- Dabigatran etexilate is an oral DTI (see Chapter 7 for further details).
- See **Table 5-1** for further pharmacokinetic/pharmacodynamics information.

PHARMACOKINETICS/PHARMACODYNAMICS

TABLE 5-1: **Pharmacokinetics of Available Parenteral Direct Thrombin Inhibitors**[3-5]

Agent	Argatroban	Bivalirudin
Source	Synthetic	Analog of hirudin
Route of administration	IV	IV
Plasma half-life (healthy subjects)	31–51 min	25 min
Primary elimination route	Hepatic	Enzymatic
Fraction excreted unchanged in the urine	16%	20%
Effect on INR (depends on the amount of DTI present; this may correlate to an elevation in the aPTT or ACT level in the sample)	Moderate	Mild

ACT: activated clotting time, aPTT: activated partial thromboplastin time, IV: intravenous, min: minutes

Parenteral DTIs are most commonly used in acutely ill patients who may have reduced organ function and elimination.

Time to steady-state may take longer, and effects may last more than a few hours after stopping the infusion.

DOSING/ADMINISTRATION

- Post-marketing experiences have suggested lower dosing approaches than those used in clinical trials, especially in acutely ill patients.
- The initial dosing regimen for a DTI will depend on the indication for anticoagulation, clinical presentation of the patient, and the desired intensity of parenteral anticoagulation, similar to how heparin is utilized (**Tables 5-2**, **5-3**, and **5-4**).
- Specific factors that may influence the dosing and target ranges include the following:
    - *Presence of thrombosis, acute thrombosis*—consider higher doses with aPTT target ranges of 2–2.5x normal baseline initially (2–3x normal baseline for argatroban).

      Note: The higher aPTT target for argatroban is based on the targets set in the original ARG 911 trial. No trial was done for bivalirudin in heparin-induced thrombocytopenia (HIT); however, published single-center experiences in over 1,000 individuals typically follow