



Anticoagulation with Bivalirudin in Infants and Children

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Bivalirudin, became the first direct thrombin inhibitor (DTI) available in the United States when it was approved by the Food and Drug Administration (FDA) on December 15, 2000. It is currently indicated for use with aspirin in adults with unstable angina undergoing percutaneous transluminal coronary angioplasty and for use with glycoprotein IIb/IIIa inhibitors in adults undergoing percutaneous coronary intervention.¹ The clinical applications for bivalirudin have expanded to include off-label use in cardiopulmonary bypass during cardiac surgery and in patients receiving extracorporeal life support (ECLS) or being supported with ventricular assist devices. Bivalirudin is not considered a first-line therapy, but is most often used as an alternative to heparin in children or adults with heparin-induced thrombocytopenia (HIT), heparin resistance (defined as the inability to achieve anticoagulation goals with heparin doses ≥ 70 units/kg/hr), or evidence of significant clot formation or extension.

There are currently two DTIs available in the United States, argatroban and bivalirudin. Lepirudin, a third DTI, was removed from the market by its manufacturer, Bayer Healthcare, in 2012. The DTIs offer several advantages over heparin, including the ability to effectively antagonize thrombin in the setting of reduced levels of antithrombin. Several studies have shown that endogenous antithrombin levels are lower after cardiopulmonary bypass and during ECLS.^{3,4} Many centers rely on administration of supplemental antithrombin or fresh frozen plasma during ECLS to optimize heparin responsiveness. This practice may not be necessary with the use of a DTI. These drugs are also effective against both free and clot-bound thrombin, as opposed to heparin which is only able to form a complex with and inactivate circulating thrombin. The use of DTIs is limited, however, because of their cost and the lack of controlled studies demonstrating their safety and efficacy in the pediatric population.

In a 2014 survey of 56 pediatric institutions throughout the United States, Oschman found that argatroban was the most commonly used DTI, available in 80% of hospitals, with bivalirudin available in 41% and lepirudin in 4%.⁵ The majority of respondents (41%) used DTIs two to four times per year. Only 19% of institutions used DTIs more frequently. The primary reasons for use were the development of HIT or thrombus extension during heparin therapy.

Although not common in pediatrics, the use of DTIs has slowly increased over the past decade. In a September 2014 analysis of the Pediatric Health Information System (PHIS) database, Moffett and Teruya found that 208 children received a DTI during 2004-2011.⁶ The PHIS database includes information from 43 pediatric hospitals throughout the United States. The majority of DTI use was in children with congenital heart disease. Argatroban was the most frequently used DTI overall. While there was no change in the annual rate of argatroban use during the study, the use of bivalirudin increased from 13.6% of the patients given a DTI during 2004-2007 to 26.9% during 2008-2011 ($p = 0.04$). The authors also found that the rate of bleeding documented after DTI use was significantly lower with bivalirudin than argatroban (18.8% versus 41.5%, $p = 0.002$).

Mechanism of Action

Bivalirudin is a reversible direct thrombin inhibitor.¹ It acts by binding to both the catalytic site and the anion-binding exosite of thrombin. Bivalirudin produces a rapid anticoagulant effect with the start of therapy. Measures of anticoagulation typically return to baseline an hour after discontinuing treatment, as thrombin slowly cleaves the bivalirudin bonds resulting in recovery of thrombin function. Administration of bivalirudin produces dose and concentration-dependent anticoagulant activity, as measured by activated clotting time (ACT), activated partial thromboplastin time (aPTT), thrombin time (TT) and prothrombin time (PT).

Pharmacokinetics

Bivalirudin exhibits linear pharmacokinetics over the standard dosing range.^{1,7} It is not bound to plasma proteins or red blood cells. Bivalirudin is renally cleared, in addition to proteolytic cleavage in the blood. It undergoes minimal hepatic metabolism. In adults with normal renal function, bivalirudin has a clearance of 3.4 mL/min/kg and an elimination half-life of 25 min. The clearance of bivalirudin is reduced by approximately 20% in adults with moderate to severe renal impairment and by 80% in patients with end stage renal disease. Doses may require adjustment in patients with renal impairment, but no specific dosing guidelines are available for this population.

The pharmacokinetic and pharmacodynamic profiles of bivalirudin were studied by Forbes and colleagues in 110 children undergoing cardiac catheterization.⁸ The open-label study was conducted by the manufacturer in response to a written request by the FDA for pediatric information. A total of 22 neonates, 33 infants, 32 young children, and 34 adolescents with congenital heart disease were enrolled. All patients received the standard adult PCI regimen: a 0.75 mg/kg bolus dose followed by a 1.75 mg/kg/hr infusion. The resulting pharmacokinetic and dynamic parameters were similar to those reported in adults. When normalized for weight, clearance was more rapid in neonates and decreased with increasing age. There was a positive correlation between ACT and bivalirudin plasma concentrations in all age groups.

Use in Prophylaxis or Treatment of Thrombosis

In 2007, Young and colleagues published a pilot study of bivalirudin as primary treatment in infants with thrombosis.⁹ This open-label dose-finding and safety study, conducted as part of a FDA Investigational New Drug Application, enrolled 16 infants less than 6 months of age. Efficacy was determined by evidence of resolution at 48-72 hrs and by measurement of molecular markers of thrombin generation, including D-dimer, thrombin-antithrombin complexes (TAT), and prothrombin fragment 1.2 at baseline, and 12, 24, 48 and 72 hours, as well as 7 and 14 days after treatment initiation. Patients received a bolus dose of 0.125 mg/kg, 0.25 mg/kg, or 0.5 mg/kg, followed by an infusion of 0.125 mg/kg/hr or 0.25 mg/kg/hr. Doses were adjusted to maintain an aPTT of 1.5-2.5x the patient's baseline aPTT.

Thirteen of the 16 patients had an aPTT measurement within the target range 15 minutes after their initial bolus dose, with a median of 1.87x baseline (range 1.1-2.5). The initial infusion rate produced an aPTT within the target range in 15 of the 16 patients at the 4-hour

measurement, with a median of 1.97x baseline (range 1.6-2.7). One patient in the 0.25 mg/kg/hr group was above the desired aPTT range. A dose-response relationship was demonstrated with both aPTT and aPTT ratio. Thirty-seven percent of patients had partial or complete resolution of their thrombus at 48-72 hours. All three molecular markers of thrombin generation were significantly lower after initiation of bivalirudin. Two patients were considered to have major bleeding, with gross hematuria that resolved with dose reduction.

The following year, these investigators published a retrospective study of 16 children (4 months to 14 years of age) at the Children's Hospital of Illinois given bivalirudin for prophylaxis or treatment of thrombosis.¹⁰ Therapy was initiated with a bolus dose of 0.25 mg/kg followed by an infusion of 0.05-0.25 mg/kg/hr titrated to achieve an aPTT 1.5-2.5x baseline. The mean effective dose was 0.16 ± 0.07 mg/kg/hr. Ultrasound studies performed in 10 children at 72 hours demonstrated evidence of thrombus regression in all cases. One patient experienced gross hematuria that resolved with temporary discontinuation of treatment. Bivalirudin was reinstated the following day without incident. In both studies, the authors concluded that bivalirudin may be a safe and effective alternative to heparin for anticoagulation in infants and children.

Use during Extracorporeal Life Support

The greatest experience with bivalirudin in children to date has been with ECLS. One of the first reports was published by Pollak and colleagues in the March 2011 issue of the *Journal of Extracorporeal Technology* describing a 5-day-old infant with congenital diaphragmatic hernia receiving ECLS.¹¹ The neonate developed evidence of HIT as well as small vessel arterial thrombosis. A transition from heparin to bivalirudin allowed for a successful ECLS course without further complications.

Later that year, Ranucci and colleagues compared bivalirudin to heparin in a retrospective study of 21 patients on ECLS, including nine children.³ The mean starting dose in the 13 bivalirudin patients was 0.05 mg/kg/hr (range 0.05-0.1 mg/kg/hr). Patients in the bivalirudin group had longer ACTs, aPTTs, and reaction times measured by thromboelastography compared to the patients in the heparin group. In addition, the bivalirudin group received less fresh frozen plasma and fewer platelet transfusions, as well less antithrombin. There were no differences in thromboembolic complications. The authors concluded that bivalirudin provided an effective alternative to heparin for anticoagulation and may have the

potential to reduce blood product administration and costs during ECLS.

In the May 2013 issue of *Pediatric Critical Care Medicine*, Nagle and colleagues at the University of California, Davis Medical Center reported their experience with bivalirudin in 12 children on ECLS.⁴ The patients ranged in age from 1 day to 6 years (median 8 days). The median duration of bivalirudin use was 92 hrs (range 60-230 hrs) with a median duration of ECLS of 226 hrs (range 111-913 hrs). All patients initially received heparin and were transitioned to bivalirudin for evidence of HIT, heparin resistance, or clot formation within the circuit.

Four patients initially received bolus doses of bivalirudin during the transition from heparin (median dose 0.1 mg/kg, range 0.04-0.14 mg/kg). Bivalirudin infusions were initiated at a dose of 0.05-0.3 mg/kg/hr. The median time to achieve an aPTT level within the goal range was 4 hrs (range 1-25 hrs). The average percentage of time spent within 10% of the goal aPTT range was 70% ± 11%. The median effective maintenance dose was 0.16 mg/kg/hr, with a range of 0.05 to 0.48 mg/kg/hr. Subgroup analysis revealed no correlation between dose and age or indication. Eight patients survived to discharge. Routine intracranial ultrasounds revealed no evidence of hemorrhage, but two patients developed transient pulmonary hemorrhage. Three patients were successfully treated with low-dose factor VII (≤ 30 mcg/kg) to reverse the effects of bivalirudin prior to a surgical procedure.

Use with Ventricular Assist Devices

In 2013, Rutledge and colleagues conducted a retrospective analysis of six pediatric patients at two hospitals who received bivalirudin while being supported with a Berlin Heart EXCOR ventricular assist device (VAD).¹² The patients ranged in age from 9 months to 14 years, with durations of VAD support ranging from 21 to 155 days. All patients had previously received heparin; three had developed thrombosis, two had HIT, and one was considered a high-risk patient due to a prosthetic mitral valve. Bivalirudin was initiated according to the Edmond protocol at 0.5 mg/kg/hr in patients with normal renal function, 0.3 mg/kg/hr in those with moderate renal impairment, and 0.2 mg/kg/hr in those with severe renal impairment. No loading doses were used. The infusion was titrated to achieve an aPTT of 1.5-2x baseline, with an effective bivalirudin infusion rate ranging from 0.1-0.8 mg/kg/hr. Additional therapy included epoprostenol, aspirin, dipyridamole, and/or clopidogrel. One patient developed a cerebrovascular infarct with complete recovery; there were no other complications. Five patients survived to successful transplantation.

Use during Cardiopulmonary Bypass

Almond and colleagues used bivalirudin to provide anticoagulation for a 5-year-old girl receiving cardiopulmonary bypass (CPB) during cardiac transplantation.¹³ The patient had received ECMO prior to transplantation and developed HIT with a platelet count of 41,000/mm³, thrombosis of the distal extremities, and a positive test for PF4 antibodies. She was transitioned to an argatroban infusion for the remainder of her ECMO course. Twenty-five days after decannulation, she received a donor heart. Rather than restarting argatroban, the authors chose bivalirudin for anticoagulation during surgery. The authors elected to initiate bivalirudin at 10% of the recommended adult dose, with an initial bolus dose of 0.15 mg/kg followed by a continuous infusion of 0.25 mg/kg/hr. An additional 50 mg of bivalirudin was added to the bypass circuit to produce an ACT greater than 400 sec. An additional bolus of 0.1-0.5 mg/kg was given as needed for subtherapeutic ACT levels during CPB. Following a successful surgery, the patient received fresh frozen plasma, packed red blood cells, and recombinant factor VII to reverse the anticoagulation at the time of separation from the CPB circuit.

Precautions and Adverse Effects

Bivalirudin should not be used in patients with a known hypersensitivity to any of its components. It should be used with caution in patients at risk for bleeding. Treatment is contraindicated in patients with significant bleeding.¹

In adults, the rate of major bleeding with bivalirudin use during procedures is 2.3-3.7% with a rate of minor bleeding of 13.6%.¹ Thrombocytopenia, defined as a platelet count <100,000/mm², has been reported in 0.3-0.7% of patients. Other adverse effects reported in clinical trials of bivalirudin include nausea (in up to 15% of patients), hypotension (12%), hypertension (6%), bradycardia (5%), vomiting (6%), and injection site pain (8%). While limited experience prevents an accurate assessment of the adverse effect profile of bivalirudin in children, the papers published to date suggest a rate of bleeding or thrombotic events of approximately 8-12%. There have been few reports of major bleeding in children receiving bivalirudin. In the open-label catheterization study, 2 of the 110 patients (1.8%) had major bleeding events.⁸

Drug Interactions

Concomitant use of bivalirudin and other anticoagulants may lead to an increased risk for bleeding. Patients receiving combination therapy or being transitioned from one agent to another should be closely monitored.¹

Availability and Cost

Bivalirudin (Angiomax[®]) is available as a lyophilized powder in single-use 250 mg vials, with an acquisition cost of approximately \$400 per vial.¹⁴ For comparison, the acquisition cost of heparin is approximately \$1 to \$2 per dose. Bivalirudin requires reconstitution and dilution to a concentration between 0.5 mg/mL and 5 mg/mL for infusion. Reconstituted and diluted bivalirudin solutions are stable for 24 hrs.¹

Dosing Recommendations

There is no established dosing range for bivalirudin in infants and children. Based on the pilot dose-finding study in neonates and the pediatric clinical data published to date, an effective dosing regimen for bivalirudin would include a bolus dose of 0.125-0.25 mg/kg followed by an initial infusion of 0.125-0.2 mg/kg/hr.^{3,4,9-13} In the survey by Oschman, 75% of institutions using bivalirudin reported giving a bolus dose of 0.125 mg/kg, while 25% used the higher 0.25 mg/kg dose.⁵ Infusion rates ranged from 0.1-0.125 mg/kg/hr. Most papers have used a goal of 1.5-2.5x the baseline aPTT for subsequent dose titration.

Summary

While heparin continues to be the primary means of providing anticoagulation in the pediatric population, there is a role for DTIs such as bivalirudin in patients with HIT, evidence of heparin resistance, or clot extension during heparin treatment. Initial clinical data in children have shown that bivalirudin can provide effective anticoagulation, achieving target aPTT goals with minimal dosage adjustment, with relatively few reports of serious adverse effects. Its primary disadvantages remain cost and the need for continuous infusion because of its short half-life. Additional research is needed to determine the optimal dosing strategy for bivalirudin in children, as well as to better define the frequency of significant bleeding with its use.

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Formulary Update

The following actions by the Pharmacy and Therapeutics Committee at their December 2014 meeting:

1. The restriction on abciximab was amended to include treatment of acute thrombosis in peripheral endovascular small vessel interventions.
2. Dasatinib (Sprycel[®]) was added with restriction to Hematology/Oncology.
3. Degarelix (Firmagon[®]) was added with restriction to Hematology/Oncology and Urology.
4. The following metered-dose inhalers were deleted: fluticasone-salmeterol (Advair[®]), mometasone (Asmanex[®]), and the ProAir[®] formulation of albuterol, with implementation of therapeutic interchange to Formulary agents.

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