JPPT

Review Article

Bivalirudin as an Alternative to Heparin for Anticoagulation in Infants and Children

Marcia L. Buck, PharmD

Departments of Pharmacy Services and Pediatrics, University of Virginia Children's Hospital, Charlottesville, Virginia

Bivalirudin, a direct thrombin inhibitor, is a useful alternative to heparin for anticoagulation in infants and children. It has been found to be effective in patients requiring treatment of thrombosis, as well as those needing anticoagulation during cardiopulmonary bypass, extracorporeal life support, or with a ventricular assist device. While it has traditionally been used in patients who were unresponsive to heparin or who developed heparin-induced thrombocytopenia, it has recently been studied as a first-line agent. Bivalirudin, unlike heparin, does not require antithrombin to be effective, and as a result, has the potential to provide a more consistent anticoagulation. The case reports and clinical studies currently available suggest that bivalirudin is as effective as heparin at reaching target activated clotting times or activated partial thromboplastin times, with equivalent or the lower rates of bleeding or thromboembolic complications. It is more expensive than heparin, but the cost may be offset by reductions in the costs associated with heparin use, including anti-factor Xa testing and the need for administration of antithrombin. The most significant disadvantage of bivalirudin remains the lack of larger prospective studies demonstrating its efficacy and safety in the pediatric population.

INDEX TERMS: anticoagulation, bivalirudin, cardiopulmonary bypass, extracorporeal life support, ventricular assist devices

J Pediatr Pharmacol Ther 2015;20(6):408–417

INTRODUCTION

The direct thrombin inhibitors (DTIs), bivalirudin and argatroban, offer an alternative to unfractionated heparin (heparin) for providing intravenous anticoagulation. Bivalirudin was the first DTI to be marketed in the United States, approved by the Food and Drug Administration (FDA) on December 15, 2000.[1] 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. The clinical applications for bivalirudin have expanded to include off-label use in cardiopulmonary bypass (CPB) during cardiac surgery and in patients receiving extracorporeal life support (ECLS) or being supported with a ventricular assist device (VAD) as a bridge to cardiac transplantation. As experience with bivalirudin has grown in adults, clinicians have begun to explore its potential in the pediatric population. While it is not yet considered a first-line therapy by most clinicians, it has been found to be an effective alternative to heparin in both children and adults with heparin-induced thrombocytopenia (HIT), heparin resistance (inability to achieve anticoagulation goals with heparin doses > 70 units/kg/hr), or evidence of continued clot formation or extension during treatment with heparin.[2–16]

Direct thrombin inhibitors have several advantages over heparin, including the potential to produce more consistent anticoagulation. Heparin acts through potentiation of endogenous antithrombin and is known to be less effective in patients with low levels. Studies have shown that serum antithrombin levels are naturally low in neonates and may be reduced in patients undergoing CPB and ECLS, placing patients at risk for clot formation in spite of appropriate heparin dosing.[17–19] Many hospitals have begun to develop guidelines for antithrombin supplementation to optimize heparin response, either

by administration of human or recombinant antithrombin or the use of fresh frozen plasma, which contains antithrombin. This can lead to significant fluctuations in coagulation parameters, as well as increasing costs and creating a greater reliance on donor blood products. Use of a DTI avoids the need for antithrombin supplementation entirely. Direct thrombin inhibitors are also effective against both circulating and clot-bound thrombin, as opposed to heparin, which forms a complex only with circulating thrombin, which may also add to a more consistent and effective level of anticoagulation in patients requiring long-term treatment. In spite of these advantages, the use of DTIs continues to be limited by the small number of studies demonstrating their safety and efficacy in the pediatric population.

PHARMACOKINETIC AND PHARMACODYAMIC PROFILE

Bivalirudin is a synthetic analogue of hirudin, the anticoagulant found in the saliva of the leech *Hirudo medicinalis*. Following intravenous administration, it exhibits linear pharmacokinetics over the standard dosing range.[1,20] Bivalirudin is not bound to plasma proteins other than thrombin. It is cleared by proteolytic cleavage in the blood, with approximately 20% cleared renally. In adults with normal renal function, bivalirudin has a clearance of 3.4 mL/min/kg and an elimination half-life of approximately 25 minutes.[1] The shorter half-life of bivalirudin offers an advantage compared to the 40-minute half-life of argatroban, making it a safer choice when rapid discontinuation of anticoagulation is needed. 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. While little is known of the effects of renal dysfunction on bivalirudin clearance in children, a published case report describes potential accumulation in a 2-month-old who had been receiving a bivalirudin infusion for occlusive iliac and femoral deep vein thromboses.[2] When the patient's serum creatinine rose to 0.98 mg/mL on day 5 of therapy activated partial thromboplastin times (aPTTs) values began to rise, suggesting reduced drug clearance. Lowering the infusion rate by 20% each day for the next 2 days failed to bring aPTT values below 400 seconds, and the patient developed pulmonary bleeding. Bivalirudin was discontinued, resulting in normalization of aPTT values and resolution of the bleeding.

Bivalirudin is a bivalent DTI, binding to both the catalytic site and the anion-binding exosite of circulation and clot-bound thrombin.[1] Administration produces an immediate anticoagulant effect. Measures of anticoagulation typically return to baseline an hour after discontinuing treatment, as thrombin slowly cleaves the bivalirudin bonds, reversing its effects and resulting in recovery of thrombin function. Administration of bivalirudin produces dose and concentration-dependent anticoagulation, as measured by activated clotting time (ACT), aPTT, prothrombin time (PT), and thrombin time (TT). The best method for monitoring anticoagulation produced by DTIs, however, has not yet been established. While the manufacturer recommends monitoring ACT for adults undergoing cardiac procedures, the majority of hospitals use aPTT as their primary indicator of efficacy outside of the procedural or operative settings.[21,22] The use of aPTT for monitoring may not always accurately reflect the degree of anticoagulation. A recent *in vitro* experiment using 235 plasma samples from 82 adults treated with a DTI found that aPTT was only poorly correlated with other tests of DTI activity: the ecarin chromogenic assay (ECA) to assess the ability to block thrombin generation, the dilute thrombin time (dTT), and a prothrombinase-induced clotting time (r^2 = 0.04-0.23).[23] The best correlation was between dTT and ECA (r^2 = 0.92). Additional studies will be needed to determine if any of these newer tests will provide a reliable and timely assessment of DTI-induced anticoagulation that can be incorporated into routine clinical practice.

The pediatric pharmacokinetic and pharmacodynamic profile of bivalirudin was studied in 110 children undergoing cardiac catheterization.[5] This open-label study was conducted by the manufacturer in response to a written request by the FDA for pediatric information. Twenty-two neonates, 33 infants, 32 children 2 to 6 years of age, and 34 children 6 to 16 years of age with congenital heart disease were enrolled. All patients received the standard adult percutaneous coronary intervention regimen: a 0.75 mg/kg bolus dose followed by a 1.75 mg/kg/hr infusion. There were pharmacokinetic differences across all age groups. Neonates had a more rapid

clearance of bivalirudin, as well as a lower mean maximum concentration (C_{max}), mean area under the concentration time curve (AUC_{0-t}), and mean average concentration (C_{ave}) than older children. There was a trend towards increasing mean C_{max} and mean AUC_{0-t} with increasing age, resulting in values approximately 1.5-fold higher in the older children compared to the neonates. This was offset by a decreasing clearance with age, from 11.2 ± 4.3 mL/min/kg in the neonates to 5.98 ± 1.3 mL/min/kg in the older children. As a result, half-life was similar among all age groups, ranging from 0.25 to 0.28 hours. There was also a positive correlation between bivalirudin plasma concentrations and ACT values in all age groups.

ADVERSE EFFECTS

In adults, the rate of major bleeding with bivalirudin use during procedures is 2.3% to 3.7%, with a rate of minor bleeding of 13.6%.[1] Thrombocytopenia, defined as a platelet count <100,000/mm^2, has been reported in 0.3% to 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, initial studies suggest results similar to those in adults.[2–16] In the open-label pediatric pharmacokinetic and pharmacodynamic study described earlier, 2 of the 110 subjects (1.8%) developed hematomas at the site of sheath removal that met the criteria for a major bleeding event.[5] Minor bleeding was reported in 12 subjects (11%), primarily bleeding or small hematomas at the catheterization site. Thrombosis was reported in 8 patients (7.3%). Three patients had a thrombus form in the sheath during their procedure, with the remainder developing a thrombus after the catheterization was completed. Only one required thrombolysis with alteplase.

CLINICAL EXPERIENCE

A recent survey of pharmacists at 56 hospitals throughout the United States evaluated the availability and use of DTIs within their pediatric patient population.[21] Thirty-four percent of the respondents were at free-standing pediatric hospitals, with 62.5% at hospitals providing both pediatric and adult care. Most institutions had more than 1 DTI on their formulary. Argatroban was the most common, available in 80% of hospitals, with bivalirudin available in 41%. Lepirudin was available in 4% of hospitals prior to its removal from the market by Bayer Healthcare in 2012. Use of a DTI in infants and children was uncommon. The majority of respondents (41.1%) used DTIs 2 to 4 times per year. Another 33.9% reported using DTIs less than twice a 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. A 2014 analysis of the Pediatric Health Information System (PHIS) database found that 208 children between 2 and 12 years of age received a DTI during the period from 2004 to 2011.[22] The PHIS database includes information from 43 tertiary care pediatric hospitals throughout the United States, making it a reasonable representation of medication use in the United States. The diagnosis of HIT led to the use of a DTI in 15.6% of cases. Of the patients managed with a DTI, 73.1% were treated with argatroban, 23.1% received bivalirudin, and 7.7% received lepirudin. 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 ($p < 0.05$). 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%, $p = 0.002$). The most common complications were hemorrhage or hematomas following a procedure, reported in 11% of cases and hemoptysis, reported in 5.8%. The same authors also used the PHIS database to investigate anticoagulant use in children supported by a VAD.[24] A total of 466 patients were identified during the period from 2000 to 2011. Heparin was used in 98.3% of patients, while argatroban was used in only 0.9% of patients, bivalirudin in 0.6%, and lepirudin in 0.2%.

TREATMENT OF THROMBOSIS

The first pilot study of bivalirudin as primary treatment of thrombosis in infants was published in 2007 (Table).[3] This open-label dose-finding and

Table. Clinical Experience With Bivalirudin in Infants and Children

Reference	Patient Number (Age)	Initial Bolus Dose (Infusion)	Monitoring Goal	Adverse Effects
Treatment of thrombosis				
Malloy et al[2]	1 (2 mo)	0.1 mg/kg (0.2 mg/kg/hr)	aPTT 1.5-2.5× baseline	Bloody chest tube drainage
Young et al[3]	16 (< 6 mo)	0.125-0.5 mg/kg (0.125-0.25 mg/kg/hr)	aPTT 1.5-2.5× baseline	Minor bleeding 7/16 (43.8%) Major bleeding 2/16 (12.5%)
Rayapudi et al[4]	16 (newborn-14 yr)	0.05-0.25 mg/kg (0.05-0.25 mg/kg/hr)	aPTT 1.5-2.5× baseline	One case of hematuria
Cardiac catheterization				
Forbes et al[5]	110 (newborn-16 yr)	0.75 mg/mg (1.75 mg/kg/hr)	ACT goal not specified; ACTs during procedure ranged from 250-450 sec	Minor bleeding 12/110 (10.9%) Major bleeding 2/110 (1.8%)
Zamora[6]	1 (2 mo)	0.5 mg/kg (0.25 mg/kg/hr)	ACT > 400 sec	None
Breinholt et al[7]	1 (2 yr)	0.75 mg/kg (1.75 mg/kg/hr)	ACT 500-600 sec	None
Cardiopulmonary bypass				
Argueta-Morales et al[8]	2 (not specified)	1 mg/kg, 2.5 mg/kg/hr (50 mg added to CPB circuit)	ACT > 400 sec	None
Almond et al[9]	1 (5-yr)	0.15 mg/kg, 0.25 mg/kg/hr (50 mg add to the CPB circuit)	ACT 200-500 sec	Bleeding at the time of CPB separation requiring blood products and factor VII
Gates et al[10]	1 (5 mo)	0.5-1 mg/kg (2.5 mg/kg/hr, 50 mg/kg bivalirudin added for every 400 mL CPB prime)	ACT > 400 sec	None
Dragomer et al[11]	1 (17 mo)	0.5-1 mg/kg (2.5 mg/kg/hr, no bivalirudin added to the CPB circuit)	ACT > 400 sec	Minimal bleeding
Extracorporeal life support				
Pollak et al[12]	1 (5 days)	0.4 mg/kg (0.15 mg/kg/hr)	ACT 160-200 sec	None
Ranucci et al[13]	21 (12 adults, 9 children)	Heparin 100 unit/kg bolus (5-10 units/kg/hr) Bivalirudin 0.03-0.05 mg/kg/hr	ACT 160-180 sec aPTT 50-80 sec TEG 12-30 min	Greater bleeding in heparin group One thrombotic complication in bivalirudin group
Nagle et al[14]	12 (1 day-6 yr)	0.1 mg/kg (0.05-0.3 mg/kg/hr)	aPTT goal not specified	2 patients with pulmonary hemorrhage, 8 patients with clots in the ECLS circuit
Preston et al[15]	1 (8 yr)	0.75-1.6 mg/kg (1.2-1.8 mg/kg/hr)	aPTT 60-80 sec	None
Ventricular assist devices				
Rutledge et al[16]	6 (7 mo-14 yr)	0.2-0.5 mg/kg/hr	aPTT 1.5-2.5× baseline ACT 400-500 sec for transplantation surgery	One patient with cerebrovascular infarction; one with transient limb ischemia, one patient with intraoperative bleeding requiring blood products and factor VII

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; ECLS, extracorporeal life support; TEG, thromboelastography

safety study, conducted as part of a FDA Investigational New Drug Application, enrolled 16 infants less than 6 months of age. Eight patients had extremity deep vein thromboses, 4 had right atrial thromboses, 3 had inferior vena cava thromboses, and 1 had a right ventricular outflow tract thrombus. Efficacy was determined by evidence of clot resolution at 48 to 72 hours and by measurement of aPTT 15 minutes after the bolus and at 4, 12, and 24 hours. In addition, molecular markers of thrombin generation, including D-dimer, thrombin-antithrombin complexes (TATs), and prothrombin fragment 1.2 were assessed at baseline, 12, 24, 48, and 72 hours, and 7 and 14 days after treatment initiation. The first 5 patients received a bolus dose of 0.25 mg/kg. The remaining patients where then divided into 2 cohorts who received a bolus dose of either 0.125 mg/kg or 0.5 mg/kg. The patients were also divided into 2 groups for their initial infusion rate, with the first 9 receiving 0.25 mg/kg/hr as their rate and the remainder starting therapy at 0.125 mg/kg/hr. The infusion rates chosen by the authors were similar to those reported in studies of adults with HIT, ranging from 0.03 to 0.25 mg/kg/hr.[25] Doses were adjusted to maintain an aPTT of 1.5 to 2.5× the patient's baseline.

Thirteen of the 16 patients had an aPTT measurement 15 minutes after their bolus dose; 12 (75%) had an aPTT within their target range (1.5-2.5× baseline), with a median of 1.87× baseline (range 1.1-2.5). The initial infusion rate produced an aPTT within the target range in 15 of the 16 patients (94%) at the 4-hour measurement, with a median of 1.97× baseline (range 1.6-2.7). One patient in the 0.25 mg/kg/hr group was above the desired aPTT range. Infusion rates were increased or decreased by 50% for subsequent aPTT values outside of the patient's target range. A dose–response effect for the continuous infusion was demonstrated for both aPTT and aPTT ratio ($p < 0.0001$ and $p < 0.001$, respectively). All 3 molecular markers of thrombin generation were significantly lower after initiation of bivalirudin, indicating adequate thrombin inhibition. Three infants had complete resolution of their thrombus by 72 hours, while another 3 had partial resolution. None of the patients had progression of their thrombus. Two patients were considered to have major bleeding, with gross hematuria that resolved with dose reduction. Minor bleeding was reported in 9 patients. The authors concluded that the results from their pilot study supported further research into the role of bivalirudin as an alternative to heparin in infants.[3]

The following year, the authors published a single-center retrospective study of 16 children from 4 months to 14 years of age given bivalirudin for prophylaxis or treatment of thrombosis.[4] Three children received bivalirudin after developing HIT; 7 had evidence of heparin resistance, and 6 had compromised hepatic and renal function. Therapy was initiated with a bolus dose of 0.05 to 0.25 mg/kg in 10 patients, while the other 6 did not receive a bolus dose. The bivalirudin infusion was started at 0.05 to 0.25 mg/kg/hr, based on prescriber preference, and titrated to achieve an aPTT 1.5 to 2.5× 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 after urethral catheterization that resolved with temporary discontinuation of treatment. Bivalirudin was reinstituted the following day without incident. There were no other adverse effects reported.

CARDIAC CATHETERIZATION

Bivalirudin has been used successfully in several case reports of children undergoing cardiac catheterization.[5–7] The first report described a 2-month-old infant with DiGeorge syndrome who developed acute kidney injury after surgery in the first week of life to place a right ventricle-to-pulmonary arterial conduit.[6] When the patient needed cardiac catheterization to place a stent in the conduit, the patient's clinical status, along with a low serum antithrombin level, led the medical team to select bivalirudin for anticoagulation. A bolus dose of 0.5 mg/kg was given, followed by a bivalirudin infusion of 0.25 mg/kg/hr. Within 15 minutes after initiation of the infusion, ACT had increased to 353 seconds and remained at goal (>200 seconds) throughout the procedure. Within 30 minutes of discontinuing bivalirudin, the ACT had dropped to 180 seconds. There were no bleeding complications.

A second case described a 2-year-old boy with ventricular inversion, mitral atresia, pulmonary atresia, and malposition of the great vessels.[7] After a Blalock-Taussig shunt as a neonate and a Glenn procedure at 6 months, the patient had

a St. Jude aortic valve implanted and a Gortex shunt placed from the aorta to the superior vena cava to supplement pulmonary blood flow at 18 months. He developed HIT during the postoperative course following the last surgery. Six months later, he required a cardiac catheterization for stent placement and was managed with bivalirudin. He was treated according to the recommendations for adults undergoing percutaneous coronary interventions: a bolus dose of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/hr.[1] Within 15 minutes of initiation, the ACT was 522 seconds. Stent placement was successful. At bivalirudin discontinuation, the ACT was 632 seconds; within 30 minutes it had fallen to 307 seconds. As in the previous case, there were no bleeding complications even with the use of a much larger dose.

CARDIOPULMONARY BYPASS

There are a small number of case reports describing the use of bivalirudin during CPB, beginning in 2006.[8–11] An early case report described the use of bivalirudin for anticoagulation during CPB in 2 infants with HIT after previous surgery. After a bolus of 1 mg/kg, an infusion of 2.5 mg/kg/hr was started and continued throughout the case to maintain ACT values over 400 seconds. An additional 50 mg was added to the CPB circuit prime.[8] This dose has previously been reported as effective in adults undergoing bypass.[26] Successful surgery was also reported in a 5-year-old girl receiving CPB during cardiac transplantation.[7] The patient had received extracorporeal membrane oxygenation (ECMO) prior to transplantation and developed HIT with a platelet count of 41,000/mm^3, 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 because of its shorter half-life and potentially better elimination by dialysis if needed. Not having access to any pediatric dosing information at the time, 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. A supplemental dose of 50 mg was added to the bypass circuit to produce an ACT greater than 400 seconds. Additional bolus doses of 0.1 to 0.5 mg/kg were given and the infusion increased as needed for subtherapeutic ACT levels. Following surgery, the patient received fresh frozen plasma, packed red blood cells, and recombinant factor VII to decrease bleeding at the time of separation from the CPB circuit. No adverse bleeding or thrombotic events were noted during the postoperative period.

A third case report described an infant with hypoplastic left heart syndrome who developed HIT following Norwood surgery complicated by bowel ischemia requiring resection.[10] For her second stage cardiac surgery, the now 5-month-old infant was given bivalirudin for anticoagulation during CPB. After completion of the sternotomy, a 1 mg/kg bivalirudin bolus dose was administered, producing an ACT of 286 seconds. A bolus of 0.5 mg/kg was given 5 minutes later to produce an ACT of 597 seconds (goal > 400 seconds). An infusion was then started at 2.5 mg/kg/hr, which maintained ACT values between 461 and 597 seconds. The CPB circuit was also primed with 50 mg of bivalirudin per 400 mL circuit volume. There was no clot formation in the CPB circuit and no evidence of bleeding after surgery. In a fourth case, a 17-month-old with HIT following an arterial switch after birth for transposition of the great arteries was given bivalirudin for CPB during pulmonary arterioplasty.[11] Bivalirudin administration was initiated with boluses of 1 mg/kg and two 0.5 mg/kg doses to achieve an ACT of 370 seconds, followed by an infusion of 2.5 mg/kg/hr. The last ACT prior to discontinuation was 945 seconds, with an aPTT of 167 seconds. After modified ultrafiltration (MUF), the ACT had dropped to 389 seconds. The patient was given fresh frozen plasma and cryoprecipitate to ensure no residual bleeding. There were no complications noted.

EXTRACORPOREAL LIFE SUPPORT

The greatest experience with bivalirudin in children to date has been with ECLS.[12–15,27] One of the first reports was published in 2011, describing a 5-day-old infant with congenital diaphragmatic hernia who developed HIT as well as small vessel arterial thrombosis while receiving ECLS.[12] A transition from heparin to bivalirudin, using a loading dose of 0.4 mg/kg followed by an

infusion of 0.15 mg/kg/hr titrated to an ACT of 180 to 200 seconds allowed for a successful ECLS course without further complications. Later that year, the safety and efficacy of a bivalirudin-maintained ECLS was compared to traditional heparin–based anticoagulation in a retrospective study of 21 patients, including 9 children.[13] The first 8 consecutive patients were managed with the institution's traditional heparin-based anticoagulation, followed by 13 patients managed with bivalirudin. The heparin group received a loading dose of 100 units/kg at cannulation, followed by an initial dose of 5 to 10 units/kg/hr titrated to achieve a target ACT of 160 to 180 seconds and an aPTT of 50 to 80 seconds. Thromboelastography (TEG) was also performed every 8 hours with a target value of 12 to 30 minutes. The mean bivalirudin starting dose of 0.05 mg/kg/hr (range 0.05-0.1 mg/kg/hr) was adjusted in the same manner as heparin. In comparison, studies of bivalirudin in adult ECMO have used doses as low as 0.025 mg/kg/hr without a loading dose.[28]

Patients in the bivalirudin group had longer ACTs, aPTTs, and reaction times measured by TEG compared to the patients in the heparin group. In addition, the bivalirudin group had less bleeding, 16 ± 13 mL/kg/day, versus 51 ± 46 mL/kg/day in the heparin group ($p = 0.015$), and received significantly less fresh frozen plasma, fewer platelet transfusions, and less antithrombin (all $p < 0.05$). There was a trend towards lower costs with bivalirudin in the adults, but the difference reached statistical significance in the children, largely the result of reduced blood product and antithrombin use.[13] There were no significant differences in rates of bleeding or 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 a letter following publication of their study, the lead author cautioned readers that slower intracardiac blood flow during ECLS may allow for greater proteolytic cleavage of bivalirudin and a risk for less effective anticoagulation.[25] It is suggested that ECLS patients on bivalirudin maintain some degree of pulsatile flow to prevent areas of stagnation and that periodic echocardiographic evaluation for movement of the heart valves be used to document good blood flow.

In 2013, a case series described bivalirudin use in another 12 children on ECLS.[14] The patients ranged in age from 1 day to 6 years (median 8 days). All patients initially received heparin and were transitioned to bivalirudin for evidence of HIT, heparin resistance, or clot formation within the circuit. Four patients 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 0.05 to 0.3 mg/kg/hr. The aPTT goals were determined for each patient individually based on underlying disease and risk factors. The median time to achieve an aPTT level within the goal range was 4 hours, with a range of 1 to 25 hours. The median duration of bivalirudin use was 92 hours, with a range of 60 to 230 hours. The average percentage of time spent within 90% to 110% of the goal aPTT range was 70.3% ± 10.9%. The median effective maintenance dose was 0.16 mg/kg/hr, with a range of 0.05 to 0.48 mg/kg/hr. There was a positive correlation between dose and aPTT ($r^2 = 0.264$, $p = 0.044$). Subgroup analysis revealed no correlation between the effective maintenance dose and patient age or indication. Eight patients survived to discharge. Routine intracranial ultrasounds revealed no evidence of hemorrhage, but 2 patients developed transient pulmonary hemorrhage. While one of the known disadvantages of anticoagulation with a DTI is the inability to reverse its effects with protamine, the authors noted that 3 patients were successfully treated with low-dose factor VII (≤ 30 mcg/kg) prior to surgical procedures to minimize the risk of excessive bleeding.

A recent case report describes an additional twist on bivalirudin use during ECLS.[15] An 8-year-old patient was placed on venovenous ECLS as a bridge to lung transplantation. The patient had initially been anticoagulated with heparin during ECLS, but developed HIT with a positive antibody assay. Bivalirudin was chosen to replace heparin and initiated with an infusion of 1.2 mg/kg/hr. As a part of his transplantation evaluation, the patient was found to have significant allosensitization and underwent 2 plasma exchanges within 48 hours to reduce antibody titers. During the exchanges, aPTT was monitored every 15 to 20 minutes. Bivalirudin bolus doses of 0.75 to 1.6 mg/kg were given and the infusion titrated to maintain values of 60 to 80 seconds. The infusion was increased to 1.6 mg/

kg/hr during the first plasma exchange and 1.8 mg/kg/hr during the second. The patient tolerated both plasma exchanges without incident; there were no clots in the ECLS circuit or clinical concerns for bleeding.

VENTRICULAR ASSIST DEVICES

A recent retrospective study described 6 pediatric patients at 2 hospitals who received bivalirudin while being supported with a Berlin Heart EXCOR VAD.[16] 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; 3 had developed thrombosis, 2 had HIT, and 1 was considered a high-risk patient due to a prosthetic mitral valve. Bivalirudin was initiated according to institutional 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 subsequently titrated to achieve an aPTT target of 1.5 to 2× baseline. The median effective bivalirudin infusion rate was 0.685 mg/kg/hr, with a range of 0.1 to 0.8 mg/kg/hr. Patients also received an epoprostenol infusion to reduce platelet aggregation, with the addition of aspirin, dipyridamole, or clopidogrel as needed. One patient developed a cerebrovascular infarct with complete recovery and 1 patient experienced ischemia in a foot where an arterial line had been placed; there were no other complications. Five patients underwent successful cardiac transplantation. Bivalirudin was continued during surgery, with an additional dose of 1 mg/kg used to prime the CPB circuit and bolus doses of 0.1 to 0.5 mg/kg and titration of the bivalirudin infusion to maintain target ACTs of 400 to 500 seconds. One patient had significant bleeding in the operating room managed with blood products and factor VII.

RECOMMENDATIONS FOR ADMINISTRATION

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 to 0.25 mg/kg followed by an initial infusion of 0.125 to 0.25 mg/kg/hr in patients requiring prophylaxis or treatment for thrombosis.[2–16] Larger bolus doses, 0.5 to 1 mg/g, with an infusion rate of 0.25 to 2.5 mg/kg/hr have been used to produce adequate anticoagulation for cardiac catheterization or CPB. Several institutions reported adding an additional 50 mg of bivalirudin directly into the CPB circuit prior to surgery. Most hospitals monitored their patients with aPTT, with a goal of 1.5 to 2.5× baseline, typically checked every 2 to 4 hours. In patients undergoing cardiac catheterization or CPB, ACTs should be checked at 15-minute intervals. The goal ACT varies among the published bivalirudin cases, but most centers have aimed for ACTs of 400 to 500 seconds. Monitoring for ECLS and VADs for patients varies among centers, but may include ACT, aPTT, and TEG.

Bivalirudin is available in single-use 250-mg vials, with an average wholesale price of $1150 per vial.[29] This does not include the cost of relatively frequent monitoring. A cost analysis of bivalirudin versus heparin use in ECLS or other pediatric indications has not been completed. While certainly much more expensive than heparin, the indirect costs of using heparin, including anti-factor Xa monitoring and administration of exogenous antithrombin or fresh frozen plasma to potentiate heparin, must also be taken into consideration.

CONCLUSION

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 infants and children have shown that bivalirudin can provide effective anticoagulation, achieving target ACT, aPTT, and TEG goals with minimal dosage adjustment and a relatively low incidence of serious hemorrhagic or thrombotic complications. The primary disadvantage of bivalirudin continues to be the lack of pediatric studies. Additional research is needed to better define its safety and efficacy in infants and children, as well as to determine the optimal dosing strategy and monitoring parameters for this patient population.

Disclosure The author declares no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Abbreviations ACT, activated clotting time; aPTT activated partial thromboplastin time; AUC, area under the concentration time curve; C_{ave}, average concentration; C_{max}, maximum concentration; CPB, cardiopulmonary bypass; DTI, direct thrombin inhibitor; dTT, dilute thrombin time; ECA, ecarin chromogenic assay; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; HIT, heparin-induced thrombocytopenia; MUF, modified ultrafiltration; PHIS, Public Health Information System; PT, prothrombin time; TAT, thrombin-antithrombin complex; TEG, thromboelastography; TT, thrombin time; VAD, ventricular assist device

Correspondence Marcia L. Buck, PharmD, Department of Pharmacy Services, Box 800674, University of Virginia Health System, Charlottesville, VA 22908, email: mlb3u@virginia.edu

REFERENCES

1. Angiomax prescribing information. The Medicines Company, May 2013. http://www.angiomax.com/downloads/Angiomax_US_PI_June_2013.pdf. Accessed March 14, 2015.
2. Malloy KM, McCabe TA, Kuhn RJ. Bivalirudin use in an infant with persistent clotting on unfractionated heparin. *J Pediatr Pharmacol Ther.* 2011;16(2):108-112.
3. Young G, Tarantino MD, Wohrley J, et al. Pilot dose-finding and safety study of bivalirudin in infants < 6 months of age with thrombosis. *J Thrombosis Haemostasis*. 2007;5(8):1654-1659.
4. Rayapudi S, Torres A Jr, Deshpande GG, et al. Bivalirudin for anticoagulation in children. *Pediatr Blood Cancer.* 2008;51(6):798-801.
5. Forbes TJ, Hijazi ZM, Young G, et al. Pediatric catheterization laboratory anticoagulation with bivalirudin. *Catheter Cardiovasc Interv.* 2011;77(5):671-679.
6. Zamora R. Successful anticoagulation with bivalirudin in antithrombin-deficient pediatric patient undergoing stent placement. *Catheter Cardiovasc Interv.* 2006;68(2):292-295.
7. Breinholt JP, Moffett BS, Texter KM, et al. Successful use of bivalirudin for superior vena cava recanalization and stent placement in a child with heparin-induced thrombocytopenia. *Pediatr Cardiol.* 2008;29(4):804-807.
8. Argueta-Morales IR, Olsen MC, DeCampli WM, et al. Alternative anticoagulation during cardiovascular procedures in pediatric patients with heparin-induced thrombocytopenia. *J Extra Corpor Technol.* 2012;44(2):69-74.
9. Almond CSD, Harrington J, Thiagarajan R, et al. Successful use of bivalirudin for cardiac transplantation in a child with heparin-induced thrombocytopenia. *J Heart Lung Transplant.* 2006;25(11):1376-1379.
10. Gates R, Yost P, Parker B. The use of bivalirudin for cardiopulmonary bypass anticoagulation in pediatric heparin-induced thrombocytopenia patients. *Artif Organs.* 2010;34(8):667-669.
11. Dragomer D, Chalfant A, Biniwale R, et al. Novel techniques in the use of bivalirudin for cardiopulmonary bypass anticoagulation in a child with heparin-induced thrombocytopenia. *Perfusion.* 2011;26(6):516-518.
12. Pollak U, Yacobobich J, Tamary H, et al. Heparin-induced thrombocytopenia and extracorporeal membrane oxygenation: a case report and review of the literature. *J Extra Corpor Technol.* 2011;43(1):5-12.
13. Ranucci M, Ballotta A, Kandil H, et al. Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. *Critical Care.* 2011;15:R275.
14. Nagle EL, Dager WE, Duby JJ, et al. Bivalirudin in pediatric patients maintained on extracorporeal life support. *Pediatr Crit Care Med.* 2013;14(4):e182-e188.
15. Preston TJ, Dalton HJ, Nicol KK, et al. Plasma exchange on venovenous extracorporeal membrane oxygenation with bivalirudin anticoagulation. *World J Pediatr Congenit Heart Surg.* 2015;6(1):119-122.
16. Rutledge JM, Cakravarti S, Massicotte P, et al. Antithrombotic strategies in children receiving long-term Berlin heart EXCOR ventricular assist device therapy. *J Heart Lung Transplant.* 2013;32(5):569-573.

17. Perry R, Stein J, Young G, et al. Antithrombin III administration in neonates with congenital diaphragmatic hernia during the first three days of extracorporeal membrane oxygenation. *J Pediatr Surg.* 2013;48(9):1837-1842.
18. Niimi KS, Fanning JJ. Initial experience with recombinant antithrombin to treat antithrombin deficiency in patients on extracorporeal membrane oxygenation. *J Extra Corpor Technol.* 2014;46(1):84-90.
19. Ryerson LM, Bruce AK, Lequier L, et al. Administration of antithrombin concentrate in infants and children on ECLS improves anticoagulation efficacy. *ASAIO Journal.* 2014;60(5):559-563.
20. Yee DL, O'Brien SH, Young G. Pharmacokinetics and pharmacodynamics of anticoagulants in paediatric patients. *Clin Pharmacokinet.* 2013;52(11):967-980.
21. Oschman A. Survey results: characterization of direct thrombin inhibitor use in pediatric patients. *J Pediatr Pharmacol Ther.* 2014;19(1):10-15.
22. Moffett BS, Teruya J. Trends in parenteral direct thrombin inhibitor use in pediatric patients: analysis of a large administrative database. *Arch Pathol Lab Med.* 2014;138(9):1229-1232.
23. Lind SE, Boyle ME, Fisher S, et al. Comparisons of the aPTT with alternative tests for monitoring direct thrombin inhibitors in patient samples. *Am J Clin Pathol.* 2014;141(5):665-674.
24. Moffett BS, Cabrera AG, Teruya J, et al. Anticoagulation therapy trends in children supported by ventricular assist devices: a multi-institutional study. *ASAIO Journal.* 2014;60(2):211-215.
25. Vo QT, Lin JK, Tong LM. Efficacy and safety of argatroban and bivalirudin in patients with suspected heparin-induced thrombocytopenia. *Ann Pharmacother.* 2015;49(2):178-184.
26. Grubb KJ, Salehi P, Chedrawy EG. Bivalirudin: alternative anticoagulation during cardiopulmonary bypass in patients with heparin-induced thrombocytopenia. *Recent Pat Cardiovasc Drug Discov.* 2010;5(1);20-24.
27. Pieri M, Agracheva N, Bonaveglio E, et al. Bivalirudin versus heparin as an anticoagulant during extracorporeal membrane oxygenation: a case-control study. *J Cardiothorac Vasc Anesth.* 2013;27:30-34.
28. Ranucci M. Bivalirudin and post-cardiotomy ECMO: a word of caution. *Critical Care.* 2012;16:427.
29. Micromedex 2.0 (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. http://www.micromedexsolutions.com/. Accessed March, 14, 2015.