



December 2009: VOLUME 7, NUMBER 3

Neonatal Anticoagulation

In this Issue...

Venous thromboembolism (VTE) in neonates and infants is on the rise. The use of anticoagulants in children poses special challenges, including difficult venous access for delivery of medications and therapeutic monitoring, and a dynamic, age-dependent coagulation system. Although unfractionated heparin (UFH) is a mainstay of treatment for VTE, data on its safety and efficacy in infants are extremely limited. Because of its subcutaneous administration and more predictable pharmacokinetics, low-molecular-weight heparin (LMWH) has become an increasingly popular treatment option. Yet, in very small patients, accurate dosing and subcutaneous delivery can be problematic. Over the past decade, newer anticoagulants such as direct thrombin inhibitors have become part of the armamentarium for treating adults with thrombosis. Perhaps now is the time to learn how to use these agents safely in children.

In this issue, we review current data on the safe and effective delivery of heparin, and discuss the published experience on the use of new anticoagulants in neonates.



Program Information

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Length of Activity

1.0 hour Physicians
1 contact hour Nurses

Release Date

December 17, 2009

Expiration Date

December 16, 2011

Next Issue

January 14, 2009

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Describe how unfractionated heparin (UFH) dosing differs between neonates and older children/adults
- Evaluate the advantages and disadvantages of low-molecular-weight heparin vs UFH for the treatment and prevention of thrombosis in the neonate
- Discuss other options for anticoagulant therapy when heparin is contraindicated or ineffective in neonates

IMPORTANT CME/CNE INFORMATION

ACCREDITATION STATEMENTS

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Nurses

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STATEMENT OF RESPONSIBILITY

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INTENDED AUDIENCE

This activity has been developed for neonatologists, NICU nurses, and respiratory therapists working with neonatal patients. There are no fees or prerequisites for this activity.

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Select a post-test link at the end of the newsletter.

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LAUNCH DATE

April 30, 2009; activities expire two years from the date of publication ending on March 31, 2012.

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- **Edward E. Lawson, MD** has indicated a financial relationship of grant/research support from The National Institutes of Health (NIH). He also receives financial/material support from Nature Publishing Group as the Editor of *Journal of Perinatology*.
- **Lawrence M. Nogee, MD** has indicated no financial relationship with any commercial supporters.
- **Christoph U. Lehmann, MD** has indicated a financial relationship of honoraria from Mead Johnson and Pediatrux.
- **Mary Terhaar, DNSc, RN** has indicated no financial relationship with any commercial supporters.
- **Anthony Bilenki, MA, RRT** has indicated no financial relationship with any commercial supporters.

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HARDWARE & SOFTWARE REQUIREMENTS

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Guest Faculty Disclosure

Dr. Takemoto disclosed that he has received grant or research support from the National Institutes of Health for serving as the PI of study 5R01HL077178; served as a consultant on the NIH Safety consultant protocol 08-0048; and received honoraria from the American Society of Pediatric Hematology/Oncology.

Reviews



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Dr. Strouse has no relevant financial relationships to disclose.

Unlabeled/Unapproved Uses

Drs. Takemoto and Strouse will reference the off-label or unapproved uses of the following agents:

- Enoxaparin
- Bivalirudin
- Argatroban

[Program Directors' Disclosures](#)



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In this podcast, Drs. Cliff Takemoto and JJ Strouse present patient scenarios that illustrate the challenges in caring for neonates with thrombosis. They address available treatment options and the variables that must be evaluated when determining a therapeutic plan.

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COMMENTARY

The epidemiology of venous thromboembolism (VTE) in children was recently reported by Raffini and colleagues. Their findings confirm what has been suspected by those of us who manage these conditions: the incidence of thrombosis in infants has increased dramatically.¹ Over a 6-year period from 2001 to 2007, the annual rate of VTE admissions in infants <28 days of age increased by 70%; in children <1 year of age, the rate over this time period increased by 100%. Although the reasons for these findings are not entirely clear, they are most likely due, in part, to the success of neonatologists and pediatric intensivists. The majority of VTE cases in children develop in sick patients and are often associated with vascular catheter usage. The key question for those who care for infants with thromboses is: How do we provide safe and effective treatment?

Unfractionated heparin (UFH) is the historical standard for treatment and prevention of thrombosis, yet guidelines for its use in children have been extrapolated, in large part, from adult studies and expert opinion.² Remarkably, few pediatric-specific studies of UFH exist. Differences between the hemostatic system of children and adults, including baseline activated partial thromboplastin time (aPTT) values (used to monitor heparin), antithrombin activity (through which heparin works), and coagulation factor activities (targeted by heparin), highlight the need for a better understanding of how to assess the effects of this agent in young patients. Current recommendations use aPTT prolongation over control to monitor the efficacy of anticoagulation.² Is this the best measure of the efficacy of UFH in children? The study by Newall and colleagues (reviewed in this issue) compared different measures of UFH activity in a prospective cohort study of children <16 years of age. Of the patients evaluated, 54 were <1 year of age. The major finding of this study was that aPTT prolongation correlates poorly with UFH activity (as measured by anti-Xa and anti-IIa activity) in neonates. What is neither known nor addressed in this study, however, is the critical question: What is the best measure of clinical efficacy and safety for UFH use in neonates? Further research is needed to appropriately address this question. These investigators' findings, however, suggest that caution should be used if monitoring UFH effect by aPTT alone, and that such additional measures as anti-Xa levels may be warranted in neonates.

Given the challenges associated with venous access in neonates, low-molecular-weight heparin (LMWH) has become an increasingly popular choice for anticoagulation in this population. A number of studies have detailed the pharmacokinetics of LMWH, and its safety and efficacy in infants. Despite the attractiveness of subcutaneous delivery of this medication, premature infants with little subcutaneous fat or sick children with edema may

pose challenges for the administration and absorption of the drug. The case series by Crary and collaborators describes a small experience with intravenous LMWH (enoxaparin) in 7 children for the treatment or prophylaxis of thrombosis. Of the 7 children evaluated, 5 were ≤ 4 months of age. The authors found peak activity (measured by anti-Xa levels) at 1 to 2 hours, as opposed to the 4 to 6 hours observed with subcutaneous delivery. The activity decreased substantially after 6 to 8 hours, suggesting that more frequent administration (every 8 hours for children < 1 year of age in this study) may be required for adequate anticoagulation. Since this was a small retrospective study, no firm conclusions can be drawn about efficacy and safety. However, the investigators reported no serious bleeding complications, and 4 of 5 patients with thrombosis experienced either complete or partial resolution.

Another challenge associated with the treatment of small children with LMWH is the delivery of accurate doses. This problem arises because LMWH is packaged at a high concentration for ease of administration in adults, rendering the titration of small doses difficult. A common practice used with the LMWH enoxaparin is to dilute the standard formulation (100 mg/cc) to 20 mg/cc, facilitating accurate dosing to a fraction of a milligram.³ However, medication dilution may cause confusion over the appropriate volume to administer and can result in frequent dosing errors. To address this issue, Bauman and associates (reviewed in this issue) from the Pediatric Thrombosis Program at the Stollery Children's Hospital in Edmonton, Alberta, Canada, report their experience with whole milligram, undiluted dosing of enoxaparin. The medication was delivered with an insulin syringe in increments of 0.01 mL of a 100-mg/cc solution (for whole milligrams). A total of 138 of the patients were < 3 months of age and ranged in weight from 900 to 4700 grams. All children achieved a therapeutic anti-Xa activity, with a mean time frame of 2 days (range, 1 to 6 days). No child required a fraction of milligram dosing to achieve a therapeutic level, and $< 1\%$ of the children had a supratherapeutic level. No hemorrhagic events or dosing errors were reported in those supratherapeutic patients. Although counterintuitive, as one might assume that tighter titration of weight-based dosing is safer, this study suggests that whole milligram dosing is an acceptable and safe way to deliver LMWH to neonates.

Heparin-induced thrombocytopenia (HIT) is a well-described complication of heparin therapy, with a reported incidence of 1% to 3% in adults.⁴ The data on HIT incidence in pediatric patients is limited, but it is estimated to be in a similar range and may be underrecognized.⁵ In the past decade, several direct thrombin inhibitors have been approved for the treatment of HIT, including argatroban and bivalirudin; these anticoagulants are now the recommended treatment for adults with this complication.⁴ Although HIT may be an uncommon occurrence in children, continued routine exposure of pediatric patients to heparin ensures that HIT will occur in this population. The diagnosis of HIT precludes the use of UFH or LMWH, and necessitates the use of such alternatives as direct thrombin inhibitors. Two reports on the use of direct thrombin inhibitors in pediatric patients are reviewed in this issue. The case series by Potter and coworkers describes the treatment of 3 critically ill children with HIT and thromboembolic complications who required extracorporeal life support (ECLS). Argatroban was used, rather than UFH, to anticoagulate the ECLS circuits and for the treatment of thrombi. In a dose-finding study of bivalirudin, Young and colleagues provide important pharmacokinetic data on infants < 6 months of age. Of the 16 children who were treated, 2 experienced major bleeding and 6 had partial or complete resolution of their thromboses. These small experiences provide information about dosing in infants, but additional studies will be needed to address the questions of safety, appropriate monitoring, and efficacy in this population. Bivalirudin may offer advantages over heparin in neonates, as its anticoagulant effect is not dependent on antithrombin — a protein that is significantly lower in neonates than in adults.

VTE is on the rise in children, and anticoagulant treatment in this population poses numerous challenges. Data on these anticoagulants in infants are critical to their safe and effective use in this patient population. While the papers we review address some of these age-dependent issues, further investigations are needed.

Commentary References

1. Raffini L, Huang YS, Witmer C, Feudtner C. [Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007](#). *Pediatrics*. 2009;124(4):1001-1008.

2. Monagle P, Chalmers E, Chan A, et al; American College of Physicians. [Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines \(8th Edition\)](#). *Chest*. 2008;133(6 suppl):887S-968S.
3. Dager WE, Gosselin RC, King JH, Christensen CL, Owings JT Larkin EC. [Anti-Xa stability of diluted enoxaparin for use in pediatrics](#). *Ann Pharmacother*. 2004;38(4):569-573.
4. Warkentin TE, Greinacher A, Koster A Lincoff AM; American College of Physicians. [Treatment and prevention of Heparin-Induced Thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines \(8th Edition\)](#). *Chest*. 2008;133(6 suppl):340S-380S.
5. Risch L, Huber AR, Schmutz M. [Diagnosis and treatment of heparin-induced thrombocytopenia in neonates and children](#). *Thrombosis Research*. 2006;118(1):123-135.

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UNFRACTIONATED HEPARIN: HOW TO MEASURE ANTICOAGULANT EFFECTS IN INFANTS AND CHILDREN

Newall F, Ignjatovic V, Summerhayes R, et al. **In vivo age dependency of unfractionated heparin in infants and children**. *Thromb Res*. 2009;123(5):710-714.

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Current guidelines recommend that UFH be titrated to prolong the aPTT in a range that corresponds to 0.35 to 0.7 anti-Xa U/mL. In infants, the baseline aPTT differs from that in adults, which makes monitoring UFH difficult. In addition, UFH exerts its anticoagulant effect through antithrombin (by binding and activating it). Antithrombin levels are lower in neonates compared with adults, potentially influencing the anticoagulant effect of heparin. The major aim of this study was to determine the impact of age on in vivo measures of UFH response. This was a prospective, observational study of 85 children, between 0 and 16 years of age, in a pediatric intensive care unit who were treated with UFH. Indications for UFH therapy included thromboembolic prophylaxis or treatment, and extracorporeal membrane oxygenation (ECMO). Plasma samples were analyzed for markers of the anticoagulant effect of UFH, including anti-Xa and anti-IIa activity, and endogenous thrombin potential (ETP). In addition, antithrombin activity, as well as aPTT, was measured. The results of these assessments were grouped based on age (<1, 1 to 5, 6 to 10, and 11 to 16 years). The majority of patients (63%) were <1 year of age.

Age-dependent differences included a decrease in antithrombin levels in younger children (compared with age-matched norms). In addition, the standard measure of heparin effect — anti-Xa activity — was below the accepted adult target range with UFH (ie, 0.35 to 0.7 U/mL), suggesting that the anticoagulant effect of UFH was suboptimal. Concurrent with this finding was low anti-IIa activity (although this is not a standard measure of UFH activity). The effect of UFH is due to the inhibition of thrombin. ETP is a measure of thrombin activity, and the authors found that ETP inhibition was lower in younger children on heparin. Low antithrombin levels in neonates have been thought to be a mechanism for the decreased anti-Xa and anti-IIa effect of UFH. However, antithrombin was added exogenously to samples with low antithrombin levels, and the anti-Xa activity did not improve.

The significance of this study is that it highlights the marked differences in the anticoagulant effects of heparin in children vs adults. It has been previously established that a higher dose of UFH per kilogram of body weight is required to achieve the same aPTT prolongation target in children compared with adults. This study confirms that higher doses of UFH per kilogram are required to achieve the target range for other markers of anticoagulation — namely, the anti-Xa effect of heparin. What this study does not address, however, is whether these target ranges of anticoagulant effect (degree of aPTT prolongation, anti-Xa activity) translate into effective, safe treatment and prophylaxis for thrombosis in children.

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 NEWSLETTER ARCHIVE

INTRAVENOUS ENOXAPARIN IN CRITICALLY ILL INFANTS

Crary SE, Van Orden H, Journeycake JM. **Experience with intravenous enoxaparin in critically ill infants and children.** *Pediatr Crit Care Med.* 2008;9(6):647-649.

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Enoxaparin and other LMWHs are usually administered subcutaneously. This is often difficult in premature infants with fragile skin and minimal subcutaneous tissue, however, and absorption may be affected by edema or vasoconstriction in critically ill children receiving vasopressor support. For these reasons, enoxaparin has been administered intravenously, but few pharmacodynamic or clinical data are available to guide dosing in this situation. Because of the lack of data in children, Crary and colleagues describe their experience with intravenous enoxaparin. The authors retrospectively reviewed the medical records of all pediatric patients (N=7) treated with intravenous enoxaparin in the intensive care unit at Children's Medical Center, Dallas, Texas, between April 1, 2005, and March 31, 2006. Anti-Xa levels were standardized between different dosing schedules (every 8 or 12 hours) using the following equation: anti-Xa level (U/mL)/(total daily dose of enoxaparin/kg).

Five of the children were ≤ 4 months of age, but no body weights were reported. All of these children had congenital heart disease, and indications for anticoagulation were intracardiac thrombus (n=2), isolated deep venous thrombosis (n=1), vena caval and cerebral sinus thrombosis (n=1), and prophylaxis (n=1). Enoxaparin was administered every 8 hours in the children ≤ 4 months of age and monitored with a total of 45 anti-Xa levels. Anti-Xa levels for all 7 children (including a 3-year-old and a 4-year-old) were highest 1 to 2 hours after enoxaparin administration (mean, 0.68 U/mL or 0.19 U/mL/mg/kg/day) and decreased to a mean of 0.13 U/mL or 0.03 U/mL/mg/kg/day by 6 to 8 hours. The mean therapeutic dose for children ≤ 4 months of age was 2.4 mg/kg (\pm standard deviation [SD] 0.58) vs 1.11 mg/kg (\pm SD 0.13) in children ≥ 1 year of age. No child experienced serious bleeding; 3 had complete resolution of thrombus, 1 a partial resolution, and 1 died of underlying cardiac disease prior to reevaluation.

Despite being limited by the small number of patients, and dosing and monitoring at the discretion of the treating physician, this study provides the first data to guide intravenous dosing of enoxaparin in infants. Infants required much higher (2.4 mg/kg/dose) and more frequent (every 8 hours) doses of intravenous enoxaparin to achieve therapeutic anti-Xa levels (typically, 0.5 to 1.0 U/mL peak levels and 0.1 to 0.3 U/mL trough levels) than generally needed subcutaneously (1.5 mg/kg every 12 hours). This most likely reflects the more rapid absorption and clearance of enoxaparin after administration by the intravenous route. The different pharmacokinetics of intravenous enoxaparin and the potential variation among the critically ill infants make therapeutic monitoring with anti-Xa levels an essential element in the use of enoxaparin in this population.

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NEW DOSING METHOD FOR ENOXAPARIN REDUCES DOSING ERRORS IN NEONATES

Bauman ME, Black KL, Bauman ML, Belletrutti M, Bajzar L, Massicotte MP. **Novel uses of insulin syringe to reduce dosing errors: a retrospective chart review of enoxaparin whole milligram dosing.** *Thromb Res.* 2009;123(6):845-847.

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Enoxaparin is an LMWH frequently used for anticoagulation in neonates because of the ease of administration and therapeutic monitoring (via anti-Xa levels) compared with UFH or warfarin. The agent is often diluted in young children, as the available solution (100 mg/mL) is difficult to measure precisely for the small volumes needed (typical doses are 1.5 mg/kg every 12 hours for children <2 months of age). The primary objective of this study was to determine the rate of supratherapeutic anticoagulation, as classified by peak anti-Xa levels >1.0 U/mL when enoxaparin doses were rounded to the nearest whole milligram and administered as an undiluted solution using an insulin syringe. Secondary objectives were to determine whether anti-Xa levels >1.0 U/mL were associated with hemorrhagic events, if therapeutic anti-Xa levels could be achieved and maintained with whole-milligram dosing, and the impact of using insulin syringes and undiluted enoxaparin on dosing errors. The investigators retrospectively reviewed the records of 514 consecutive children treated between August 2003 and June 2007 with enoxaparin using insulin syringes and doses rounded upwards to the nearest whole milligram. Hemorrhagic events were defined as bleeding into a major organ or cavity, and errors in dose measurement were identified through a centralized risk management system.

Of the 514 children, 138 (27%) were <3 months of age, with body weights between 900 and 4700 grams. The most common reasons for anticoagulation were deep venous thrombosis (63%), extracardiac shunts (24%), and mechanical heart valves (10%). Therapeutic anticoagulation was achieved for all children using whole-milligram dosing in an average of 2 days (range, 1 to 6 days) and a mean of 1.5 venipunctures (range, 1 to 4 venipunctures). The mean dose was 1.8 mg/kg for infants <3 months of age (range, 1.0 to 2.56 mg/kg). Five of the 514 children had anti-Xa levels >1.0 U/mL (1.04 to 1.36 U/mL) with the initial dose; they required a single whole-milligram dose reduction to enter and stay within the therapeutic range. There were no reported major hemorrhagic events with supratherapeutic anti-Xa levels or enoxaparin dose measurement errors in any of the children.

Although retrospective, this study supports the safety and efficacy of using undiluted enoxaparin in neonates as treatment for and prophylaxis against VTE. The investigators used insulin syringes to deliver the doses on an every-12-hour schedule and rounded up to the nearest whole milligram to reduce the risk for dosing errors. With these modifications, the authors reported no additional dosing errors (as compared with about 1 error per week at their institution with the use of diluted enoxaparin). Their conclusions may not apply to the smallest infants, however, as they presumably have few premature infants in their study (number not reported), and rounding up to the nearest whole milligram may increase the dose significantly in children with body weights <1000 grams.

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THE DIRECT THROMBIN INHIBITOR ARGATROBAN FOR ANTICOAGULATION IN NEONATES WITH HEPARIN-INDUCED THROMBOCYTOPENIA RECEIVING ECMO

 RECOMMEND TO A COLLEAGUE

 NEWSLETTER ARCHIVE

Potter KE, Raj A, Sullivan JE. **Argatroban for anticoagulation in pediatric patients with heparin-induced thrombocytopenia requiring extracorporeal life support.** *J Pediatr Hematol Oncol.* 2007;29(4):265-268.

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HIT is a complication of treatment with heparin (especially unfractionated preparations) in adults, but it is rarely recognized in infants or older children. It is an immune-mediated disorder caused by heparin-dependent antibodies to platelet factor 4. These antibodies activate the platelets, resulting in thrombocytopenia and a greatly increased risk for venous and arterial thrombosis. The diagnosis is clinical (based on timing of thrombocytopenia in relation to heparin exposure), with confirmation by laboratory tests to detect antibody or activation of platelets by heparin. The cornerstone of treatment for HIT is to discontinue all heparin exposure and use an alternative anticoagulant (most commonly a direct thrombin inhibitor, such as argatroban, lepirudin, or bivalirudin) that does not cross-react with the heparin-dependent antibodies. Potter and associates retrospectively reviewed 3 children (2 infants and a 1-year-old) treated with ECMO and argatroban as an alternative anticoagulant after developing HIT.

The first infant was a term 2.7-kg female admitted at 11 days of age with enteroviral myocarditis. She required ECMO with heparin anticoagulation, and her platelet count fell from 212,000/ μ L to a nadir of 7000/ μ L despite transfusion. On day 10 in the hospital, she had ischemic areas of the bilateral great toes, leading to the diagnosis of HIT. The infant was placed on a new ECMO circuit primed with argatroban (30 μ g), and an argatroban infusion was initiated at 0.1 μ g/kg/min. Within 2 minutes, she had inadequate venous return, and an echocardiogram showed minimal cardiac flow and fibrinous strands consistent with extensive thrombus confirmed on autopsy.

The second infant was a term 4.7-kg female who had a Norwood repair for hypoplastic left heart syndrome at 3 days of age. She received heparin prophylaxis in the neonatal intensive care unit, and heparin anticoagulation beginning postoperative day 2 for thrombus of the right atrium and superior vena cava. On postoperative day 6, she required ECMO for poor myocardial function; on day 7, she developed ischemic changes of both feet and cyanosis of the fingers. Her platelet count was 17,000/ μ L. She was given a presumptive diagnosis of HIT, and argatroban anticoagulation was initiated on day 11 in the hospital, with 50 μ g to prime the circuit and an infusion of 0.5 μ g/kg/min, titrated to a kaolin activated clotting time of 200 to 220 seconds. An HIT antibody test was negative. On day 13 in the hospital, ECMO was discontinued secondary to a thrombus in the circuit, but argatroban was continued for bilateral lower-limb ischemia and digit necrosis. On day 18 in the hospital, she became acutely hypotensive during a cardiac catheterization and arrested. Autopsy demonstrated extensive thromboembolic disease.

This report of 2 cases of HIT in neonates on ECMO demonstrates the challenges associated with the diagnosis and treatment of infants with this disorder. Other causes of thrombocytopenia are common in critically ill neonates, and both the ECMO circuit and congenital heart disease increase the risk for arterial and venous thromboembolism. In addition, the management of alternative anticoagulation with direct thrombin inhibitors in ECMO is quite difficult, with little experience in neonates to guide initial dosing or titration.

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BIVALIRUDIN FOR THE TREATMENT OF THROMBOSIS IN INFANTS

Young G, Tarantino MD, Wohrley J, Weber LC, Belvedere M, Nugent DJ. **Pilot dose-finding and safety study of bivalirudin in infants <6 months of age with thrombosis.** *J Thromb Haemost.* 2007;5(8):1654-1659.

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Bivalirudin is a direct thrombin inhibitor with a short half-life (25 minutes). The agent is cleared predominantly by nonrenal and nonhepatic elimination, and does not require antithrombin for its effect — characteristics which may provide some advantages over UFH in sick neonates. This was an open-label, dose-finding safety study on the use of the direct thrombin inhibitor bivalirudin in 16 neonates. The patients evaluated were <6 months of age, with an objectively confirmed thrombus and no contraindication to anticoagulation treatment. The infants were divided into 3 dosing cohorts with 3 different boluses (0.5 mg/kg, 0.25 mg/kg, and 0.125 mg/kg) and 2 infusion rates (0.25 mg/kg/h or 0.125 mg/kg/h). The dose was titrated for a goal aPTT ratio of 1.5 to 2.5 times the patient's baseline aPTT. The major objectives of the study were to determine the safety profile of bivalirudin and the appropriate dose required to achieve the goal aPTT ratio. A secondary objective was to assess early efficacy with repeat imaging of thrombi at 48 to 72 hours.

Of the 16 patients, 2 experienced major bleeding (both with gross hematuria, 1 with bloody stool). No other serious adverse effects were reported. Among the 16 patients, 9 experienced minor bleeding (such as microscopic hematuria, occult blood in the stool, oozing from venipuncture site). The lowest effective dose to achieve the goal aPTT ratio was a bolus of 0.125 mg/kg, followed by an infusion of 0.125 mg/kg/h. With respect to efficacy, there was no progression of thrombus in all patients at 48 to 72 hours. Six of the 16 patients had improvement at this early time point (3 experiencing complete resolution, 3 experiencing partial resolution). Although not a major endpoint of the study, 9 patients had follow-up imaging between 1 and 9 weeks. Six patients had either a complete or partial response and three had no response.

The major finding in this study is that bivalirudin is relatively well tolerated in neonates, with acceptable bleeding risks to warrant additional studies. The dose required to achieve a therapeutic level (0.125-mg/kg bolus, 0.125-mg/kg/h infusion) is similar to the recommended dose for adults with HIT (0.15 mg/kg/h). The aPTT prolongation is the standard method to monitor anticoagulant effect in adults, but as we know is the case with UFH, this may not be the most appropriate measure in children. The 72-hour reduction in clot burden observed in the subset of patients (6 of 16) is intriguing, as UFH is not known to result in this rapid a response. This experience provides an important first step for the use of bivalirudin in pediatric patients. Additional studies are needed to assess anticoagulant monitoring, and its safety and efficacy compared with heparin use, in neonates.

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