Pediatric VTE: Direct Thrombin Inhibitors

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As many as 1 in 200 hospitalized children may experience a thromboembolic event. Since there are no FDA approved parenteral anticoagulant therapies for the pediatric population, pharmacists may be unfamiliar or uncomfortable with the treatment options. This program will educate pharmacists, nurses, and pharmacy technicians on the direct thrombin inhibitors, argatroban and bivalirudin, as alternatives to heparin for the treatment of pediatric thromboembolism. It will cover the challenges of heparin use in pediatrics as well as the advantages, disadvantages, dosing and monitoring of bivalirudin and argatroban.

Learning Objectives

Pharmacist

1. Identify the challenges associated with the use of heparin in pediatric patients.
2. Describe the advantages and disadvantages of the use of direct thrombin inhibitors in pediatric patients.
3. Describe dosing and monitoring of bivalirudin in pediatric patients, based on two dose-finding, safety and efficacy studies in pediatric patients.
4. Describe dosing and monitoring of argatroban in pediatric patients, based on a dose finding, safety and efficacy study in pediatric patients.

Pharmacy Technician

1. Identify the challenges associated with the use of heparin in pediatric patients.
2. Describe the advantages and disadvantages of the use of direct thrombin inhibitors in pediatric patients.
3. Recognize dosing and monitoring of bivalirudin in pediatric patients, based on two dose-finding, safety and efficacy studies in pediatric patients.
4. Recognize dosing and monitoring of argatroban in pediatric patients, based on a dose finding, safety and efficacy study in pediatric patients.

Nurse

1. Identify the challenges associated with the use of heparin in pediatric patients.
2. Describe the advantages and disadvantages of the use of direct thrombin inhibitors in pediatric patients.
3. Describe dosing and monitoring of bivalirudin in pediatric patients, based on two dose-finding, safety and efficacy studies in pediatric patients.
4. Describe dosing and monitoring of argatroban in pediatric patients, based on a dose finding, safety and efficacy study in pediatric patients.
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
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<tr>
<td>ACT</td>
<td>Activated Clotting Time</td>
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<td>aPTT</td>
<td>Activated Partial Thromboplastin Time</td>
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<td>DTI</td>
<td>Direct Thrombin Inhibitor</td>
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<td>DVT</td>
<td>Deep Vein Thrombosis</td>
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<td>ECT</td>
<td>Ecarin Clotting Time</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>INR</td>
<td>International Normalized Ratio</td>
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<td>LMWH</td>
<td>Low Molecular Weight Heparin</td>
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<td>PE</td>
<td>Pulmonary Embolism</td>
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<tr>
<td>PT</td>
<td>Prothrombin Time</td>
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<td>UFH</td>
<td>Unfractionated Heparin</td>
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<tr>
<td>VTE</td>
<td>Venous Thromboembolism</td>
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### Background

Heparin, first isolated in 1918 by William Henry Howell, has been a mainstay of anticoagulation for the past century. With recent advances, many new drugs have entered the market and have found their place among recommendations and guidelines but unfractionated heparin (UFH) remains one of the most commonly used short term anticoagulants, particularly in hospitalized patients. (Wardrop)

Since the development of heparin, many new anticoagulants have become available. Options for the treatment of venous thromboembolism (VTE) vary widely in adults but pediatric treatment options have been limited by a lack of testing and published research for these drugs in children. A majority of the current recommendations are based on observational studies or historical practices and are often extrapolated from adult data. In fact, there are no anticoagulants approved by the FDA for pediatric use, including the most widely used anticoagulants in pediatrics, unfractionated heparin (UFH) and low molecular weight heparins (LMWH). (young 2007), (Monagle) Here we will discuss
direct thrombin inhibitors (DTIs) as an alternative to heparin for the short-term treatment of thrombosis in hospitalized pediatric patients. This discussion will be based on three studies evaluating the use of argatroban and bivalirudin in pediatric patients, as well as the package inserts for these drugs and available FDA guidance.

**Epidemiology and Etiology**

Venous thromboembolism (VTE) can include both deep vein thrombosis (DVT) and pulmonary embolism (PE). At first glance, VTE may not seem like a true pediatric problem. But, while the incidence of VTE among all children is estimated to be only 0.07 in 10,000 children per year, the incidence among hospitalized children jumps to around 1 in 200. In adults, unprovoked VTE is quite common, around 40%, but in children and adolescents it is estimated that 90% of thromboembolic events are associated with one or more of the following risk factors. (betensky), (radulescu)

- Systemic infections
- Complex medical conditions (cardiac or renal disease and cancer)
- Inherited or acquired thrombophilias
- Central venous catheters
- Trauma
- Surgical complications
- Obesity
- Use of estrogen containing contraceptives

Therefore, VTE in critically ill and hospitalized children has become a considerable concern. In addition, the incidence of pediatric VTE has been increasing. There are many theories as to why this is happening. Advances in medicine have prolonged the survival of many critically ill children, allowed for better and earlier detection of clots in children, and increased the number of complex medical procedures. These may all be precipitating factors. (Radulescu)

**Current Guidelines for Pediatric Anticoagulation**

Unfractionated heparin (UFH) is the most commonly used anticoagulant for the short-term treatment of VTE in children. In recent years, the use of DTIs has been trending upwards, despite the lack of FDA approval for pediatric use. Argatroban does include pediatric supplement labeling which has FDA approved dosing for use in children in the
setting of heparin induced thrombocytopenia (HIT). (Young 2008) The most common reason for the use of an anticoagulant other than unfractionated heparin or a low molecular weight heparin is the incidence of HIT or suspected HIT. In these cases, argatroban is the most commonly used alternative, followed by bivalirudin. The use of bivalirudin in particular has doubled in the period from 2008 to 2011 since the period from 2004 to 2007. (Buck), (Moffett) Recommendations for alternatives to unfractionated heparin are needed as it is clear that health care providers are increasingly looking for other options.

Guidelines published by the American College of Chest Physicians (ACCP) in 2012 discuss unfractionated heparin and low molecular weight heparins almost exclusively for the acute treatment of pediatric thrombosis. These drugs are recommended for short term use in the hospital until patients can be transitioned to a long-term anticoagulant, most commonly warfarin. Alternatives to UFH are briefly addressed in the most recent guidelines with a single sentence: "Danaparoid, hirudin and argatroban are alternatives to UFH in children with HIT." (Monagle)

**Why do we need an alternative to heparin?**

Despite the fact that they are not FDA approved for pediatric use, unfractionated heparin and low molecular weight heparins are the most commonly discussed anticoagulants in pediatric guidelines. The following is a discussion of the challenges associated with heparin use in pediatric populations.

The first challenge is associated with antithrombin deficiencies. Antithrombin is a substance that acts to inactivate circulating clotting factors. Heparin binds to antithrombin and increases its activity up to 10,000-fold. (Whalen) This means that heparin is dependent upon circulating antithrombin to be an effective anticoagulant. Levels of circulating antithrombin are naturally low in neonates leading to decreased efficacy of heparin. (buck) To overcome this, some health systems have started co-administering antithrombin with heparin. This can lead to increased costs, greater drug burden, and only serves to cause greater fluctuations in the coagulation parameters of these patients. (buck) While antithrombin can reach adult levels by 7 months, it is still unpredictable in children and adolescents, ranging anywhere from 80-120% of normal levels all the way up into adulthood. (Appel)

The second challenge is heparin resistance. Heparin resistance is the inability to achieve anticoagulation at doses higher than 70 units/kg/hr. (buck) There is an increased incidence of heparin resistance in patients with antithrombin deficiencies. This puts neonates and children at higher risk of heparin resistance and increases their risk of thrombotic complications due to inadequate anticoagulation. (Heparin)
The next challenge is heparin induced thrombocytopenia (HIT). Thrombocytopenia, a low platelet count, occurs in up to 30% of adult patients receiving heparin. Thrombocytopenia can rapidly progress to HIT if the patient's platelet count drops below 100,000. Thrombocytopenia does progress to HIT in approximately 0.5-5% of adults. The overall incidence of HIT in children has been difficult to characterize as prospective studies are lacking, and data has relied on published case series and reviews. (Obeng 2015) However, the incidence of HIT appears to be lower in pediatric populations with reports suggesting an incidence rate of 1% and as high as 3%. (young 2007), (radulescu)

Lastly, heparin presents the risk of bleeding. Approximately 26% of adult patients receiving heparin can experience minor bleeding and 4-9% can experience a major bleed. (bivalirudin lexi) In one study, 24% of children who received heparin experienced major bleeding. (Monagle) Newborns, particularly premature infants are more susceptible to the development of intraventricular hemorrhage. (Radulescu) While the risk of bleeding increases with the use of any anticoagulant, in adults the risk of bleeding with heparin has been shown to be higher than the risk with DTIs. More studies are needed to confirm these results in children but the data currently available appears to be similar to the data in adults. (young 2007)

**Direct Thrombin Inhibitors**

In the US, there are two DTIs available for IV administration, bivalirudin and argatroban. Though not FDA approved, these DTIs have been studied in several small groups of children for the treatment of thromboembolism and they have shown promising results as alternatives to heparin in these studies.

**Bivalirudin**

**Pharmacology**

Bivalirudin is one of two available IV DTI. It is an analog of hirudin, a DTI derived from leech saliva. Bivalirudin exhibits its anticoagulant effect by inhibiting the catalytic sites of free and clot-bound thrombin. (Whalen) This inhibits coagulation by preventing thrombin from cleaving fibrinogen to fibrin and subsequently activating factors V, VIII, and XIII. (bivalirudin lexi)

**Advantages**

Bivalirudin provides a more consistent and effective level of anticoagulation in children because it is not dependent on circulating antithrombin. Unlike heparin, it binds to both
circulating and clot-bound thrombin causing an immediate anticoagulation effect. Bivalirudin is not bound to any plasma proteins (other than thrombin) which is an advantage in pediatrics due to the unpredictable and fluctuating nature of certain plasma proteins in children. Up to 80% of bivalirudin is cleared by proteolytic cleavage in the blood. Anticoagulants with a short half-life are preferred in critically ill children due to their easy reversal even without an anti-dote, by simply stopping the infusion. The elimination half-life of Bivalirudin is around 25 minutes, a suitably short half-life. For comparison, the half-life of unfractionated heparin is around 30 minutes.

Disadvantages

Around 20% of bivalirudin is cleared renally making dose adjustments necessary in patients with renal impairment, compared to heparin which requires no dose adjustments for renal or hepatic impairment. The half-life in patients with severe renal impairment (CrCl 10-29 ml/min) is increased to approximately 57 minutes. There is no reversal agent for bivalirudin but with a 25-minute half-life, reversal is usually unnecessary as the infusion can simply be stopped. There are also few studies evaluating the use of bivalirudin in children and these are mostly small, uncontrolled, or retrospective. All uses of bivalirudin in pediatric patients are considered off-label.

Research

A pilot dose finding study was conducted in 16 patients all less than 6 months old, diagnosed with thrombosis. Three dosing protocols were established, and patients were randomized into the three groups. The lowest bolus (0.125 mg/kg) and infusion (0.125 mg/kg/h) doses were determined to be the most appropriate at the conclusion of the study as these were the minimum doses for effectiveness to achieve the desired activated partial thromboplastin time (aPTT) goal. Of the 16 total patients, 2 patients had a major bleed and 9 had a minor bleed. Major bleeds consisted of gross hematuria and none of the minor bleeds were considered significant. Three patients had complete thrombus resolution at 48–72 hours and 3 had partial resolution. Unrelated to the protocol, 9 patients had follow-up imaging occurring 1-9 weeks after study initiation. These follow-up images identified 6 patients with partial or complete clot resolution and 3 with no response.

A subsequent study was conducted in 18 patients between 6 months and 17 years old. Only one bolus dose and infusion dose were used in this study as they were defined as the most appropriate doses by the previous study. In addition, the follow-up study used a more refined dosing protocol for dose modifications. This may be the reason that
there were fewer adverse events and a higher success rate in regards to thrombus resolution. Of the 18 patients, none experienced a major bleed, 1 experienced a minor bleed, 9 had thrombus resolution at 48-72 hours and 16 had thrombus resolution at 25-35 days. (young 2007), (obrien) Study results are compared in Table 1 below.

<table>
<thead>
<tr>
<th></th>
<th>Young, 2007 (n=16)</th>
<th>Obrien, 2015 (n=18)</th>
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<tbody>
<tr>
<td>Major Bleeding</td>
<td>2 (13%)</td>
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<td>*Thrombus Resolution at 48-72 hours</td>
<td>6 (38%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>*Thrombus Resolution including during follow up</td>
<td>12 (75%)</td>
<td>16 (89%)</td>
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</table>

*Characterized as complete/partial response

Clot resolution in such a short time is not a result usually seen with heparin due to its inability to act on clot bound antithrombin. Also, as previously discussed, the rate of major bleeding in children receiving heparin is around 24%, a much higher rate than has been demonstrated here with bivalirudin. (Monagle) Further head to head studies are needed to compare the safety and efficacy of bivalirudin and heparin. (young 2007), (obrien)

Dosing and Monitoring

The following dosing recommendations are based on the two dose-finding, safety, and efficacy studies that were previously discussed. In the studies performed, mean AUC and C Max increased with age and clearance decreased with age. As a result, half-life remained the same across all age groups. Therefore, dosing of bivalirudin can be the same across all age groups. (young 2007), (obrien), (forbes) This concept is demonstrated in Figure 1.

Figure 1
**Bolus Dose:** 0.125 mg/kg \(^{(young 2007), (obrien)}\)

**Initial Infusion Rate:** 0.125 mg/kg/hr \(^{(young 2007), (obrien)}\)

**Renal Impairment:** In adults with renal impairment the bolus dose is generally not modified, but a modified infusion rate is appropriate as well as more careful monitoring and more frequent dose adjustments. Bivalirudin has not been studied for the treatment of thrombosis in children with renal impairment. \(^{(angiomax)}\)

**Continuous Infusion Rate:** Of the two studies, the second used a more sophisticated and refined dose adjustment protocol which has been replicated below in **Table 2**. Each patient's aPTT was checked at baseline and then again 15 minutes after their bolus dose of bivalirudin. \(^{(obrien)}\)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>aPTT</th>
<th>Dose Adjustment</th>
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<tbody>
<tr>
<td><strong>Initial aPTT measured 15 minutes post-bolus</strong></td>
<td>&gt;2.5 x baseline</td>
<td>Hold infusion for 1 hour and recheck aPTT</td>
</tr>
<tr>
<td></td>
<td>&lt;= 2.5 x baseline</td>
<td>Continue infusion at same rate and recheck aPTT at hours 3 and 4</td>
</tr>
<tr>
<td><strong>Each aPTT subsequent to the post-bolus aPTT</strong></td>
<td>&gt;4 x baseline</td>
<td>Hold infusion for 1 hour and resume infusion at 20% lower rate. Recheck aPTT 3 to 4 hours after resuming infusion</td>
</tr>
<tr>
<td></td>
<td>&gt;2.5-4 x baseline</td>
<td>Hold infusion for 1 hour and resume infusion at 10% lower rate. Recheck aPTT 3 to 4 hours after resuming infusion.</td>
</tr>
<tr>
<td></td>
<td>1.5 - 2.5 x baseline</td>
<td>Continue infusion at same rate and recheck aPTT at next scheduled time-point</td>
</tr>
<tr>
<td></td>
<td>&lt;1.5 x baseline</td>
<td>Increase infusion rate by 10% and recheck aPTT in 3-4 hours</td>
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</table>
While these studies showed a poor correlation between infusion rate and aPTT, it is unfortunately one of the few relevant lab tests available at most health care institutions. It should be noted that the package insert recommends using activated clotting time (ACT) for monitoring, but this test is usually only used in patients undergoing vascular procedures. Ecarin clotting time (ECT) has also been found to be a more accurate way of monitoring anticoagulation status and has been discussed in multiple studies but it is not a lab value used readily in US institutions.

Patients should also be monitored for resolution of thrombus and bleeding. In one study, major bleeding was observed in 2 of the 16 patients. In both cases, the dose of bivalirudin was decreased but not discontinued, and the bleeding was resolved with no other complications. In the second trial there were no major bleeding events. In the event of a bleed, the dose of bivalirudin can be decreased or held until bleeding has been resolved due to the relatively short half-life, similar to the recommendations for heparin.

Adverse reactions that occur in more than 10% of adult patients include minor bleeding (14%) and hypotension as well as pain, headache, and nausea. The limited data available in children suggests that rates of certain adverse events are similar in children, but it can be difficult to measure. For example, a very young child may not be able to say that they are feeling pain or nausea and therefore, it may go unnoticed. Patients should be closely monitored.

**Transitioning to warfarin:** Bivalirudin has the potential to increase PT and INR so, if it is decided that long-term anticoagulation with warfarin is appropriate, an overlap of at least 5 days should be considered, even in the presence of higher-than-expected INR.

**Argatroban**

**Pharmacology**

Argatroban is one of two available IV DTIs. It is derived from l-arginine. Argatroban, like bivalirudin, is not dependent upon antithrombin for efficacy. Argatroban reversibly binds to free and clot bound thrombin, inhibiting fibrin formation and preventing activation of factors V, VIII and XIII as well as protein C.

**Advantages**

Like bivalirudin, argatroban provides more consistent and effective levels of anticoagulation due to the fact that it is not dependent upon antithrombin for efficacy.
Argatroban may be used in patients with renal dysfunction as it is not metabolized renally. The short elimination half-life of 39-51 minutes is also an advantage as it allows for easy reversal, although not as short as that of heparin or bivalirudin. (Whalen)

Disadvantages

Argatroban is metabolized hepatically which leads to a need for dose adjustment in patients with hepatic dysfunction, a disadvantage compared to warfarin which requires no dose adjustments. (Heparin), (Whalen) As previously discussed, the half-life is slightly longer than the other agents at around 39-51 minutes which means that effects take longer to reverse when an infusion is stopped. (Whalen) There is also no reversal agent for argatroban. (young 2011) Argatroban does bind to albumin (20%) and alpha1-acid glycoprotein (34%), which are plasma proteins that can be unpredictable in children, particularly those who are critically ill. (argatroban lexi)

Research

As a result of a small study conducted and published in 2011, the FDA has allowed a section in the package insert on the use of argatroban in seriously ill pediatric patients with thrombosis and HIT who require an alternative to heparin. It also includes a statement reminding prescribers that the safety and efficacy of argatroban has not been established in pediatric patients. (young 2011), (argatroban) The package insert provides a guide to dosing in pediatric patients that can be used when an alternative to heparin is absolutely necessary. Dosing in children with hepatic impairment has also been established. (young 2011)

In the study, 2 of 18 patients experienced thrombosis or thromboembolic complications while on argatroban and 3 (28%) others had a thrombotic event within the 30-day follow up window. Major bleeding occurred in 2 (11%) of the 18 patients, both of whom died within 30 days secondary to bleeding. This is an improvement on the previously reported rates of thrombosis in patients with HIT which were around 81%. (young 2011)

Dosing and Monitoring

Normal Hepatic Function: 0.75 mcg/kg/min adjusted to achieve aPTT 1.5 - 3 x baseline (young 2011)

Check aPTT at baseline and 2 hours after initiating the infusion. Adjust the infusion rate in increments of 0.1 - 0.25 mcg/kg/min (young 2011)

Hepatic Impairment: 0.2 mcg/kg/min adjusted to achieve aPTT 1.5-3 x baseline (young 2011)
Check aPTT at baseline and 2 hours after initiating the infusion. Adjust the infusion rate in increments of 0.05 mcg/kg/min or less. (young 2011)

Adverse reactions occurring in more than 10% of adult patients receiving argatroban include hematuria, hypotension and chest pain. Bleeding of any kind is the most common adverse event and, like with bivalirudin, some symptoms can be difficult to gauge in children, especially those who are very young and unable to communicate things like pain, headache and nausea. However, rates of most adverse events in children do appear similar to rates in adults. Mores studies are needed to confirm this. Patients should be closely monitored. (argatroban lexi), (argatroban), (young 2011)

Transitioning to warfarin: Argatroban also has the potential to increase PT and INR. Therefore, if it is decided that long-term anticoagulation with warfarin is appropriate, an overlap of at least 5 days should be considered, even in the presence of higher-than-expected INR. (radulescu)

Summary

Table 3 compares the studies evaluating bivalirudin and argatroban as well as heparin.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Heparin: Kuhle, 2007 (n=38)</th>
<th>Bivalirudin: Young, 2007 (n=16)</th>
<th>Bivalirudin: Obrien, 2015 (n=18)</th>
<th>Argatroban: Young, 2011 (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>9 (24%)</td>
<td>2 (13%)</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>0 (0%)</td>
<td>9 (56%)</td>
<td>1 (6%)</td>
<td>n/a</td>
</tr>
<tr>
<td>*Thrombus Resolution at 48-72 hours</td>
<td>n/a</td>
<td>6 (38%)</td>
<td>9 (50%)</td>
<td>n/a</td>
</tr>
<tr>
<td>*Thrombus Resolution during follow up</td>
<td>n/a</td>
<td>12 (75%)</td>
<td>16 (89%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Thrombosis during therapy or during 30-day follow up</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Amputation or death due to thrombosis</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Characterized as complete/partial response
There are many barriers to providing effective anticoagulation to pediatric patients experiencing a thrombotic event. Guidelines such as those published by ACCP only describe a few limited options for the acute management of thromboembolism in pediatrics. None of the currently available options are FDA approved for use in pediatrics and little data is available to guide clinicians in choosing an appropriate agent. Only argatroban includes FDA approved dosing as a pediatric labeling supplement for pediatric patients with HIT. DTIs should be considered as reasonable alternatives to heparin, despite the lack of recognition in the guidelines. While efficacy and safety have not been proven, particularly in direct comparison to heparin, pilot studies have established dosing for bivalirudin and argatroban and have shown promising results in regards to safety and efficacy that cannot be ignored. Clinicians should consider these anticoagulants in the future for treatment of thrombosis in their pediatric populations, especially in those experiencing heparin resistance, or HIT, or those who are at higher risk for HIT.

References:


Activity Test
Pediatric VTE: Direct Thrombin Inhibitors

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1. Which of the following is a disadvantage of argatroban use in pediatrics?
   a. It has no reversal agent
   b. It is metabolized renally
   c. It has a short half-life
   d. A and B
   e. A, B, and C

2. Which of the following is a disadvantage of using heparin in pediatrics?
   a. Heparin requires circulating anti-thrombin for efficacy
   b. Heparin is hepatically cleared
   c. Heparin has a short-half life
   d. Heparin is renally cleared

3. Which of the following is an appropriate initial infusion dose of argatroban for a 20 kg child with normal hepatic function?
   a. 50 mg/min
   b. 1 mcg/min
   c. 1 mg/min
   d. 0.1 mcg/min
   e. 15 mcg/min

4. Which of the following is an advantage of using bivalirudin in pediatrics?
   a. It is FDA approved for pediatric use
   b. It has a short half-life
   c. It does not depend on anti-thrombin for efficacy
   d. A, B, and C
   e. B and C

5. Which of the following is an advantage of argatroban use in pediatrics?
   a. It has a reversal agent
   b. It is metabolized hepatically
   c. It is not dependent on anti-thrombin for efficacy
   d. None of the above
6. Which of the following values is generally used for monitoring of direct thrombin inhibitors?
   a. aPTT
   b. CBC
   c. ING
   d. Hgb A1C

7. What is the aPTT goal for argatroban?
   a. 2.5 - 3 x baseline
   b. 5 - 7 x baseline
   c. 1 - 2 x baseline
   d. 1.5 - 3 x baseline

8. Why are pediatric patients at a higher risk for heparin resistance?
   a. They have naturally high anti-thrombin levels
   b. They cannot metabolize heparin
   c. They have naturally low anti-thrombin levels
   d. They cannot absorb heparin

9. Which of the following is a disadvantage of using bivalirudin in pediatrics?
   a. There is no reversal agent
   b. It is not FDA approved for use in pediatrics
   c. It is 20% renally metabolized
   d. A, B, and C
   e. A and C

10. What is the aPTT goal for bivalirudin?
    a. 5 - 10 x baseline
    b. 1.5 - 2 x baseline
    c. 3 - 4 x baseline
    d. 2 - 3 x baseline

11. Which of the following is an appropriate bolus dose of bivalirudin for a 20 kg child?
    a. 1 mg
    b. 2.5 mg
    c. 0.125 mg
    d. 10 mg
    e. 20 mg