New Anticoagulants in Children

Guy Young[1]

[1]*Children's Hospital Los Angeles, Los Angeles, CA*

Thromboembolic complications are increasing in children and the use of anticoagulation has seen a dramatic increase despite the lack of randomized clinical trials. The most widely used agents in children are heparin, low-molecular-weight heparins (LMWH), and warfarin. These agents, however, have significant limitations that are exaggerated in children. Novel anticoagulants such as direct thrombin inhibitors and the selective factor Xa inhibitor, fondaparinux, have been approved for use in adults and have properties that suggest they may be safer and more efficacious than the standard agents; however, until recently, publications using these agents in children were limited to case reports. Recently, clinical trials for two direct thrombin inhibitors, bivalirudin and argatroban, have been completed and a clinical trial of fondaparinux is under way. This review will compare the standard agents with the novel agents and briefly review the results of the clinical trials.

Historical Context

Thrombosis has been recognized in children for over 100 years;[1] however, the first reports on the use of anticoagulants in children were not until much later. Heparin was discovered in 1916, human trials were conducted in 1935 and widespread human use began in 1937. The first reported use of heparin in children appeared in a case report from 1954 in 2 children with cavernous sinus thrombosis.[2] Coumarins were discovered in 1929 and warfarin was developed in 1948; however, it was not used as an anticoagulant until 1954. The first publication on warfarin use in children was in 1976, though the authors state their initial use in patients less than 18 was in 1962.[3] Low-molecular-weight heparins (LMWH) were initially described in the 1970s and brought to clinical use in the 1980s. The widespread use of LMWH in children began in the 1990s.[4] While the leech protein hirudin was discovered in 1884, it was not until the 1950s that its mechanism of action as a direct thrombin inhibitor was discovered and not until 1997 that the recombinant form, lepirudin, was approved in Europe (1998 in the US). The first report on the use of a direct thrombin inhibitor (lepirudin) in children was in 1999.[5] Fondaparinux (initially called pentasaccharide) was first synthesized in 1985 and was approved in 2001. The first report on its use in a child was in 2004.[6]

Interestingly, the time lag between initial use of an anticoagulant in humans and its use in children has gotten shorter and shorter with each new anticoagulant discovered. This suggests that pediatricians have less reluctance to adapt such medications for pediatric thrombosis; however, this has been done despite a lack of clinical trials on the use of anticoagulants in children. This brings into question whether the efficacy and safety that has been demonstrated in adults applies to children, especially given the fact that the approved indications in adults such as joint arthroplasty, atrial fibrillation, and percutaneous coronary interventions rarely apply to pediatrics. Thus, while historically, anticoagulants have come to pediatric use without the benefit of prospective trials, it will be imperative that such trials be done for indications that apply to pediatric patients with thrombosis.

Lastly, no discussion of the historical aspects of childhood thrombosis and, in particular, treatment of childhood thrombosis is complete without mentioning the two pioneers of this field, the late Maureen Andrew and Marilyn Manco-Johnson. These two exceptional physicians and scientists essentially defined a new field of study within pediatrics and published numerous important studies in the field, but perhaps most importantly, have inspired a generation of young physicians from all over the world to engage in the study of pediatric thrombosis.

Introduction

The incidence of thromboembolic disease in children has been increasing in recent years.[7] This is in large part due to technologic advancements in the care of critically ill children. Central venous catheters (CVC) are a major cause of thromboembolic disease in children and thus children in intensive care units or those with malignancies and congenital heart disease account for a large proportion of those who develop thrombosis. There are few prospective clinical trials in children to provide evidence-based information regarding any aspect of therapy such as whom to treat, with what agent, at what intensity, and for how long. Nevertheless, clinicians caring for children with thrombosis must make therapeutic decisions with the available data.[8] The published guidelines for the management of children with thromboembolic complications are based on randomized trials in adults, non-randomized trials in children, case series and case reports.[9] This review will focus on the rationale behind the need for study-

ing new anticoagulants in children and will review the data currently available on these agents.

Differences between Adults and Children

Many of the current recommendations regarding anticoagulant therapy in children are derived from adult studies. It is important to note that there are many significant differences between adults and children that have important implications regarding the management of patients.[10] First, the physiology of the hemostatic system in children is different from adults and, in particular, the concentrations of various coagulation proteins change throughout childhood. For example, levels of the vitamin K–dependent coagulation proteins, factors II, VII, IX, and X and the natural inhibitors proteins C and S are significantly reduced in the newborn period and, in fact, don't reach adult levels until much later in childhood.[10] In addition, antithrombin levels are well below adult normal levels in infancy and early childhood. This leads to differences in the response to and the dosing of anticoagulants in children. Second, the method of administration of medications to children, especially infants and young children, pose additional challenges, particularly when it comes to providing oral or subcutaneous medications.

The most commonly utilized agents in the management of thrombosis in children are heparin, LMWH and warfarin. These all have significant limitations.[11] The inter- and intra-individual variability of heparin pharmacokinetics in adults has been well described.[12] This problem is compounded in young children (especially below age 6 months) due to the reduced level of antithrombin as compared with adults leading to relative heparin resistance. Furthermore, the level of antithrombin changes rapidly in the first 6 months of life, making the adequate control of therapeutic levels more difficult. Administration of antithrombin in some respects can overcome heparin resistance; however, this can lead to more difficulty in maintaining therapeutic levels due to the addition of another variable with its own half-life and clearance. In addition, the deaths and other adverse events resulting from the recent heparin contamination lend further rationale to the application of synthetic medications in pediatrics.[13]

Although the pharmacokinetics of LMWH are much more predictable, they also rely on the level of antithrombin leading to dosing which varies significantly from adults. In addition, the subcutaneous route of administration is difficult in young children and the twice daily regimen, which is the most widely accepted approach for treatment of thrombosis, is another disadvantage (see discussion of once-daily dosing regimens in the LMWH section below). Furthermore, since LMWH is a biological agent, it is possible that the pharmacokinetics will be less predictable than the synthetically manufactured fondaparinux (see discussion later). Lastly, as LMWH are derived from heparin, they are also subject to the risk of contamination as has occurred in Australia.[14]

The use of warfarin (or other oral vitamin K antagonists) is difficult in children for a number of reasons. First, these agents are available as tablets only and forming liquid preparations is difficult and, in fact, hazardous due to the insolubility of this formulation, which may lead to significant dose-to-dose variability, thus leading to administration difficulties. In addition, children are often placed on short courses of antibiotics or other medications that affect the metabolism of warfarin, further complicating the management. One publication noted the significantly poor reliability of obtaining therapeutic INRs in infants on warfarin.[15]

Several novel anticoagulants have recently been approved for the use in adults for a variety of clinical conditions including heparin-induced thrombocytopenia (HIT), percutaneous coronary interventions (PCI) and deep vein thrombosis prophylaxis.[16] These agents have unique properties that make them particularly attractive agents for use in pediatrics (**Table 1**), though none are licensed for use in children (pediatric argatroban dosing is now approved). *In vitro* studies have demonstrated age-related differences in response to heparin and lepirudin (both of which inhibit thrombin), but not danaparoid or fondaparinux which are anti-Xa inhibitors.[17,18] The novel anticoagulants, discussed below, include the direct thrombin inhibitors lepirudin,

Table 1. Pharmacologic properties of new anticoagulants.

Medication	Metabolism	Half-life*	Dosing**	Monitoring
Argatroban	100% liver	45 min	0.75 µg/kg/min	1.5-3 × baseline PTT
Bivalirudin	75% proteolysis 25% renal	25 min	0.125 mg/kg bolus 0.125 mg/kg/hr	1.5-2.5 × baseline PTT
Fondaparinux	100% renal	18 hrs	0.1 mg/kg once daily	0.5-1 mg/L 4 hours post-dose†

*Half-lives reported are based on pharmacokinetic studies in adults.

**Dosing for argatroban is based on a prospective clinical trial in children from birth to 16 years of age[33] and additional information regarding dosing can be found in the prescribing information in the Physician's Desk Reference, www.argatroban.com, or the FDA website.
Dosing for bivalirudin is based on a prospective study in children less than 6 months of age.[32] There are no data available for older children.
Dosing for fondaparinux is based on the dose in the current prospective clinical trial. Thus far all 11 patients reached the target therapeutic level.

†Fondaparinux levels are based on an anti-Xa level using a fondaparinux standard curve which is mathematically transformed to a concentration expressed in mg/L.

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bivalirudin, and argatroban, which will be contrasted with heparin as all are short-acting agents that are generally given by continuous infusion, as well as the selective anti-factor Xa inhibitor fondaparinux, which will be contrasted with LMWH as these agents are longer-acting, given subcutaneously, and thus used more for chronic anticoagulation. Lastly, a brief comparison of warfarin and new oral agents will be made.

Short-Acting Agents

Heparin is the most commonly used anticoagulant in children. It is used for the treatment and prevention of thrombosis as well as for maintaining the patency of extracorporeal circuits and venous and arterial catheters. There are numerous publications that describe its use in children in a variety of clinical settings as well as published guidelines regarding dosing.[9] Heparin has several significant drawbacks, in particular, its poor pharmacokinetics, which have been demonstrated in several studies.[19] Furthermore, heparin can lead to HIT, which occurs in approximately 1% of children exposed to heparin[20] and may lead to devastating consequences. Despite these limitations, heparin is still considered the first-line therapy for the prevention of thrombosis in patients undergoing cardiac catheterization and extracorporeal circulation as well as for the management of acute deep vein thrombosis. (Note: LMWH has supplanted unfractionated heparin (UFH) in some situations as the first line agent in clinical settings in which this is appropriate).

The main class of short-acting anticoagulants that have the potential to replace heparin are the direct thrombin inhibitors (DTI).[21] These agents can be divided into analogs of hirudin and small molecule inhibitors. The hirudin-like molecules lepirudin and bivalirudin are currently licensed for the treatment of HIT and PCI including patients with HIT undergoing PCI, respectively. The synthetic molecule, argatroban, is currently licensed for the treatment of HIT and for PCI in patients at risk for HIT. These medications all have relatively short half-lives and are therefore not useful for outpatient therapy.

DTIs have several theoretical advantages over heparin that make them attractive for further study in children.[11] These agents all selectively bind to and inhibit thrombin. Unlike heparin, they do not bind to other plasma proteins or cells and thus are unaffected by day-to-day fluctuations in blood chemistry or blood counts. As a result, their pharmacokinetics are much more predictable than heparin, leading to a significantly higher proportion of children achieving the target therapeutic range. Secondly, these agents inhibit thrombin directly as their name implies and are thus not subject to low and fluctuating levels of antithrombin, further improving their reliability particularly in young children. In addition, studies in adults have demonstrated significantly less bleeding than heparin for the same anticoagulant effect (as measured by clotting time tests), par-

ticularly for bivalirudin.[22] Although this remains to be confirmed in children, it is possible the same effect will be noted. Furthermore, these agents inhibit both clot-bound and circulating thrombin (heparin and LMWH only inhibit circulating thrombin), which may lead to improved efficacy, and finally, DTIs do not cause HIT. The most significant drawback is the lack of an available antidote, though several animal and in vitro studies have demonstrated that rFVIIa can reverse the anticoagulant effect of DTIs.[23,24]

Until recently, the only reports on the use of these agents in children were case reports.[6,25-31] There are now two prospective, dose-finding, pharmacodynamic, safety and efficacy studies performed in children evaluating bivalirudin and argatroban. There are no prospective studies of lepirudin nor is the author aware of any planned studies with this agent. The first utilized bivalirudin in infants less than 6 months of age for the treatment of venous or arterial thrombosis.[32] This age group was chosen for the pilot study as such infants are physiologically deficient in antithrombin and it was felt they would thus have the highest benefit-to-risk ratio. The study comprised 16 patients and has defined the dosing for this age group for the above indications. Safety was demonstrated as only 2 of the 16 infants met the predefined clinical criteria for severe bleeding, both of whom had gross hematuria (one with a supratherapeutic aPTT and another at the upper limit of the therapeutic aPTT) and both resolved with lowering the infusion rate. There were no episodes of intracranial or other deep tissue hemorrhage in this vulnerable population, and there were no non-bleeding adverse events. Efficacy was demonstrated by reassessing via diagnostic imaging the thrombus at 48-72 hours after infusion initiation. Three of 16 patients (37.5%) had complete clot resolution and 3/16 (37.5%) had partial resolution at this early time point. Experience suggests that this is not expected with heparin, although comparative studies with heparin will need to be performed to prove this outcome.

The second study utilized argatroban and included children with HIT, suspected HIT, at risk for HIT or children requiring an alternative to heparin without HIT.[33] This study enrolled 18 children between birth and 16 years of age, of whom 15 either had HIT, suspicion of HIT or were at risk for HIT. The patients enrolled on this study were all critically ill with multiple medical problems as evidenced by all the patients being in the intensive care unit while on study (though this was not mandated per the study). Detailed pharmacodynamic analysis has been performed and dosing recommendations are now available in the prescribing information available at the FDA website, the argatroban website (www.argatroban.com) or the Physician's Desk Reference. With respect to safety, 2 of 18 patients had severe bleeding events resulting in death. One patient was a 4 month old with viral myocarditis who required extracorporeal membrane oxygenation (ECMO) and developed HIT.

The day after argatroban was discontinued, the patient developed cerebral infarction and had intracranial hemorrhage 2 days after discontinuing argatroban. The second patient is a 5 year old with idiopathic dilated cardiomyopathy who developed HIT. The patient received argatroban while on ECMO and awaiting a heart transplant. On the 25th day of argatroban, the patient developed a subarachnoid hemorrhage. The patient was ultimately not considered a good candidate for heart transplant and the family elected to withdraw support. With respect to efficacy, 2 of 18 patients developed thrombotic events while on argatroban for HIT (approximately 50% of patients with HIT will develop thrombosis if left untreated). One patient developed superior vena cava syndrome and another lower extremity arterial thrombosis. An additional 3 patients developed thrombotic events 1, 8 and 17 days after discontinuation of argatroban. Considering the severity of the patients' health and the natural history of HIT, argatroban was felt to be efficacious at preventing thrombotic complications. Argatroban is the first anticoagulant to have pediatric dosing approved by the FDA.

Another important area in which DTI have significant potential advantages over heparin involves anticoagulation of extracorporeal circuits. Both cardiopulmonary bypass (CPB) and ECMO involve blood contacting external prothrombotic surfaces. Anticoagulation is a necessary element of such therapy, and bleeding and thrombotic complications are relatively common. An agent with more predictable pharmacodynamics and less bleeding for the same anticoagulant effect has the potential to improve the outcome of both CPB and ECMO. In adults, DTI have been shown to be effective and safe anticoagulants in patients with or at risk for HIT undergoing CPB. There are limited data on their use in children undergoing extracorporeal circulation.[27,30,34] A study comparing heparin and argatroban utilizing sham ECMO circuits demonstrated significantly less thrombin generation in the circuits with argatroban compared to heparin.[35] Although these data are intriguing and point to a potential role for DTI in ECMO, confirmation of this finding is required including clinical trials before DTI can be recommended as alternatives to standard therapy with heparin.

The role of DTI as an alternative to heparin in pediatrics remains to be defined, though early clinical studies are promising. Currently, the only clear indication for the use of DTI in children is in patients with HIT. Although any DTI could be used, only argatroban has been prospectively evaluated for this indication. The other situations in which a DTI can be considered are in patients with heparin resistance in whom escalating doses of heparin are not effective. Lastly, some patients with more severe thrombi (e.g., superior vena cava syndrome) in whom thrombolysis would ordinarily be indicated may have a contraindication to thrombolysis. In such situations, one could consider the

use of bivalirudin as it has demonstrated efficacy in resolving thrombi rapidly, albeit in only one small study.[32] This author does not recommend lepirudin in children for several reasons. First, it has not been formally studied in children. Second, it seems to have a higher risk for bleeding and finally, it can lead to antibody formation enhancing its effect and potentially increasing the risk for bleeding further.[36]

Long-Acting Parenteral Agents

LMWH have found broad use in children in place of both unfractionated heparin and warfarin. These agents have more predictable pharmacokinetics, and dosing and safety have been demonstrated in several studies, mostly in children with deep vein thrombosis.[37-39] LMWH are largely utilized in two situations in pediatrics. The first is for in-patient use in place of unfractionated heparin for children in whom venous access is problematic (neonates, particularly those without central venous access, congenital heart disease patients with poor venous access). The second is for out-patients in whom warfarin is problematic, such as those who cannot swallow tablets or for patients on multiple medications with interactions with warfarin.

The selective anti-factor Xa inhibitor fondaparinux is in wide clinical use for multiple indications in adults.[16] Several advantages of fondaparinux relative to LMWH form the rationale for studying this agent in children.[6,40] First, the longer half-life will likely allow for once-daily dosing as opposed to twice-daily dosing for LMWH. While once-daily dosing of LMWH is in clinical use in children, the data supporting this practice is based on underpowered studies that did not perform detailed pharmacokinetics. On the other hand, prospective pharmacodynamic studies of enoxaparin[41] and tinzaparin[42] suggest that once-daily dosing is not appropriate. In the enoxaparin study, among 8 children who had detailed pharmacokinetic analysis, 7 had subtherapeutic anti-Xa levels by 12 hours and 4 had unmeasurable anti-Xa activity at 18 hours. In the tinzaparin study, the half-life in the various age cohorts was on average about 5 hours, with essentially no anti-Xa activity measurable at 24 hours. Second, as fondaparinux is a synthetic drug, issues of contamination are not a concern (of note, contamination of several lots of enoxaparin were found in Australia[14]). Third, since fondaparinux does not bind to cells, the risk for HIT is essentially zero (though there is now one report documenting fondaparinux-induced thrombocytopenia[43]) and there is a reduced concern for osteoporosis.[44] The main disadvantage of fondaparinux is the lack of an available antidote, though it should be noted that protamine is only partially effective for LMWH. In addition, in vitro studies have demonstrated that similar to DTIs, rFVIIa can reverse the anticoagulant effects.[24] Currently, a prospective, dose-finding and safety study of fondaparinux in children is nearing completion with complete data available in 2009. Among the first 11 patients,

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Box 1. Suggested guidelines for the use of novel anticoagulants in children (medications in bold are first choice if applicable).

Definite indication
    Heparin-induced thrombocytopenia
        Acute management
            Argatroban
            Bivalirudin
        Long-term management
            Fondaparinux (if warfarin is not feasible)

Strong recommendation
    Failure to adequately achieve anticoagulation with heparin
        Argatroban
        Bivalirudin

Moderate recommendation
    Severe thrombotic event and contraindication to thrombolysis
        Bivalirudin
        Argatroban

Weak recommendation
    Concern for heparin contamination (e.g., from parents)
        Acute management
            Argatroban
            Bivalirudin
        Long-term management
            Fondaparinux
    Desire for once-daily dosing of subcutaneous agent
        Fondaparinux

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no patient required more than once-daily dosing and the only bleeding event was occult blood in the stools in one patient (Young, unpublished data).

Oral Agents

The vitamin K antagonists (VKA) are the only currently available oral anticoagulants. Most of the published data in children with oral agents use warfarin,[15] although there are some data with acenocoumarol and phenprocoumon. The major advantage of VKA is the oral route of administration and long half-life allowing for once-daily dosing. Several significant limitations to the use of VKA are particularly more problematic in children and were discussed earlier. In comparison to VKA, the ideal oral anticoagulant would have a much higher efficacy-to-safety ratio (therapeutic index), would lead to therapeutic levels more rapidly, would not require laboratory monitoring, would have no (or at least far fewer) drug and food interactions, and would be available in a liquid (or other child-friendly) preparation. Currently, several new oral anticoagulants are in late stages of development for use in adults and will likely become available in the near future. The most advanced of these is rivaroxaban, a direct factor Xa inhibitor.[45] A pediatric clinical trial is currently in the planning stages and should be under way by early 2009.

Conclusion

The only anticoagulants in broad clinical use in children are heparin, LMWH and warfarin. A number of new anticoagulants have been approved for use in adults in the last 10 years. Currently, some early clinical trials have been completed (for bivalirudin and argatroban), others are under way (fondaparinux) and others are in planning (rivaroxaban). See **Box 1** for current suggested uses of new anticoagulants in children. Through these and future studies, the choices for anticoagulating children will expand. Given the properties of the new agents, it is likely that superior pharmacodynamics will lead to improved safety and efficacy with the newer agents; however, this can only be proven in randomized studies comparing the so-called standard agents with the new agents.

Disclosures

Conflict-of-interest disclosure: The author receives research funding from the US Food and Drug Administration, and is a consultant for Bayer and The Medicines Company.
Off-label drug use: Bivaliirudin, argatroban, fondaparinux, enoxaparin, dalteparin are all used to treat thrombosis in children and are not approved for use in children. Pediatric dosing of argatroban has been approved by the FDA.

Correspondence

Guy Young, MD, Children's Hospital Los Angeles, 4650 Sunset Blvd., Mail Stop 54, Los Angeles, CA 90027; Phone: 323-361-4628; Fax: 323-361-7128; e-mail: gyoung@chla.usc.edu

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