Review Article

Anticoagulant therapy in pediatrics

Abstract

Thromboembolic episodes are disorders encountered in both children and adults, but relatively more common in adults. However, the occurrence of venous thromboembolism and use of anticoagulants in pediatrics are increasing. Unfractionated Heparin (UH) is used as a treatment and prevention of thrombosis in adults and critically ill children. Heparin utilization in pediatric is limited by many factors and the most important ones are Heparin Induced Thrombocytopenia (HIT) and anaphylaxis. However, Low Molecular Weight Heparin (LMWH) appears to be an effective and safe alternative treatment. Hence, it is preferred over than UH due to favorable pharmacokinetic and side effect profile. Direct Thrombin Inhibitors (DTI) is a promising class over the other anticoagulants since it offers potential advantages. The aim of this review is to discuss the differences between adult and pediatric thromboembolism and to review the current anticoagulants in terms of pharmacological action, doses, drug reactions, pharmacokinetics, interactions, and parameters. This review also highlights the differences between old and new anticoagulant therapy in pediatrics.

Key words:
Direct thrombin inhibitors, low molecular weight heparin, pediatrics, thromboembolic disorders, unfractionated heparin, vitamin K antagonist

Introduction

Thromboembolic disorders in pediatric patients are relatively rare compared to adults due to the various physiologic protective mechanisms involved.[1,2] During the past decade, there has been an increase in the incidence of venous thromboembolism (VTE) in children.[3] It is reported that the annual rate of VTE has increased by 70% over 7 years. This increase was observed in neonates, infants, children, and adolescents.[3] The use of anticoagulant drugs in pediatric patients differs from adults, where children require more frequent monitoring.[4,5] Most recommendations regarding drug use in pediatrics are based on extrapolation from adults and in some circumstances such extrapolation may be inappropriate.[6]

The following are reasons that delineate differences that exist between the management of adult and pediatric patients thromboembolism.

First, the epidemiology of thromboembolism in pediatric differs from adult patients.[7]

Access this article online	
Website: www.jbclinpharm.org	Quick Response Code
DOI: 10.4103/0976-0105.134947	

Second, the hemostatic cascade is a dynamic, evolving process that affects not only the frequency and natural history of thromboembolism in children, but also the response to therapeutic agents.[8] The coagulation system of children differs from adults where antithrombin (AT) concentrations may interact with some anticoagulants such as unfractionated heparin (UFH) resulting in children requiring higher doses to maintain adult therapeutic ranges of activated partial thromboplastin time (aPTT).[9] Third, some pharmacokinetic parameters as distribution, binding, half-life, and clearance are age dependent.[10,11] Fourth, the frequency, severity and type of illnesses vary with age. Fifth, the concurrent and kind of medications vary with age. Sixth, the choice is influenced by the limited vascular access because some drugs are administered through parenteral route that reduces the ability to effectively deliver some therapies. Seventh, the anticoagulant choice is affected also by diet. Finally, compliance is difficult to assess in small infants who cannot understand the need for therapy and are unable to cooperate.[6] The aim of this paper is to discuss the differences between adult and pediatric thromboembolism and review the current anticoagulant drugs in terms of pharmacological action, doses, adverse drug reactions,

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pharmacokinetics, interactions, and monitoring parameters. In addition, highlights the differences between old and new anticoagulant therapy in pediatrics. Peer-reviewed clinical trials, review articles, pharmacology studies and treatment guidelines were identified from PubMed and Medline (between 1975 and 2011) using the search terms UFH, low molecular weight heparin (LMWH), vitamin K antagonists (VKAs), and direct thrombin inhibitors (DTI). Furthermore, related textbooks were also used for exploring the pharmacology of anticoagulants. Citations from available articles were also reviewed for additional references.

Anticoagulant Drugs

Unfractionated heparin

Heparin, a polysaccharide compound derived from porcine intestine, functions as an anticoagulant by potentiating the inhibitory effects of AT on thrombin and factor Xa. It is often used for the prevention and treatment of thrombosis in adults and in critically ill children.[12,13] UFH is given to millions of patients annually, and around 15% of inpatients in tertiary pediatric centers.[14,15]

The advantages of heparin include many years of clinical experience, short half-life, and easy reversibility with an antidote in overdoses, which are advantageous in the critical care and surgical setting where the risk for bleeding is higher.[12]

Heparin has several limitations: First, laboratory monitoring to assess the degree of anticoagulation for heparin in children is challenging and leads to significant difficulty in achieving the objectives.[13] Second, therapeutic levels are not easily achieved because of the high degree of inter- and even intra-patient variability in dosing, which can lead to the potential for worsening thrombosis or bleeding. Furthermore, therapeutic anticoagulation is limited because AT levels are low in neonates.[16] Third, heparin can cause heparin-induced thrombocytopenia (HIT), which can lead to threatening consequences. HIT is associated with thrombocytopenia and increased risk of thrombosis despite a reduction in platelet count occurring 5-10 days after heparin exposure.[17] HIT is the result of a complex antigen-antibody interaction, and the therapeutic intervention once it is diagnosed is the immediate withdrawal of all heparinoid anticoagulants, and substitution with nonheparinoid drugs until the risk of thrombosis is ameliorated.[18]

Heparin-induced thrombocytopenia is rare in children in comparison to adults with an incidence rate of 1% versus 3-5% and the rationale for this is unclear.[15,19] Fourth, the use of UFH mandates venous access for both administration and monitoring, which is least preferred route in neonates.[20] Lastly, as heparin is a biologic compound, it is subject to potential contamination, which has led to severe complications.[21] A vital approach to minimize this risk is to ensure that children only receive UFH when the risks are clearly outweighed by the benefits.

Heparin loading dose is 75 U/kg intravenous (IV) given over 10 min, followed by initial maintenance dose of 28 U/kg/h for infants <1 year old, and 20 U/kg/h for children above 1 year old. Heparin maintenance dose is adjusted to maintain aPTT between 55 and 85 s. If aPTT is <50, then another bolus dose is given, whereas if aPTT is between 50 and 95s, the same maintenance dose is continued. If aPTT is between 96 and 120s, thus, heparin must be held for 30 min, whereas if it is >120, therapy must be held for 60 min. aPTT is usually assessed 4 h after heparin loading dose and 4 h after every change in the infusion rate. Once therapeutic levels are achieved, then it must be measured daily.[20,22]

The most important adverse effect from heparin use in children is bleeding, yet this risk in children remains unknown.[23] For minor bleeding, discontinuation of heparin-infusion is usually sufficient, since heparin has a short half-life [Table 1]. For serious bleeding, reversal of heparin-effect by protamine sulfate and/or blood product support may be required. The dose of protamine sulfate required to antagonize heparin action is dependent on the total amount of UFH administered. For instance, 1 mg of protamine sulfate is required to neutralize 100 units of heparin. Children who have allergies to fish, or who have previously received protamine may be at risk for hypersensitivity reactions and should be closely monitored.[6,24]

In terms of other adverse effects, there are few case reports of pediatric UFH-induced osteoporosis. These patients received other concomitant drugs as steroids or high UFH doses for a prolonged period that augment osteoporosis risk.[25]

Table 1: Pharmacokinetics parameters for anticoagulants

Anticoagulants	Unfractionated heparin	Vitamin K antagonists	Argatroban	Bivalirudin	Dabigatran	Rivaroxaban	Apixaban
Metabolism	Hepatic and reticulo-endothilial system	Hepatic	Hepatic	Intravascular proteolysis	Renal	Hepatic	Hepatic
Half-life	90 min*	20-60 h*	39-51 min	15-18 min*	12-17 h*	5-9 h*	9-14 h*
Route of administration	Intravenous	Oral	Intravenous	Intravenous	Oral	Oral	Oral
Monitoring method	Antifactor Xa activity and activated partial thromboplastin time	International normalized ratio	Activated partial thromboplastin time	Not established	Not established	Not established	Not established
Antidote	Protamine sulfate	Vitamin K	Not established	Not established	Not established	Not established	Not established
Pediatric labeling (US)	No	No	Yes	No	No	No	No

*Based on data from adults

However, given the supported relationship between UFH and osteoporosis in adults, pediatricians should avoid long term use of UFH in children and alternative anticoagulants should be administered.

Another adverse event from UFH is anaphylaxis, which accounted for multiple deaths due to an unintended contaminant introduced in the manufacturing process.[26]

Despite these limitations, heparin is widely used in children, and is still considered the first line therapy for the prevention of thrombosis.

Low molecular weight heparin

Low molecular weight heparins have become the anticoagulant of choice in many pediatric patients for primary prophylaxis and treatment of thromboembolism.[27] Potential advantages of LMWH include predictable pharmacokinetic profile that reduce the need for monitoring, long half-life allowing for outpatient use, lack of drugs or diet interaction, lower risk of HIT and osteoporosis.[28] Most commonly used LMWHs in neonates and children are enoxaparin, dalteparin, reviparin, and tinzaparin.[29] However, most clinical data with respect to LMWH use in pediatric patients are derived from studies that used enoxaparin.[30,31] LMWHs have no intrinsic anticoagulant activity. Instead, they bind to AT, inducing a conformational change in AT that renders its reactive site more accessible to the target protease. Thus, it is a "suicide substrate" for these proteases. This conformational change accelerates the rate at which it inhibits various coagulation proteases. AT inhibits activated coagulation factors involved in the intrinsic and common pathways. LMWHs act in a catalytic fashion. After binding to AT and promoting the formation of covalent complexes between AT and target proteases, it dissociates from the complex and can then catalyze other AT molecules. Due to its low molecular weight, it induces the conformational change in AT that accelerates inhibition of factor Xa. LMWHs has greater antifactor Xa activity than antiIIa activity, and the ratio ranges from 3:1-2:1 depending on the preparation.[32] Doses of LMWHs depend on the agent used, for example, enoxaparin and tizaparin are age-dependent dose, reviparin, it is weight-dependent dose, dalteparin is neither age dependent, nor weight dependent [Table 2].[6] Doses must be adjusted to achieve an antiXa activity range of 0.5-1 unit/ml 4-6 h after injection or a range of 0.5-0.8 unit/ml 2-6 h after injection.[30] LMWHs are given subcutaneously for prophylaxis and treatment of thrombosis except for tinzaparin only used as a treatment.[6] LMWHs in pediatrics appear to be an effective and safe treatment. Most reported adverse event were bleeding where a review done by Nowak-Göttl, *et al*., have reported that in 308 children treated with therapeutic LMWH for venous thrombosis (from six studies), 9 (2.9%) had major bleeding, and 72 (23.4%) had minor bleeding.[33] The use of protamine sulfate will partially reverse the LMWH activity. In addition, temporary hair loss was reported in one out of 13 patients treated with enoxaparin,[34] and elevated liver enzymes were reported in 34% of cases with tinzaparin.[35] Multicenter randomized studies are required to determine risk of osteoporosis and HIT in children exposed to LMWH.

Table 2: Dosing of low molecular weight heparins

LMWH	Enoxaparin (mg//kg/dose every 12 h)	Dalteparin (U/kg/dose every 24 h)	Reviparin (U/kg/dose every 12 h)	Tinzaparin (U/kg/day)
Prophylaxis dose	< 2 months: 0.75 > 2 months: 0.5	92±52	< 5 kg: 50 > 5 kg: 30	Not used
Treatment dose	< 2 months: 1.5 > 2 months: 1	129±43	< 5 kg: 150 > 5 kg: 100	0-2 months: 275 2-12 months: 250 1-5 years: 240 5-10 years: 200 10-16 years: 175

LMWH: Low molecular weight heparin

Fondaparinux

Fondaparinux exerts its anticoagulant activity through a similar mechanism of action as UFH and LMWH. It does not interact with platelets or PF4; hence, it does not initiate pathogenetic HIT cascade observed with UFH or LMWH. For this, fondaparinux is widely admired in the management of patients who have HIT, although it is not approved for this purpose. Young *et al*., showed that a dose of 0.1 mg/kg once daily in children above 1-year-old have a comparable pharmacokinetic profile to adult dosing in patients with DVT and HIT, and the major adverse event reported was bleeding.[36]

Vitamin K antagonists

Vitamin K antagonists are oral anticoagulants used in the treatment or prophylaxis of thrombosis in pediatrics and possess many limitations. Some of these limitations are the need of frequent monitoring, presence of vitamin K in milk of infant formula, availability of tablets as the sole dosage form in most countries, drug interactions, and food interactions.[37] VKA acts by inhibiting vitamin K epoxide reductase needed for reductive metabolism of inactive vitamin K epoxide back to its active form. Reduced vitamin K must be regenerated from the epoxide since vitamin K serves as a cofactor for a glutamyl carboxylase that catalyzes the carboxylation process of coagulation factors II, VII, IX, and X and the anticoagulant proteins C and S. Therefore, blocking the γ-carboxyglutamates in factors II, VII, IX, and X.[32] VKA used in practice are warfarin, acenocoumarol and phenprocoumon.[38]

Warfarin is the most commonly used VKA in children.[39] It is a racemic mixture of S-and R-warfarin, where S-warfarin is 3-5 fold more potent than R-warfarin, metabolized by CYP2C9 in the liver and excreted in urine [Table 1]. It is 99% bound to plasma protein, half-life is 40 h, and duration of action of is 2-5 days in adults.[32]

Some European and South American countries use acenocoumarol as anticoagulant of choice in thrombosis.[40] It is a racemic mixture of R- and S-enantiomers, where the anticoagulants activity promoted by (R)-acenocoumarol since (S)-acenocoumarol is rapidly metabolized by CYP2C9.[41]

Phenprocoumon, the preferred VKA in some parts of Europe,[32] is available as a racemic mixture of R- and

S-enantiomers, where S-enantiomers are more potent. It has an elimination half-life that ranges from 76-274 h.[42]

The starting dose of VKA is 0.33 mg/kg in infant and 0.09 mg/kg in teenage to maintain an INR of 2.0-3.0,[9] except in prosthetic mechanical heart valves and recurrent thrombotic episodes where target INR is 2.5-3.5.[37] Monitoring INR levels are performed 1 or 4 times/month according to the age, change in dose, administration of other drugs, and patient compliance.[38] Most common adverse events encountered with VKA are bleeding, skin necrosis and osteoporosis.[9,43,44] Vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC) may be administered to reverse bleeding. In case of bleeding that is not life-threatening and no risk of morbidity, vitamin K given IV or SQ at a dose of 0.5-2 mg and FFP 20 cc/kg. In case of life-threatening bleeding vitamin K is given IV 5 mg and FFP 20 cc/kg or pPCC 50 U/kg.[37]

Vitamin K antagonists have numerous drug–drug interactions, in children, mostly with antibiotics and anticonvulsants. Antibiotics reduce intestinal flora, causing excessive PT prolongation in patients adequately controlled on warfarin. On the other hand, valproate, phenytoin, and fosphenytoin enhance the risk of hemorrhage through displacement of VKA from protein binding sites. Hence, dosing adjustments are necessary when those agents are initiated or discontinued, and a close monitoring of INR and signs of bleeding are required.[32]

Direct Thrombin Inhibitors

This class inhibits thrombin action directly where the effect is independent of AT levels. Furthermore, by reducing the thrombin-mediated activation of platelets, these inhibitors also have an antiplatelet effect. These inhibitors are mainly used in acute coronary syndromes with or without percutaneous coronary intervention and HIT.[32] Regarding their use in children, there are several case reports and series describing their use.[45-48]

Direct thrombin inhibitors offer several advantages over the standard agents. First, these agents have a low risk of inter-individual variability because they directly bind to thrombin forming inactive complexes and do not require the presence of AT whose levels are not predictable in pediatrics, particularly in critical ill neonates.[49] Second, DTIs have much more predictable pharmacokinetics than heparin because they are not bound to plasma proteins. Third, they have demonstrated significantly lower bleeding risk than heparin in adult patients. Fourth, these agents have better efficacy than the old anticoagulants since they inhibit both clot-bound and circulating thrombin. Finally, the DTI do not cause HIT which is a major limitation for the use of heparin. This class is considered as an alternative to UFH in children with HIT.[50,51] The most significant limitation is the lack of an available antidote though several studies documented that recombinant activated clotting factor VII can reverse DTI effect.[52,53] In addition, limited reports on the use in pediatric patients compared to the conventional anticoagulants where most of them are from case reports. Other constrains include administration by continuous infusion, which is limited by venous access in children and are suitable for hospitalized patients.[46] Table 1 provides further detailed pharmacokinetic properties on the DTIs.

The major DTIs used are bivalirudin and argatroban in children whereas lepirudin is not used because it increases bleeding risk.[54]

Argatroban

Argatroban is a small synthetic DTI molecule derived from l-arginine which binds reversibly to thrombin at the catalytic site. It is the first anticoagulant that gained pediatric labeling in the US for prophylaxis and treatment of thrombosis in patients with HIT.[55,56] Argatroban is monitored by the a PTT, where the target aPTT time should be 1.5-3 times normal range and checked 2 h after bolus administration.[56] Argatroban is given at 0.75 mcg/kg/min continuous infusion.[57,58] Dose reductions should be considered in patients with impaired hepatic function as well as in critically ill patients since it is hepatically eliminated.[59] When introducing coumarins after the acute phase of HIT under argatroban-therapy, it should be initiated without a loading dose and argatroban should be continued concomitantly until the INR is in the therapeutic range for 2 days.[60] As argatroban increases INR values during the overlap period, the therapeutic target INR should be adjusted according to the dose of argatroban administered.[56] So far, there have been no reports on anaphylactic reactions or drug-specific antibody production following argatroban administration.

Bivalirudin

Bivalirudin, a synthetic oligopeptide analog of hirudin, is a selective reversible DTI.[61] It has a predictable anticoagulation effect, as it does not interact with nonthrombin plasma proteins. It is the drug of choice in patients at risk for hepatic or renal insufficiencies since it is metabolized through intravascular proteolysis. Bivalirudin requires IV continuous infusions since it has a relatively short half-life of 25-34 min with intensive therapeutic monitoring. Pediatric dosing has not yet been added to the bivalirudin labeling in the US; although a pilot study showed the effective and safest dose is 0.125 mg/kg IV bolus followed by 0.125 mg/kg/h continuous infusion.[62,63]

Dabigatran

Dabigatran etexilate is a prodrug converted in the liver to dabigatran. It is a direct competitive thrombin inhibitor with low bioavailability around 7% that undergoes renal elimination. Peak plasma concentrations are reached quickly within 2 h after administration with mean t½ around 13 h. Owing to its predicable anticoagulant effects and lack of drug interactions, coagulation monitoring is not necessary.[64,65] The safety and effectiveness of dabigatran in pediatrics patients have not been established.

Direct Factor Xa Inhibitors

In contrast to thrombin inhibitors, factor Xa inhibitors reduce total thrombin generated, thus factor Xa may be a

more desirable anticoagulant target.[66] One major concern regarding these new agents is the lack of validated monitoring assays.[67] This is of particular relevance to the pediatric community because, as discussed above, developmental differences in coagulation factor levels and/or hepatic or renal clearance rates may vary in children, necessitating dose adjustment based upon age or developmental stage.[6,16] Similarly, the development of effective antidotes for these compounds is lagging behind clinical development of the agents. The latter is of significant concern to the treatment of the acutely bleeding, overdosed patient or the patient who requires emergent surgical intervention while fully anticoagulated.[68]

Rivaroxaban

Rivaroxaban is the first oral DTI, a highly specific inhibitor of factor Xa available for clinical use. This direct inhibitor prevents the formation of the thrombin burst by regulating the coagulation cascade at the point of amplification.[69] It is currently approved for the treatment and long term prophylaxis of deep vein thrombosis (DVT) or pulmonary embolism (PE). It is also approved for the prevention of DVT and PE in adult patients undergoing elective hip or knee replacement surgery, and stroke prevention in patients with atrial fibrillation.[70] The comparable safety profile of rivaroxaban to LMWH, high oral bioavailability around 80%, once-daily dosing, and limited requirement for monitoring makes this drug an optimal anticoagulant that warrants further investigation in children.[71] There are currently no data on safety and efficacy of rivaroxaban in pediatrics.

Apixaban

Apixaban is a selective oral direct inhibitor of factor Xa.[72] Its bioavailability is about 66% and a $t^{1}/_{2}$ of 8-15 h. Apixaban has the least renal clearance around 25% as compared with other new oral anticoagulants.[73] In the US, phase I trial for children with central venous catheters is currently enrolling patients.[74,75]

Conclusion

Given the paucity of pharmacological studies in pediatric patients, the clinical decision regarding the best anticoagulant is best managed within a dedicated pediatric anticoagulation service. Basic assumptions about anticoagulants in adult populations may not be true in children. While there remains great anxiety about the traditional anticoagulants utilization in children, there is nothing to suggest that newer agents would be less problematic, and the available clinical experience with newer drugs in children is not fully established. Thus, further research for ideal anticoagulant agent offers a simplified treatment regimen with efficacy at least comparable to the old drugs. In addition, less bleeding, rapid onset of action, predictable pharmacokinetic profile, no need for monitoring and minimal food or drug interactions will improve pediatrics quality of life.

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How to cite this article: Dabbous MK, Sakr FR, Malaeb DN. Anticoagulant therapy in pediatrics. J Basic Clin Pharma 2014;5:27-33.

Source of Support: Nil, **Conflict of Interest:** None declared.