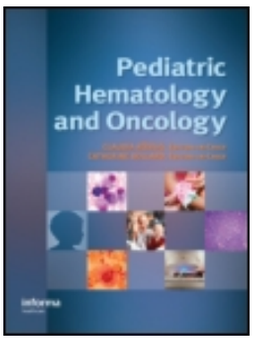

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REVIEW

A Practical Approach to the Use of Low Molecular Weight Heparins in VTE Treatment and Prophylaxis in Children and Newborns

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Low-molecular weight heparins are currently the most commonly used anticoagulants in children and newborns. However, since thrombotic complications rarely occur outside large children's hospitals, physicians often encounter some practical problems in managing these treatments when a pediatric thrombosis specialist is not available. The drug of choice is enoxaparin, due to its favorable FXa/FIIa ratio and the availability of pharmacokinetic and pharmacodynamic data. The treatment of acute thrombosis should be started with two daily injections but when compliance is an issue, a single daily administration schedule could be chosen for secondary prophylaxis ensuring careful measurement of the post 24-hour anti-FXa activity. Furthermore, a subcutaneous device may be a useful tool and a topical dermal anesthetic could be effective in controlling pain without affecting anti-FXa levels. In neonate and toddlers, where mini doses are frequently needed, the dead space of syringes and needles could represent an issue and therefore the use of insulin syringes without dead space is advisable, while a dilution of the drug is useful with other syringes. This article derives from a nonsystematic review of the available literature, with special attention to recent international guidelines and expert recommendations, combined to authors' clinical practice in large tertiary pediatric hospitals and will provide concise and practical information for the use of low-molecular weight heparin in childhood and infancy in a sort of "answering frequently asked questions."

Keywords Child, neonate, enoxaparin, treatment, prophylaxis, low-molecular weight heparin

INTRODUCTION

Childhood venous thromboembolism (VTE) is more and more widespread [1–3], and therefore it is now well known not only to pediatric hematologists, who first started to study its causes and treatment strategies (4), but also to surgeons and anesthesiologists [2, 5, 6].

The American College of Chest Physicians guidelines have been available both for infants and for children for more than 12 years. After six editions, recommendations for anticoagulation have increased from 25 to more than 100 [7, 8].

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While vitamin K antagonist (VKA) are even more limited since they are mainly used in the long-term treatment of children who undergo heart surgery, and clinical trials on new anticoagulants in children are presently still ongoing [9], Low-molecular weight heparins (LMWHs) are currently the most commonly used anticoagulants [2, 10–12].

Children and infants with VTE are much more complicated than adults, thus a pediatric hematologist or thrombosis expert should always be consulted in such situations.

However, while VTEs in children and infants may be "common" in tertiary care centers they rarely occur outside large children's hospitals, and thrombosis and hemostasis unit are not a standard facility in pediatric hospitals, thus physicians who have to start LMWH therapy in an infant or a child may encounter some practical problems which are not easily or rapidly solved by turning to the available literature.

In this paper, we will offer quick and easy solutions to the most frequent problems that physicians, pharmacists, and nurses face in such situations in a sort of "answering frequently asked questions."

- Which drug should be chosen?
- What is the right dosage for the given patient?
- How frequently should it be given?
- How long should it be continued?
- Can we improve the patient's compliance to subcutaneous injections?
- How should the problem of very small dosages be managed, especially when the calculated dosage is lower than the amount in the vial? How should it be diluted? With what?
- Should treatment be monitored? Which exams should be performed?

METHODS

This work derives from our clinical practice in a large tertiary pediatric hospital combined to a nonsystematic review of the available literature, with special attention to recent international guidelines and expert recommendations. In June 2014, we searched the literature for articles with an English language abstract on LMWHs in children and newborns using the MEDLINE (PubMed) database. After this first step, we conducted a manual research on the references of all articles found with the PubMed research.

Choice of the Drug

Based on the available Literature, among LMWHs, enoxaparin is the most frequently used drug in infants and children. Even though the reported data have mostly been obtained from cohort studies or small case series, and few clinical trials have been done for dalteparin, tinzaparin, and reviparin, there are far more articles concerning the use of enoxaparin in infants and children compared to the number of articles dealing with other LMWHs.

Besides, there are some other consistent reasons to prefer enoxaparin:

(a) Enoxaparin is, among the LMWHs, the compound with the best factor Xa/factor IIa (FXa/FIIa) inhibition ratio. The mean molecular weight of LMWH fractions is about 3500–8000 Daltons, compared with 15,000 Daltons of the unfractionated moiety. Heparin molecules with a lower molecular weight inhibit activated coagulation FXa via conformational change of the antithrombin molecule more efficiently than they inhibit thrombin (also called FIIa), with an anti-FXa to anti-FIIa activity ratio range from 1.7 to 4.0, depending upon the considered compound.

Because FXa acts earlier in the coagulation cascade than thrombin, it was hypothesized that LMWHs would produce fewer bleeding complications for a given antithrombotic efficacy [13]. This was subsequently confirmed in clinical trials even though the antithrombotic effect of LMWH, like that of UFH, occurs mainly via inhibition of thrombin and/or thrombin generation [14]. On this wave, it is advisable to prefer a compound with higher FXa/FIIa inhibition ratio.

(b) Enoxaparin has the longest half-life. In adults, a comparative study has shown that the average apparent total body clearance of enoxaparin was significantly lower (15.6 mL/minute) than that of dalteparin (33 mL/minute), tinzaparin (28.3 mL/minute), and nadroparin (21.4 mL/minute). Thus, enoxaparin is cleared more slowly from the body than dalteparin, tinzaparin, and nadroparin with an extended metabolism rate and a longer apparent half-life of 4–5 hours (dalteparin: 2.8; nadroparin 3.7; tinzaparin: 3–4 hours) [15]. This longer apparent half-life of enoxaparin implies the capability of providing a sustained anticoagulant effect still present 24 hours after administration [16, 17]; recently, in a cohort of 126 children receiving enoxaparin either as a once- or twice-daily dosing regimen [18], a median 24 hours trough level above the desired range of 0.1 IU/mL anti-FXa activity for prophylaxis was obtained in 53.2% of the patients. The relatively long half-life of enoxaparin allows for once-(q 24 hours) or twice- (q 12 hours) daily subcutaneous application, which has been shown in adults [19] and was also proposed for children [20].

The consistent pharmacokinetic and pharmacodynamic pediatric data that enoxaparin gained in the past 20 years and make this compound preferable among all LMWH, were recently reviewed [21].

However, as other LMWHs, enoxaparin must be withheld for 24 hours prior to invasive procedures, especially lumbar puncture [22]. Thus, in certain pediatric patients, enoxaparin should not be considered as first-line therapy and unfractionated heparin should be preferred..

Enoxaparin is distributed as Lovenox®/Clexane®, Sanofi-Aventis; it is available in prefilled syringes with different strength (representing the number of milligrams of enoxaparin sodium in water for Injection): 20 mg/0.2 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1 mL and the multiuse vial containing 300 mg/3 mL. Referring to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, each mg of Lovenox®/Clexane® has an activity of 100 anti-Xa units. Recently, FDA approved for US a generic enoxaparin product by Sandoz Inc, Broomfield, Colorado in the following strengths: 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL.

Both Lovenox® and generic enoxaparin are also distributed in the United States in a higher concentration (120 mg/0.8 mL and 150 mg/mL prefilled Syringes). We will not consider these preparations in this work.

DOSAGE

Table 1 summarizes the most commonly used enoxaparin doses [8]. Table 2 shows the nomogram for enoxaparin dose adjustment when monitoring is required [23]. It's worth mentioning that one review of some clinical reports suggested higher initial doses for neonates, especially for preterm babies [24]; the authors suggest 1.7 mg/kg twice daily for term babies and 2.0 mg/kg twice daily for preterm neonates; however, safety and efficacy of this approach has not been confirmed by clinical studies; therefore the best policy in this setting has not been defined yet. In our experience, the

TABLE 1 Initial Doses of Enoxaparin in Children and Infants

Age	Therapeutic dose	Prophylactic dose*
<2 months	1.5 mg/kg/12 h	0.75 mg/kg/12 h
>2 months	1 mg/kg/12 h	0.5 mg/kg/12 h

*See timing of injection in the text.
Modified from (1).

recommended doses [8] were consistent with the targeted anti-Xa level in most patients although some neonates required the highest schedule as already suggested [24].

FREQUENCY OF ADMINISTRATION

Injection-related pain and discomfort should be taken into account when prescribing enoxaparin treatment in children and infants. The treatment of acute thrombosis should be started with two daily injections; indeed, this schedules frequently rising compliance issues. Recently, a pharmacokinetics study was conducted in 126 children exposed to a once or twice daily subcutaneous enoxaparin regimen. The results show the possibility of achieving a median post 24 hours trough level above the desired range of 0.1 IU/mL anti-FXa activity in 53% of the patients [18]. On the wave of these results, we can suggest that when compliance is an issue a single daily administration schedule could be effective for secondary prophylaxis ensuring careful measurement of the post 24 hours anti-FXa activity.

DURATION OF TREATMENT

In general, LMWH would be used for the initial 5–10 days of VTE treatment in children and adults with transition to warfarin. Only infants < 2 years of age would continue on LMWH(8). however, several reason may lead the treater to maintain the enoxaparin for all the scheduled period. We will consider here only the case where the treater decides to complete the treatment with enoxaparin.

VTE can be classified as provoked (secondary) or unprovoked (idiopathic), depending on the presence or absence of associated risk factors [25]. Secondary VTE, which accounts for most cases in children and infants, should be treated for at least 3 months in the child and 6 weeks in the infant while idiopathic VTE needs to be treated twice as long [8]. In case of persistent risk factors, like active nephrotic syndrome, L-asparaginase therapy, central venous lines, persistent antiphospholipid syndrome, secondary prophylaxis must be continued as long as risk factors are present [8, 22, 26].

TABLE 2 Nomogram for Adjusting the Therapeutic Dose of Enoxaparin in Children and Infants

Anti-FXa units/mL	Wait for the next dose	Dose changes	Next measurement of anti-FXa
<0.35	–	+25%	4 hours after the next dose
0.35–0.49	–	+ 10%	4 hours after the next dose
0.5–1.0	–	–	After 24 hours, then after 7 days
1.1–1.5	–	−20%	Before the next dose
1.6–2.0	3 hours	−30%	Before the next dose
>2.0	Until anti-FXa = 0.5 units/mL	−40%	Before the next dose

Modified from (1).

Moreover, the author of a recent and significant review on pediatric VTE management, basing on her experience and some literature reports, suggests to consider treatment for 1 year or more when vessel patency is not achieved, if high risk thrombophilia is present (FVIII level greater than 150 U/dL, D-dimer level greater than 500 ng/mL, at least three trait thrombophilia and persistent antiphospholipid antibodies) or in the presence of postthrombotic syndrome [22]. Finally, indefinite anticoagulation is suggested for children with recurrent VTE secondary to structural venous abnormalities [8]. Indeed, for such long-term treatments, repeated subcutaneous injections may be very demanding for both children and parents and anticoagulation therapy longer than 3 months is usually performed with VKA.

For further details, readers should refer to more specific articles [8, 22, 26, 27].

HOW TO IMPROVE COMPLIANCE

Standard LMWH treatment deserves twice daily subcutaneous injections, and the repeated injections are a burden for children and parents too.

A subcutaneous device that was initially created for insulin administration may be a useful tool in this scenario (Insuflon®, Maersk Medical, Lynge, Denmark). It is a small device with minimum "dead space" (0.0075 mL) that is inserted subcutaneously and can be left in situ for one week thus reducing the injection-related pain and discomfort. It makes treatment more feasible for parents who have to administer the drug and who usually prefer to use this tool rather than to inject their child every day [22, 27, 28]. However, infant studies demonstrate up to 56% incidence of local adverse effects at the indwelling subcutaneous catheter insertion site, induration, leakage, bruises, hematomas [29], and compartment syndrome [30]. Thus it should be used with caution in infants especially in very low birth weight infants, as already recommended [24, 31].

Another possibility is to apply a topical dermal anesthetic. In the literature, the use of a cream containing liposomal-lidocaine 4% (Maxilene or L.M.X.4®; Ferndale laboratories, Ferndale, Michigan, USA) is effective in controlling pain without significantly affecting anti-FXa levels [32] while there is no reported results using the Eutectic Mixture of Local Anesthetics (EMLA, Astra Zeneca, Wilmington, Delaware) which requires a 60-minute pre-procedure application time, causes local vasoconstriction, and decreases tissue perfusion. Consequently, drug absorption may be altered [33, 34]. Another important clinical limitation of using EMLA with children is that prilocaine toxicity results in methemoglobinemia [35, 36]. For these reasons, it is preferable to avoid the use of EMLA for LMWH administration.

The twice daily schedule is quite demanding for pediatric patients, and often parents ask for a reduction to one injection every 24 hours. A cohort study published a few years ago showed that after the first 15 days of therapy administered at 1 mg/kg twice daily, the treatment can be continued at 1.5 mg/kg daily without compromising its efficacy [20]. However, this study was done on a small number of patients, and the results reporting a level of anti Xa > 0.1 in only 53% of patients would not indicate sufficient therapeutic effect. Thus the recommended twice daily schedule should be respected and only when a once daily schedule is adopted to accomplish significant compliance problems, the trough level measurement is recommended [18].

Lastly, enoxaparin can be administered intravenously if a central venous catheter is available [37, 38]. However, while this route of administration is effective in avoiding needle discomfort, it strongly affects the drug pharmacokinetic: anti-FXa levels showed a peak 1–2 hours after injection, and rapidly decreased within 6–8 hours [38]. This modified pharmacokinetic with shortened half-life of intravenous given

enoxaparin should theoretically require three daily injections making such a schedule rarely feasible and restricted to bearer of venous lines.

MANAGING MINI-DOSES

Enoxaparin doses is calculated on the patient's weight, and pediatrics patients' weight varies greatly among different ages. Thus, small babies require very small amounts of the compound. For most drugs packaged for adults, the dispensation to children and infants is prone to errors as they should be diluted [39] and a recent survey depicted that errors in drug preparation were the most common [40]. The smallest available enoxaparin prefilled syringe contains 20 mg (2000 IU) in 0.2 mL.

In neonate and toddlers, it is common to have to administer mini doses like 100–300 IU (0.01–0.03 mL). 0.01 mL is equal to one unit on the insulin syringe. It has been postulated that by whole-milligram dosing of enoxaparin using insulin syringes, enoxaparin dilution could be eliminated with only 1% supra-therapeutic anti-Xa levels [41]. However, with such small amounts, the dead space of syringes, needles and Insuflon®, the previously cited subcutaneous device, could represent an issue. Although insulin syringes without dead space are commercially available, common insulin syringes have 0.05 mL dead space, which can heavily affect the finally injected amount. Thus the first advice is to use insulin syringes without dead space.

This solution presents some weakness anyway. Indeed, although 200 IU (0.02 mL) could be theoretically taken from the prefilled syringe or from the original vial, as they correspond to two units on the insulin syringe, the finally injected quantity could be affected by the Insuflon® dead space if this device is used (Table 3). In this case, a dilution of the drug is useful to limit the effect of dead space.

It has been postulated that the content of the enoxaparin syringe (1500 IU/0.1 mL) can be diluted to 1000 IU in 0.5 mL 0.9% sodium chloride and maintained at room temperature (22–24°C) or in the fridge (4–8°C) for more than one month, regardless of light conditions, without any adverse effects on efficacy and sterility [42]. Similarly, enoxaparin was diluted in 4% glucose to a 2000 IU/mL solution and maintained at 4°C for up to 31 days with no significant decrease in anti-FXa activity, while a detectable

TABLE 3 Managing Enoxaparin Mini-Doses Using 2000 IU/0.2 ML Enoxaparin Syringe Content Through Insulin Syringes Without Dilution

Calculated dose		Volume		Infused dose through Insuflon (IU)	Lost drug in dead space (%)
mg	Units	mL	Insulin Syringe Units		
20	2000	0.2	20	1925	3.75
18	1800	0.18	18	1725	4.17
16	1600	0.16	16	1525	4.69
14	1400	0.14	14	1325	5.36
12	1200	0.12	12	1125	6.25
10	1000	0.1	10	925	7.50
9	900	0.09	9	825	8.33
8	800	0.08	8	725	9.37
7	700	0.07	7	625	10.71
6	600	0.06	6	525	12.50
5	500	0.05	5	425	15.00
4	400	0.04	4	325	18.75
3	300	0.03	3	225	25.00
2	200	0.02	2	125	37.50
1	100	0.01	1	25	75.00

TABLE 4 Managing Enoxaparin Mini-Doses by Dilution of 2000 IU/0.2 ML Enoxaparin Syringe Content in 1 ML H_2O OR 4% Glucose[#]

Calculated dose		Volume		Infused dose through Insuflon (IU)	lost drug in dead space (%)
Mg	IU	mL	Insulin syringes Units		
10.0	1000	0.50	50.0	985	1.5
9.5	950	0.48	47.5	935	1.6
9.0	900	0.45	45.0	885	1.7
8.5	850	0.43	42.5	835	1.8
8.0	800	0.40	40.0	785	1.9
7.5	750	0.38	37.5	735	2.0
7.0	700	0.35	35.0	685	2.1
6.5	650	0.33	32.5	635	2.3
6.0	600	0.30	30.0	585	2.5
5.5	550	0.28	27.5	535	2.7
5.0	500	0.25	25.0	485	3.0
4.5	450	0.23	22.5	435	3.3
4.0	400	0.20	20.0	385	3.8
3.5	350	0.18	17.5	335	4.3
3.0	300	0.15	15.0	285	5.0
2.5	250	0.13	12.5	235	6.0
2.0	200	0.10	10.0	185	7.5
1.5	150	0.08	7.5	135	10.0
1.0	100	0.05	5.0	85	15.0

#to be maintained at 4°C if not immediately injected.
*For doses above 1000 IU dilution is needed only if syringes with dead space are used.
§For doses >500 IU < 1000 IU using syringes without dead space, dilution is needed only when Insuflon is used.
Dilution is always advised below 500 IU.

decrease in efficacy was observed after similar dilution in water at the same storage conditions [43]. On this wave, in Table 4 we summarize how to dilute standard enoxaparin syringe's 20 mg–2000 IU/0.2 mL content to prepare mini-doses using insulin syringes. Briefly, doses above 1000 IU could be easily taken from the 2000 IU syringe using syringes without dead space, and no dilution is required. With syringes without dead space, dilution of enoxaparin syringe's 20 mg–2000 IU/0.2 mL content in 1 mL H_2O or 4% glucose is helpful when doses lower than 1000 IU are scheduled through Insuflon®. Finally, the same dilution is always recommended for doses below 500 IU. In Table 3 and 4, we schematized the effect of the insuflon dead space on the effectively injected amount of drug when Insuflon® is used. It is clearly evident that when the scheduled dose is below 600 IU (6 mg), the amount of uninjected drug without dilution is more than 15% of the scheduled dose.

MONITORING

Enoxaparin treatment is monitored by measuring FXa inhibition in samples drawn 4 to 6 hours after subcutaneous administration and collected in 3.2% trisodium citrate [44]. While monitoring is usually not needed in the child [8], it can be useful in newborns who generally require higher doses [24, 45] and who quickly gain weight in just a few weeks. In this setting, monitoring can initially be performed every 2 weeks, especially in patients receiving therapeutic schedules. The therapeutic range is 0.5–1 anti-FXa units/mL [46]. Clinicians should check with their laboratory the compatibility between the diagnostic assays and the drug, as different reagents are available, and some of them need dedicated curves for each heparin type. In addition, when a once daily schedule is adopted the trough level measurement is recommended [18].

FURTHER CONSIDERATIONS

Ten years ago, it was demonstrated that enoxaparin maintains its antithrombotic properties when drawn from multi-dose vials into tuberculin syringes and stored at 22° for up to 10 days [47].

On the basis of this experience, it is possible to develop policies aimed at cost savings for enoxaparin use, as at least a week's supply of enoxaparin pre-diluted mini doses, as described above, could be dispensed at a time to families, thus reducing the frequency of patients/families returning for the medication, decreasing the total drug consumption and providing a more convenient service for pediatric patients.

CONCLUSIONS

VTE in children and infants is a rare event that increases the disease burden on both the young patient who is usually affected by a severe illness, and on his/her family.

Pediatricians are more and more frequently involved in treating or preventing VTE in their young patients, however, in most peripheral and smaller pediatrics centers there is not enough experience in this area.

Here we provide concise, practical, and therefore useful information for the management of VTE in childhood and infancy with LMWH.

Declaration of Interest

The authors report no conflicts of interest The authors alone are responsible for the content and writing of the paper.

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