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REVIEW

Pharmacokinetics, efficacy, and safety of LMWHs in venous thrombosis and stroke in neonates, infants and children

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Since the early nineties it has been shown that low molecular weight heparin (LMWH) has significant advantages over unfractionated heparin and oral anticoagulants for both the treatment and the prevention of thrombosis, not only in adults, but also in children. The present review was based on an 'EMBASE', 'Medline' and 'PubMed' search including literature published in any language since 1980 on LMWH in neonates, infants and children. It included paediatric pharmacokinetic studies, the use of LMWH in children with venous thrombosis, LMWH administration in paediatric patients with ischaemic stroke, and its use in order to prevent symptomatic thromboembolism in children at risk. An increasing rate of off-label use of LMWH in children has been reported, showing that LMWHs offer important benefits to children with symptomatic thromboembolic events and poor venous access. Two well-conducted pharmacokinetic studies in this age group showed that neonates and younger infants require higher LMWH doses than older children to achieve the targeted anti-Xa levels, due to an increased extra vascular clearance. Recurrent symptomatic thromboses under LMWH occur in approximately 4% of children treated for venous thrombosis, and in 7% of children treated for stroke; major bleed was documented in 3% of children with therapeutic target LMWH anti-Xa levels, whereas minor bleeding was reported in approximately 23% of children receiving either therapeutic or prophylactic doses, respectively. Further randomized controlled trials are recommended to evaluate the optimum duration and application for different LMWH indications in children.
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Keywords: dalteparin; enoxaparin; reviparin and tinzaparin; children; safety and efficacy

Abbreviations: BID, twice daily; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin

Introduction

Venous and arterial thromboses are rare diseases in neonates, infants and children but being increasingly diagnosed and recognized in infancy and childhood, since the late 1980s. Symptomatic thrombotic manifestation is recorded in 0.07/10 000 children, 5.3/10 000 admissions of children and 24/10 000 admissions of newborns to intensive care units in Canada (Andrew, 1995). Until recently, the current standard antithrombotic therapy in children consisted of initial short-term intravenous administration of unfractionated heparin (UFH) followed by long-term oral anticoagulants (Albisetti and Andrew, 2002; Monagle *et al*., 2004). Clinical studies in adults have demonstrated several benefits of low-molecular-weight heparins (LMWH) over UFH, which are at least as effective as UFH. The frequency of bleeding complications and heparin-induced thrombocytopenia is significantly lower. An important advantage stems from the fact that the pharmacokinetics of LMWH is more predictable than those of UFH, thus, frequency of monitoring via anti-factor Xa assays can be minimized (Hirsh and Levine, 1992; Hirsh *et al*., 1998; Hainer *et al*., 2004; Hirsh and Raschke, 2004). In addition, the relatively long half-life of LMWH allows for once or twice daily (BID) subcutaneous application (Couturaud *et al*., 2001; Merli *et al*., 2001). LMWHs possess a higher specific activity *in vitro* against factor Xa along with less activity against thrombin (factor IIa) compared with UFH (Hirsh and Levine, 1992; Collignon *et al*., 1995; Samama and Gerotziafas, 2000). Controversies continue, however, regarding the appropriate dosage of LMWH in elderly patients with renal insufficiency (Lim *et al*., 2006), in patients with obesity or increased body weight due to severe multiple trauma (Wilson *et al*., 2001; Sanderink *et al*., 2002; Lee *et al*., 2003;

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Al-Yaseen *et al*., 2005; Haas *et al*., 2005), and the use of LMWH during pregnancy (Brenner *et al*., 2000; Greer and Hunt, 2004; Norris *et al*., 2004). Pharmacokinetic studies in children are sparse and have indicated that the LMWH enoxaparin can be administered subcutaneously twice or once daily (Massicotte *et al*., 1996, 2003b; Punzalan *et al*., 2000; Kuhle *et al*., 2005, Schobess *et al*., 2006).

As a basis for future studies the present review of LMWH in children will discuss literature data on paediatric pharmacokinetic studies, the use of LMWH in children with thrombosis or stroke, and the administration of LMWH to prevent symptomatic thromboembolism in children at risk. The structure of the review is as follows: (i) relevant study questions, (ii) short summary of literature data, (iii) specific questions to be answered in prospective studies.

Data selection

Sources: Medical literature published in any language since 1980 on LMWH in neonates, infants and children using 'EMBASE', 'Medline' and 'PubMed'. Additional references were identified from the reference lists of published articles.

Search strategy: Medline search terms were 'LMWH', 'certoparin', 'dalteparin', 'enoxaparin', 'logiparin', 'nadroparin', 'reviparin', 'tinzaparin' and 'neonates', 'infants' and 'children', 'paediatric thromboembolism' or 'stroke'. Searches were last updated 29 October 2006.

Selection: Studies in children with thromboembolic diseases who received one of the aforementioned LMWHs. Where available cohort studies or randomized studies were preferred. Case reports were not considered.

Paediatric pharmacokinetic studies on LMWH and monitoring

- Which information on dosing and pharmacokinetics of LMWH in paediatric patients is available, and which studies are necessary in the near future to obtain reliable and predictable data on LMWH dosing in children?
- Which monitoring has been used in children in whom LMWH was administered?
- At which time points monitoring for routine use of LMWH should be performed in children?

Pharmacokinetic studies of LMWHs in neonates, infants and children are limited and have been performed for four agents, for example enoxaparin, nadroparin, reviparin-sodium and tinzaparin, respectively (Massicotte *et al*., 1996, 2003b; Laporte *et al*., 1999; Punzalan *et al*., 2000; Kuhle *et al*., 2005). The LMWH used, the number of patients enrolled, the time to maximum level and maintenance doses to achieve the target anti-Xa range of 0.5–1.0 U ml^{-1} are shown in Table 1.

We found two prospective non-randomized dose-finding studies in this paediatric cohort, demonstrating that neonates and younger infants require higher LMWH doses than older children to achieve the targeted anti-Xa levels, possibly due to an increased extra vascular clearance (Massicotte *et al*., 1996; Kuhle *et al*., 2005).

The five studies available in which the dosing was adapted from adult study protocols clearly lack sufficient power to formally assess pharmacokinetics of LMWH in children. Furthermore, the study by Kuhle *et al*. (2005) for the first time gave evidence that the the time to maximum level is age-dependent with a faster peak in children <5 years of age.

Keeping in mind the limitations and the lack of standardization of LMWH monitoring (Greaves, 2002; Jackson *et al*., 2002; Shojania, 2004), therapeutic doses of LMWH in neonates, infants and children should be monitored: first, neonates and younger infants require higher doses than older children due to an increased extra vascular clearance; second, children with serious underlying medical conditions may develop renal impairment or acquired coagulation disorders necessitating dose adjustment for bleeding prevention and third, LMWH in children is administered for a longer period than in adults.

- Thus, to give firm dosing recommendations, future studies on different LMWH sources in paediatric populations must be (i) sufficiently powered, and (ii) take into consideration different time to peak levels, different through activities, as well as a different clearing mechanism of LMWH in younger children.

In addition, pharmacokinetic studies on different drug administration schemes, for example, once versus BID LMWH application, with respect to (i) pharmacokinetics, (ii) peak target levels, (iii) efficacy and safety are urgently needed.

Table 1 Pharmacokinetic studies on LMWH used in children: studies, source of LMWH used, duration of LMWH administration, number of patients enrolled, T_{max} and maintenance dosages to achieve target ranges are given

Author	*LMWH source*	*Duration*	*Number of patients*	T *max*	*Maintenance dose*	*Age or weight*
Massicotte, 1996	Enoxaparin	NA	19	4 h	1.6 mg kg^{-1} BID	<2 months
					1.0 mg kg^{-1} BID	>2 months
Punzalan, 2000	Enoxaparin	NA	12	3 h	1.0 mg kg^{-1} BID	>2 months
Massicotte, 2003b	Reviparin		12	4 h	100 U kg^{-1} BID	>5 kg
Laporte, 1999	Nadroparin	7 days	154	NA	146 U kg^{-1} BID	15 days–8 years
Kuhle, 2005	Tinzaparin	-3 months	10	2.2 h	280 U kg^{-1} daily	0–2 months
			8	2.3 h	245 U kg^{-1} daily	>2–12 months
			6	2.3 h	240 U kg^{-1} daily	1–<5 years
			4	3.4 h	200 U kg^{-1} daily	5–<10 years
			7	4.3 h	177 U kg^{-1} daily	10–<16 years

Abbreviations: BID, twice daily; LMWH, low-molecular-weight heparin; NA, not available; T_{max}, time to maximum.
Only first author of the reference is given.

- From the data available, the evidence indicates that future studies in paediatric populations necessitate an activated partial thromboplastin time-, antifactor Xa- and antifactor II monitoring. When LMWH is administered therapeutically a blood cell count, including platelet measurements, is also recommended.
- For routine, use the time point of the antifactor Xa monitoring must be clearly evaluated from newly designed and sufficiently powered pharmacokinetic studies.

Use of LMWH in children with thrombosis

- Which LMWH data are available for the treatment of venous thrombosis in children with respect to acute anticoagulation and secondary prevention?
- Are there any data available with respect to LMWH application, that is once versus BID administration, and duration of treatment?

In addition to the limited data available for pharmacokinetic studies of LMWH in children, there is an increasing off-label use of LMWH in children with venous thromboembolism according to the treatment guidelines derived from Europe and North (Nowak-Göttl *et al*., 2001b; Monagle *et al*., 2004). In the literature, currently 308 children received acute anticoagulation with the LMWHs dalteparin, enoxaparin and reviparin for a new symptomatic thrombotic event, and in 133 children secondary prophylaxis with dalteparin or enoxaparin was performed (Table 2). After 2–4 h treatment, target anti-Xa ranges reported for children were 0.5–1.0 U ml^{-1} for dalteparin, nadroparin and tinzaparin (Nohe *et al*., 1999; Hofmann *et al*., 2001; Kuhle *et al*., 2005), and 0.4–1.0 U ml^{-1} for enoxaparin and reviparin-sodium (Massicotte *et al*., 1996, 2003b); target ranges administered for prophylaxis in children following the initial treatment phase were 0.1–0.3 U ml^{-1} for enoxaparin, dalteparin and reviparin-sodium, and 0.2–0.4 U ml^{-1} for nadroparin, respectively (Massicotte *et al*., 1996, 2003a; Hofmann *et al*., 2001). The LMWHs enoxaparin, dalteparin, nadroparin, reviparin and tinzaparin have all been used off-label in children (Andrew *et al*., 1992; Streif *et al*., 2003; Massicotte *et al*., 1996; Nohe *et al*., 1999; Dix *et al*., 2000; Punzalan *et al*., 2000; DeVeber *et al*., 2001; Hofmann *et al*., 2001; Nowak-Göttl *et al*., 2001a, b; Shama *et al*., 2002; Ho *et al*., 2004; Kosch *et al*., 2004; Michaels *et al*., 2004; Revel-Vilk *et al*., 2004; Kreuz *et al*., 2006; Merkel *et al*., 2006; Schobess *et al*., 2006). The aforementioned LMWHs have been used effectively for the treatment of venous thrombosis, including pulmonary embolism, thrombosis of the upper and lower venous system, catheter-induced thromboses, renal vein thrombosis, and cerebral venous thrombosis. Efficacy and safety data including the number of patients enrolled, the LMWHs used and the dosages administered are summarized in Table 2.

Whereas the majority of children from North America received LMWH BID (Dix *et al*., 2000), most children treated in Germany received enoxaparin (Nowak-Göttl *et al*., 2001a; Kreuz *et al*., 2006; Merkel *et al*., 2006; Schobess *et al*., 2006), dalteparin (Nohe *et al*., 1999) or nadroparin (Hofmann *et al*., 2001) once daily. Similar to an adult randomized study (Merli *et al*., 2001), Schobess *et al*. (2006) demonstrated in a pilot study that enoxaparin administered once daily in a dosage of 1.5 mg kg^{-1} was similarly effective compared to 1 mg kg^{-1} administered every 12 h. A further promising attempt to reduce the discomfort of receiving LMWH BID for thrombosis treatment was shown by Kuhle *et al*. (2005); in their dose finding study, the authors showed that once daily tinzaparin was efficacious and safe in the cohort of children investigated.

- From the data presented here, future studies on LMWH administration in paediatric populations with thrombosis should evaluate not only the optimal dosing including the evaluation of peak target levels to be achieved but should also formally compare once versus BID administration.

Use of LMWH in children with stroke

- Which LMWH data are available for the treatment of stroke in children with respect to acute anticoagulation and secondary prevention?

With the exception of perinatal stroke (Chalmers, 2005), literature data have shown that LMWH may be safe in children with non-haemorrhagic stroke. Although one randomized double blind placebo-controlled trial in adult patients with stroke has shown an improved 6-month clinical outcome with LMWH nadroparin compared to placebo (Kay *et al*., 1995), no such controlled data are available for paediatric stroke so far. Until today, 123 paediatric patients with stroke, mainly of thromboembolic origin, were treated with the LMWH enoxaparin (Table 3). In a recent prospective but non-randomized study with a cohort of 135 consecutively recruited stroke children aged 6 months or over to 18 years or under, no significant differences were found between the use of medium dose aspirin and LMWH administered after a first symptomatic stroke with respect to incidence of stroke recurrence or drug-related adverse effects (Sträter *et al*., 2001). However, it has to be mentioned here that the latter study by Sträter *et al*. (2001) was a non-randomized survey and therefore no proof for or against efficacy can be drawn. Dosages used in stroke children ranged from 1 mg kg^{-1} daily to 1 mg kg^{-1} BID for enoxaparin, and daily dalteparin from 75 to 175 anti-Xa U kg^{-1}, respectively (Dix *et al*., 2000; Sträter *et al*., 2001; Burak *et al*., 2003; Nowak-Göttl *et al*., 2003). Data are summarized in Table 3.

- From the limited data available, one may conclude that LMWH may be safe in the treatment of stroke in children. Randomized and controlled trials in children, comparing LMWH with other agents such as aspirin or warfarin are recommended to clarify the optimal anticoagulation in children with stroke of different aetiologies.

Preventive use of LMWH in children at risk

- This review also raises the question, whether LMWH should be used for primary prophylaxis in risk situations, such as immobilization, malignancy, congenital heart

Table 2 Efficacy and safety data in children with venous thrombosis treated with therapeutic or prophylactic LMWH doses: studies, LMWH used, duration of treatment and number of patients enrolled are shown

Author	*Study design*	*LMWH: therapy*	*Daily dosing (duration)*	*Number of patients*	*Efficacy*	*Safety*		
					New thrombosis	*Major bleeding*	*Minor bleeding*	*Other LMWH-related AEs*
Nohe, 1999	Retrospective	Dalteparin	1.3 ± 0.43 IU kg^{-1} (3 weeks)	25	—	—	2	—
Dix, 2000	Prospective cohort	Enoxaparin	1.0 mg kg^{-1} [a] BID age >2 months 1.5 mg kg^{-1} [a] BID age <2 months (44 days)	101	2	6	~18	
Massicotte, 2003a	Prospective randomized	Reviparin	100 U kg^{-1} [a] (3 months)	36	2	2	32	—
Michaels, 2004	Retrospective	Enoxaparin	1.25 mg kg^{-1} [a] BID (33 days)	10	—	—	—	—
Ho, 2004	Retrospective	Enoxaparin	1.0 mg kg^{-1} [a] BID age >2 months 1.5 mg kg^{-1} [a] BID age <2 months (49 days)	56	—	1	~20	Pain injection sites
Schobess, 2006	Prospective cohort	Enoxaparin	1 mg kg^{-1} [a] BID or 1.5 mg kg^{-1} [a] (14 days)	80	—	—	—	—
Total			median: 39 days	308	4 (1.3%)	9 (2.9%)	72 (23.4 %)	
				LMWH: prevention				
Nohe, 1999	Retrospective	Dalteparin	0.95 ± 0.52 U kg^{-1} [a] (6 months)	10	—	—	—	—
Dix, 2000	Prospective cohort	Enoxaparin	0.5 mg kg^{-1} [a] BID age >2 months 0.75 mg kg^{-1} [a] BID age <2 months (11 days)	30	1	—	2	—
Hofmann, 2001	Retrospective	Enoxaparin	1 mg kg^{-1} [a] (6 months)	13	—	—	—	Temporary hair loss
Schobess, 2006	Prospective cohort	Enoxaparin	1 mg kg^{-1} [a] BID or 1.5 mg kg^{-1} [a] (4.5 months)	80	4	1	2	—
Total			Median duration: 157 days	133	5 (3.8%)	1 (0.8%)	4 (3.0%)	

Abbreviations: AE, adverse event; BID, twice daily; LMWH, low-molecular-weight heparin.
Only first author of the reference is given.
[a]Starting dose followed by antifactor Xa adjustment.

Table 3 Efficacy and safety in children with stroke treated with LMWH: studies, LMWH used, duration, number of patients enrolled, efficacy and safety data are shown

Author	*Study design*	*LMWH*	*Daily dosing (duration)*	*Number of patients*	*Efficacy*	*Safety*		
					New thrombosis	*Major bleeding*	*Minor bleeding*	*Other LMWH-related AEs*
Dix, 2000	Prospective cohort	Enoxaparin	1 mg kg^{-1} [a] BID (44 days)	29	—	1	~8	—
Sträter, 2001	Prospective cohort	Enoxaparin	1 mg kg^{-1} [a] (6 months)	86	9	—	—	—
Burak, 2003	Retrospective	Enoxaparin	1 mg kg^{-1} [a] BID (4 days)	8	—	—	—	—
Total			Median: 44 days	123	9 (7.3%)	1 (0.8%)	8 (6.5%)	

Abbreviation: AE, adverse event; BID, twice daily; LMWH, low-molecular-weight heparin.
Only first author of the reference is given.
[a]Starting dose followed by antifactor Xa adjustment.

disease or central venous lines, in the paediatric population, and which future attempts should be undertaken to optimize preventive use of LMWH in paediatric populations at risk.

There is one randomized controlled trial evaluating the role of primary prophylactic doses of LMWH in the prevention of central line associated thrombotic complications in children (Massicotte *et al*., 2003c). In this study, children were randomly assigned to reviparin-sodium or house standard of care (UFH/warfarin). Although PROTEKT was clearly underpowered and did not reach the estimated sample size during the recruitment phase scheduled, this study gave valuable information on the heparin dosages used and safety issues. In addition, further small cohort studies are reported using different LMWHs to prevent symptomatic thrombotic events in children at risk, for example children undergoing renal transplantation, immobilization, obesity, children necessitating parenteral nutrition and paediatric patients with leukaemia or other malignancies (Broyer *et al*., 1991; Laporte *et al*., 1999; Nohe *et al*., 1999; Dix *et al*., 2000; Elhasid *et al*., 2001; Hofmann *et al*., 2001). LMWHs used, dosages and adverse events are shown in Table 4.

- Thus, future randomized and sufficiently powered studies are urgently recommended to produce evidence-based guidelines on appropriate indications for primary thrombosis prophylaxis in children.

Efficacy and safety data using LMWHs in children

- Efficacy and safety is one major issue when children are treated with a new non-licensed drug. Therefore, this review aimed to search for these data in the literature separately.
- Are there any data available with respect to efficacy or to potential adverse events?

In the majority of studies reviewed, efficacy was evaluated clinically by the absence of symptomatic thrombus or stroke progression, clot extension or new thrombus formation. However, only few studies have assessed the efficacy of LMWH in comparison to other treatment options or no treatment. Safety of LMWH was assessed by determining the number of major and minor bleeding complications. Only one study evaluated sensitive indicators of drug-induced hepatocellular injury (Kuhle *et al*., 2005). Efficacy and safety of therapeutic and prophylactic doses of LMWHs in children have been evaluated in several clinical studies using enoxaparin, dalteparin, nadroparin, reviparin-sodium and tinzaparin (Tables 1–4). Overall, the LMWHs used for antithrombotic treatment in neonates, infants and children appear to be effective and safe. Rethrombosis rates and bleeding events under LMWH administration in children are comparable with adult literature data (Lee *et al*., 2003; Hirsh and Raschke, 2004; Levine *et al*., 2004; Lim *et al*., 2006; López-Jiménez *et al*., 2006).

The overall reported recurrence rates in children with venous thrombosis receiving therapeutic LMWH for anticoagulation was 4%, ranging from 0 (Merkel *et al*., 2006),

Table 4 Primary prevention with LMWH in children at risk: studies, source of LMWH, efficacy and safety data are shown

Author	*Study design*	*LMWH: primary prevention*	*Daily dosing (duration)*	*Number of patients*	*Efficacy*	*Safety*		
					Thrombosis	*Major bleeding*	*Minor bleeding*	*Other LMWH-related AEs*
Broyer, 1991	Prospective	Enoxaparin	0.5 mg kg^{-1} BID before RTX 0.4 mg kg^{-1} BID post RTX (duration not reported)	42	1	7	5	—
Nohe, 1999	Retrospective	Dalteparin	0.95 ± 0.52 U kg^{-1} [a] up to 3 months	8	—	—	—	—
Elhasid, 2001	Prospective	Enoxaparin	0.84 mg kg^{-1} (up to 3 weeks)	41	—	—	—	—
Hofmann, 2001	Retrospective	Nadroparin	1 mg kg^{-1} [a] (14 days)	62	—	—	—	—
Massicotte, 2003c	Prospective Randomized	Reviparin	30 U kg^{-1} [a] BID age > 2 months 50 U kg^{-1} [a] BID age < 2 months (up to 1 month)	85	3	—	45	—
Total			Median: 1 month	238	4 (1.7%)	7 (2.9%)	50 (21.0%)	

Abbreviation: AE, adverse event; BID, twice daily; LMWH, low-molecular-weight heparin; RTX, renal transplantation.
Only first author of the reference is given.
[a]Starting dose followed by antifactor Xa adjustment.

1.4% (Dix *et al*., 2000), 4.8% (Streif *et al*., 2003) for enoxaparin, 5.6% for reviparin-sodium (Massicotte *et al*., 2003a) and 11% in the tinzaparin trial (Kuhle *et al*., 2005). Children receiving LMWH on prophylactic dose schedules showed recurrence rates of 0 (Merkel *et al*., 2006), 3.2% (Dix *et al*., 2000) and 5% (Schobess *et al*., 2006). Recurrences in children, however, occur most often within the lower anti-Xa target range. No data are available about potential association with comorbid conditions or transient risk factors that may trigger recurrence, especially in patients receiving suboptimal therapy. Interestingly, heparin-induced thrombocytopenia has not been reported following the sole use of LMWH in children (Ranze *et al*., 1999; Newall *et al*., 2003; Bidlingmaier *et al*., 2006).

The overall major bleeding rate under LMWH administration in children was 3%, ranging from 0 to 5% for enoxaparin (Streif *et al*., 2003; Dix *et al*., 2000; Punzalan *et al*., 2000; Ho *et al*., 2004, Michaels *et al*., 2004), 3% for tinzaparin (Kuhle *et al*., 2005) and 5.6% for reviparin-sodium (Massicotte *et al*., 2003a). The overall rate of minor bleeding episodes observed under therapeutic LMWH was 23.4%, ranging from 1.5% for nadroparin (Hofmann *et al*., 2001), 4% for dalteparin (Nohe *et al*., 1999), 17% for enoxaparin (Dix *et al*., 2000), and 89% for reviparin (Massicotte *et al*., 2003a). In the latter study, however, the definition of minor bleeding also includes bruising or oozing around intravenous sites and surgical wounds, small amounts of blood from suctioning endotracheal tubes, of blood in urine or stool and minor nose bleeds, possibly leading to an over reporting compared to the other paediatric studies. Rates of 5 and 6.4% for minor bleeding episodes were reported for prophylactic use of enoxaparin (Dix *et al*., 2000; Schobess *et al*., 2006). In addition, temporary hair loss was reported in one out of 13 patients treated with enoxaparin (Hofmann *et al*., 2001), and elevated liver enzymes were reported by Kuhle *et al*. (2005) in 34% of cases. Osteoporosis is a serious, but uncommon side effect associated with prolonged use of high doses of heparin. The effect of LMWH on bones in the growing child is not known.

In children, enoxaparin was administered for primary prevention of thromboembolic events the symptomatic thrombosis and bleeding rate was 0 (Elhasid *et al*., 2001). In the PROTEKT trial, symptomatic thrombosis occurred in 3.8% in both the reviparin-sodium and house standard arm, and minor bleeding episodes were observed in 53.3% of children treated with LMWH compared with 44.7% in the standard care group (Massicotte *et al*., 2003c).

In children with stroke receiving LMWH, the overall restroke rate was 7.3%, ranging from 0 (Dix *et al*., 2000) and Burak *et al*. (2003) to 10.5% in the German cohort (Sträter *et al*., 2001). Safety data showed one major bleed in a child with stroke receiving therapeutic enoxaparin (Dix *et al*., 2000) compared to zero observed in two other studies (Sträter *et al*., 2001; Burak *et al*., 2003). Again, minor bleeding diagnosed in stroke children treated with LMWH was solely observed in eight of 29 children (27.5%) treated with therapeutic enoxaparin anti-Xa target levels (Dix *et al*., 2000).

From the data available, the overall efficacy to prevent second thromboembolic events in paediatric patients and

the LMWH-induced frequency of major bleedings were acceptable. However, liver dysfunction and bone metabolism was not evaluated. It is suggested that long-term use of LMWH (that is >3 months) should be accompanied with sensitive measurements of bone density and liver function.

As shown by Massicotte *et al*. (2003c), the best way to further evaluate efficacy will be a randomized trial with clear study end points, that is recurrent venous thrombosis (VT) or death related to VT.

Conclusion and future aspects

In summary, the use of LMWHs in children is effective and safe as in adults, however, pharmacokinetic and pharmacodynamics studies on LMWHs in children are limited. Therefore, further multicentre international and sufficiently powered treatment studies are required to solve the open questions in therapy and prophylaxis, that is the duration of LMWH administration and the mode of LMWH administration.

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Conflict of interest

The authors state no conflict of interest.

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