MCN for Neonatology
West of Scotland
Neonatal Guideline

Enoxaparin Use in Neonatal & Paediatric Critical Care

Guideline for the use of enoxaparin for treatment of thrombotic events within NICU & PICU, and for thromboprophylaxis within PICU

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Scope

Venous thrombo-embolism prophylaxis is NOT generally indicated in neonates, infants and children.

The aim of this guideline is to delineate a treatment and monitoring pathway for Enoxaparin use in the Neonatal Intensive Care Units in the West of Scotland and Paediatric Intensive Care Unit of the Royal Hospital Sick Children, Glasgow.

It does not describe the diagnostic management of potential venous thrombo-embolism or prophylaxis against venous thrombo-embolism.

Users should also refer to the appropriate pharmacy monographs

Introduction

Venous thromboembolism (VTE) is being increasingly recognized in the paediatric population. The estimated incidence of VTE is 0.7 to 1.0 per 100 000 population with a prevalence of 5.3 per 10,000 hospital admission according to the Canadian VTE registry (Andrew M et al. 1994). Recent US data has shown an incidence of 1.51 VTE's per 1000 PICU patient days or 0.74% of patients admitted to the 11 PICU's taking part in the study by Higgerson et al (2011). There is a bi-modal distribution with peaks in the neonatal and adolescent periods. Small studies have shown a greater relative risk of VTE in children than adults. (O'Brien et al, 2011).

The main risk factors in children are underlying medical or surgical risk factors (van Ommen CH et al, 2003) and central venous catheters (Revel-Vilk S et al, 2003; Higgerson et al, 2011). VTE is associated with increased mortality, recurrent thrombosis and post-thrombotic syndrome with an average follow-up period of 2.86 years (Monagle P at al, 2000; Higgerson et al, 2011).

A small but not insignificant number of neonates develop thrombi within the first few weeks of life, associated iatrogenically with the insertion of umbilical catheters or peripheral arterial lines, or secondary to traumatic delivery. A small number of infants have no identifiable risk factors.

Of these neonates, infants and children, a proportion will require treatment to minimise the risk of significant morbidity and mortality from this thrombotic event. Treatment in neonates is generally limited to those with evidence of end organ compromise or limb ischaemia secondary to thrombus formation, and is almost exclusively initiated in consultation with a paediatric consultant haematologist. **Thromboprophylaxis is not generally indicated within the neonatal population** except for in a small subgroup of infants with complex multisystem disease within paediatric critical care.

THERAPEUTIC Enoxaparin therapy

Enoxaparin should be continued for between 6 weeks and 3 months post-diagnosis of a VTE. Ensure referral to Dr Chalmers (Consultant Haematologist RHSC). Remove CVL associated with VTE as soon as possible. Ensure follow-up ultrasound to screen for extension of VTE. It is acknowledged that neonatal enoxaparin dosing can be challenging and will almost always be done in conjunction with paediatric haematology. If an infant is being discharged on enoxaparin they should be referred to haematology for follow up at discharge.

Therapeutic Enoxaparin dose regime

a. **Neonate**
   i. 2mg/kg TWICE DAILY subcutaneously
b. **1 month old**
   i. 1.5mg/kg TWICE DAILY subcutaneously
c. **2 months - 17 years**
   i. 1mg/kg TWICE DAILY subcutaneously

The following general principles apply:

- Ideally prescribe for 0600Hrs & 1800Hrs (but do not delay commencing treatment unless converting from UFH)
- Once target heparin assay achieved, consider switching to administration via insuflon (see Insuflon management following prophylactic regime)

Therapeutic Enoxaparin monitoring regime

Target heparin assay 0.5 – 1.0 U/ml

- Check heparin assay 4 hours after 1st dose
  - Order "heparin assay (LMWH) - child" on Trakcare, stating Enoxaparin therapy and dose regime and time of last dose.
- Dose adjust as per chart below
- Repeat heparin assay 4 hrs after 3rd dose and dose adjust as per chart
- Once target range achieved check heparin assay every Monday & Thursday
- Remember heparin assay results will be affected by:
  - Use of Unfractionated Heparin
  - Delayed excretion of LMWH e.g. in renal failure
  - Hepatic failure
  - Coexisting coagulopathy e.g. in sepsis
- Increase frequency of heparin assay if there are any bleeding concerns.

Heparin assay	***Dose adjustment***	***Next heparin assay***
<0.35	***Change Insuflon site Dose ↑25%***	***4 hrs post dose***
0.35 – 0.49	***Dose ↑10%***	***Next day***
0.5 – 1.0	***-***	***Next Monday or Thursday***
1.01 – 1.5	***Dose ↓10%***	***Next day***
1.51 - 2.0	***Delay dose by 12hrs & ↓25%***	
>2	***Delay dose till heparin assay is <1.0 Dose ↓40%***	***Check heparin assay every 12 hrs till <1.0 Check heparin assay 3.5 hrs after dose***

PROPHYLACTIC Enoxaparin therapy

VTE prophylaxis with Enoxaparin should be used in combination with measures including early mobilisation, removal of CVL's and TED stockings (see appendix *VTE Risk assessment*).

Prophylactic Enoxaparin dose regime

- **< 2 months or <5kg**
  - 0.75mg/kg TWICE DAILY subcutaneously
  - Prescribe for 0600Hrs & 1800Hrs
  - Once heparin assay therapeutic consider switching to administration via insuflon

- **>2 months or > 5kg**
  - 0.5mg/kg TWICE DAILY subcutaneously, maximum 40mg per day
  - Prescribe for 0600Hrs & 1800Hrs
  - Once heparin assay therapeutic consider switching to administration via insuflon

Insuflon management

- Recommendation that insuflon is changed every 7 days with date of change marked on adhesive dressing.
- Insuflon should not be flushed due to the potential for changes in dosage and drug distribution.
- If heparin assay out with the target range occur, change the Insuflon site

Prophylactic Enoxaparin monitoring regime

Target heparin assay 0.3 – 0.5 U/ml

- Check heparin assay 4 hrs after 3rd dose
  - Order "heparin assay (LMWH) - child" on Trakcare, stating Enoxaparin therapy and dose regime and time of last dose.
- Dose adjust as per chart below
- Once target range achieved check heparin assay every Monday
- Remember heparin assay results will be affected by:
  - Use of Unfractionated Heparin
  - Delayed excretion of LMWH e.g. in renal failure
  - Hepatic failure
  - Coexisting coagulopathy e.g. in sepsis
- Increase frequency of heparin assay if:
  - Bleeding concern
  - Planned surgery

Heparin assay	Dose adjustment	Next heparin assay
<0.3	**Change Insuflon site Dose ↑ 25%**	**4 hrs post dose**
0.3 – 0.5	**-**	**4 hrs post dose on next Monday**
0.5 – 1.0	**Dose ↓ 25%**	**Next day**
>1.0	**Delay dose till heparin assay is <0.5 Dose ↓ 40%**	**Check heparin assay every 12 hrs till <1.0 Check heparin assay 4 hrs after dose**

3. Background

Faustino et al surveyed 151 PICUs across the US looking at their thromboprophylaxis and VTE treatment policy. They had a 62.2% response rate. There was no uniform guidance seen across the centres. Similar findings were found in a survey undertaken in England and Wales. (Braga et al, 2011). There is guidance published in 2012 from the British Committee for Standards in Haematology which was developed in light of the available evidence and expert opinion (Chalmers, E. et al 2011). This work focuses on the investigation, management and prevention of paediatric VTE and forms the core for the majority of this guideline.

Much recent literature has focussed on the use of low molecular weight heparins (LMWH) and their role and potential benefits in relation to unfractionated heparin (UFH) in the prophylaxis and treatment of VTE (Chalmers, E. et al, 2011). Enoxaparin is a LMWH, used in the intensive care settings as the primary anti-coagulant for the prophylaxis and treatment of thrombo-embolic events. The efficacy, predictable pharmacokinetics, ease of administration and the reduced side effect profile of LMWH make it superior to unfractionated heparins as the first choice anticoagulant group(Andrew et al. 1994)depending on the clinical situation.

The benefits of LMWH versus UFH include administration in that they require to be given once or twice daily subcutaneously, compared to a continuous intra-venous infusion. Other benefits include route of administration, as the subcutaneous route negates the necessity for intravenous access, and as such reducing pain, discomfort and infection risk. Further benefits in a study by Robinson et al are identified as less time needed to prepare, no break in therapy whilst making up new heparin syringe and a reduction in cost for LMWH versus UFH (Robinson AM et al 1993). Previous adult studies have shown that LMWH is as effective in the management of VTE as UFH. Furthermore, the pharmacokinetics are more predictable. (Massicote et al, 1996). The REVIVE study assessed the efficacy and safety of different anticoagulant regimens in children with VTE. Children with a first episode of VTE were randomised to receive either LMWH (reviparin-sodium) (N=37) or UFH followed by oral anticoagulation (UFH/VKA) (N=41) (Massicotte et al 2003a). The study was underpowered but showed LMWH was an equally effective form of anticoagulation.

Medications for children are primarily dosed based on weight, and are often metabolised and distributed differently to adults. Furthermore, the haemostatic system in neonates and infants differs from that of older children and adults, and targets for therapy may differ. Dosing regimes for anticoagulants should not simply extrapolated from data based on adults but should instead be based on pharmacokinetic and pharmacodynamic data.

Trame et al described a population pharmacokinetic model where a cohort study of 126 children identified body weight as the most predictive covariate of enoxaparin clearance. Their results, measuring anti-factor Xa activity data, suggested a regime of once daily dosing with frequent monitoring (Trame et al 2010). In contrast, an open label pilot safety study by Schobess et al looked at long term safety and efficacy data where children were stratified to receive once or twice daily enoxaparin and found no difference (Schobess et al 2006). A once daily regime may be more convenient and less likely to cause distress and discomfort to the child. A Cochrane review by van Donghen et al concluded that once-daily treatment with LMWH is as effective and safe as twice daily treatment with LMWH. However, the 95% confidence interval implies that there is a possibility that the risk of recurrent VTE might be higher when patients are treated once daily (van Donghen et al 2003).

An observational study by Dix et al looked at LMWH for the treatment of VTE in neonates and children. A clinical response was demonstrated in 94% of cases. However 5% had major bleeding and in 1% a recurrent VTE occurred. (Dix et al 2000).

Thromboprophylaxis is of increasing interest in the paediatric population as the incidence of VTE becomes more apparent. The role of physical prophylaxis is more applicable to older children, usually those greater than 40kg or in their adolescence. Pharmacological intervention with agents such as LMWH's may also have a role to play.

Massicotte et al (2003) carried out the PROTEKT trial which randomised 186 children to either routine care(UFH/warfarin) or LMWH. They looked at the role of prophylactic doses of LMWH in preventing VTE. They showed a non-significant difference in incidence of VTE (12.5% vs 14.1%), although the study was underpowered

Concern has been raised that the preparations for smaller children are not appropriate with LMWH's coming in pre-filled adult dose syringes (Monagle et al. 2012)

Current literature describes the need for age-specific dosing requirements in children (Buck 2011;Ignjatovic et al. 2010;Malowany et al. 2008; Streif et al2004; Massicote et al 2003; Kuhl et a 2002). These studies suggest the following dosing schedules; for therapeutic doses, 2 mg/kg every 12 hours for children less than 2 months of age and 1.0 mg/kg for children greater than 2 months of age; for prophylactic doses, 0.75 mg/kg every 12 hours for children less than 2 months of age and 0.5 mg/kg for children greater than 2 months of age (Bauman et al. 2009;Ignjatovic et al. 2010;Massicotte et al. 2003). Variation in dosing between neonates, children and adolescents/adults arise from differences in plasma concentration of anti-thrombin, thrombin generation capacity and clearance of heparin between the age groups (Andrew et al 1998).

Monitoring enoxaparin therapy in children to ensure target levels are attained to ensure optimal effect and minimal risk of the therapy is undertaken by assessing anti-Xa levels in the patient's serum. This test is otherwise known as a Heparin assay.

Heparin assay should be assessed 4-6 hours after the dose of enoxaparin is administered. These levels can be used to monitor the effect of enoxaparin, ensuring it remains within the target range and, therefore optimising the dose. The dosing schedules mentioned above were extrapolated from adult guidelines to give a target plasma anti-Xa concentration of 0.1 - 0.3 u/ml in prophylactic patients and 0.5 – 1.0 u/ml in therapeutic patients, or 0.5 - 0.8u/ml in a sample taken 2-6 hours post dose (Chalmers et al. 2011, Monagle et al. 2012).

Rapid achievement of target levels of anti-Xa is important as any delay may place the child at needless risk of thrombosis, or extension of the pre-existing thrombus. A study by Bauman et al (2009) evaluated the dosing requirements of enoxaparin in children and infants, focusing on the effect of increasing the starting dose of enoxaparin and the length of time required to reach therapeutic anti-Xa levels. Their study concluded that a higher starting dose, with the subsequent doses titrated according to the anti-Xa level, resulted in a quicker achievement of target anti-Xa levels than is observed by following the current guidelines (Massicotte et al. 2003;Streif et al. 2003). An example of a dosing regimen with adjustments made against post-dose anti-Xa level scan be seen in table 1 (Manna; 2012). It is taken from the guidelines for the treatment of thromboembolism in use at the PICU: St George's hospital, London,

Once target levels have been achieved, it is suggested that monitoring should be done a minimum of once a week to ensure that the optimum dose of enoxaparin is being maintained (Michaels et al. 2004).

Regular anti-Xa monitoring once target levels have been met is equally as important as the monitoring at the commencement of therapy. A study by Michaels et al (2004) retrospectively reviewed a patient group on enoxaparin therapy and observed that of the 10 patients in their study; only one patient maintained a stable anti-Xa level in the therapeutic range 100% of the

time. This highlights the importance of on-going anti-Xa monitoring once target levels have been met.

Ignjatovic et al reviewed the records of 233 patients (ages 3 days to 16 years) treated with enoxaparin. All patients received enoxaparin 0.5-0.75 mg/kg twice daily. 81% were being treated with enoxaparin for a diagnosed clot, while 19% received prophylaxis. Use of anti-Xa monitoring was more frequent in patients under a year of age compared to older children and in patients treated for more than 60 days compared to those with shorter treatment courses (both comparisons, $p < 0.05$). 39% had an anti-Xa value within the target range of 0.5-1.0 IU/mL. 52% were subtherapeutic and 9% had values above 1.0 IU/mL. More infants than older children were subtherapeutic on their initial enoxaparin regimen ($p < 0.05$). While age playes a significant role in dosing, they did not find any difference between term and preterm infants. 29% experienced minor bleeding. Only 1 patient experienced major bleeding.

Sanchez et al also found that they required higher doses of enoxaparin in infants and younger children in their cardiac intensive care unit. They carried out a retrospective study on 31 patients ranging in age from birth to 2 years. 68% received treatment doses and the rest received prophylaxis. For analysis they divided into two groups: younger patients (0-2months) and older patients. Both age groups required an increase in their enoxaparin doses to achieve an anti Xa value within the target range. Furthermore, no difference was found in dosing requirements between those patients who received direct subcutaneous injection and those using an Insuflon device. No bleeding complications were identified, however, they were using small numbers.

Work in our department has shown a wide range of doses being utilised with a poor attainment of effective aXa levels for both prophylactic and therapeutic regimes (tables 1 & 2). This has led to the development of this guideline and ready reckoner for the use of Enoxaparin in PICU & NICU.

	Therapeutic group (n=15)		Prophylaxis group (n=24)		Cardiac prophylaxis group (n=11)	
	Median	Range	Median	Range	Median	Range
Duration of Enoxaparin therapy (days)	16.5	4.5 – 101.5	4.0	0.8 – 31.6	9.0	1.5 – 22.4
Starting dose (mg/kg)	1.08	0.53 – 1.75	0.5	0.31 – 1.02	0.92	0.31 – 2.05
Therapeutic dose (mg/kg)	1.51	1.08 – 4.0	0.54	0.31 – 1.02	0.88	0.49 – 1.48
Difference b/w starting and therapeutic dose (mg/kg)	0.55	0 – 2.47	0	0.0 – 0.07	0	0
	Number	Percentage	Number	Percentage	Number	Percentage
Concurrent aspirin administration	2	13.3%	3	12.5%	2	18.2%
Concurrent heparin administration	2	13.3%	3	12.5%	0	0

Table 1: RHSC Critical Care Enoxaparin dosing data (R Hunter, G Kerr, S Cassim, C Granger, E Chalmers, M Davidson)

	Therapeutic group (=15)		**Prophylaxis group (n=24)**		**Cardiac prophylaxis group (n=11)**	
	Median	Range	Median	Range	Median	Range
Time: 1st dose – anti-Xa assay taken (days)	0.8	0.1 – 8.2	1.2	0.3 – 3.6	2.1	0.7 – 6.1
Time taken to reach therapeutic level (days)	9.9	1.7 – 24.4	2.2	0.3 – 3.6	1.6	0.7 – 6.5
No. anti-Xa assays performed during Enoxaparin therapy	5	0 - 27	3	1 – 4	3	1 - 5
	Number	Percentage	Number	Percentage	Number	Percentage
Patients having anti-Xa assay performed	14	93.3%	4	16.7%	7	63.6%
Patients reaching target Anti-Xa level	8	53.3%	4	16.7%	6	54.5%

Table 2: RHSC Critical Care Enoxaparin monitoring data (R Hunter, , G Kerr, S Cassim, C Granger, E Chalmers, M Davidson)

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5. Appendix

Enoxaparin ready reckoner

Therapeutic Enoxaparin dose regime

- Prescribe for 0600h and 1800h

- **Neonate**
  - 2mg/kg bd via insuflon
- **1 - 2 months**
  - 1.5mg/kg bd via insuflon
- **>2 months or > 5kg**
  - 1mg/kg bd via insuflon
  - Prescribe for 0600Hrs & 1800Hrs

Therapeutic Enoxaparin dose management guide		
Heparin assay	**Dose adjustment**	**Next heparin assay**
<0.35	**Change Insuflon site Dose ↑ 25%**	**4 hrs post dose**
0.35 – 0.49	**Dose ↑ 10%**	**Next day**
0.5 – 1.0	**-**	**Next Monday or Thursday**
1.01 – 1.5	**Dose ↓ 10%**	**Next day**
1.51 - 2.0	**Delay dose by 12hrs & ↓ 25%**	
>2	**Delay dose till heparin assay is <1.0 Dose ↓ 40%**	**Check heparin assay every 12 hrs till <1.0 Check heparin assay 3.5 hrs after dose**

Prophylactic Enoxaparin therapy

- Prescribe for 0600h and 1800h

- **< 2 months or <5kg**
  - 0.75mg/kg bd via insuflon
- **>2 months or > 5kg**
  - 0.5mg/kg bd via insuflon

Prophylactic Enoxaparin dose management guide		
Heparin assay	**Dose adjustment**	**Next heparin assay**
<0.3	**Change Insuflon site Dose ↑ 25%**	**4 hrs post dose**
0.3 – 0.5	**-**	**4 hrs post dose on next Monday**
0.5 – 1.0	**Dose ↓ 25%**	**Next day**
>1.0	**Delay dose till heparin assay is <0.5 Dose ↓ 40%**	**Check heparin assay every 12 hrs till <1.0 Check heparin assay 4 hrs after dose**

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