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Utility of Peak Anti-Xa Monitoring in High-Risk Bleeding Patients on Low Molecular Weight Heparin – Can it Guide us to Safe Dosing of Low-Molecular Weight Heparin (LMWH)

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1. Summary

Three elderly patients were given LMWH for treatment of Venous Thromboembolism and stroke prevention on background of Atrial Fibrillation. All of them had high bleeding risks from various reasons, such as recent brain surgery with post-operative intracranial hematoma, large liver mass (>10cm) possibly newly diagnosed Hepatocellular Carcinoma, and lastly intramuscular hematoma from supra-therapeutic INR while on Warfarin.

However, none of them were obese, with extremely low body weight, or renally impaired to warrant the need for peak anti-Xa level monitoring while they were given LMWH. In this case report, we are reporting the peak anti-Xa level monitoring in these high bleeding risk patients, which guided us on safe dosing of LMWH.

2. Background

LMWH is commonly used in the treatment and prevention of venous or arterial thrombosis. There is no routine therapeutic level monitoring needed in the general population due to its predictable pharmacokinetics [1,2]. However, in some special populations, LMWH activity warrants monitoring to ensure efficacy and safety. These special population includes those with renal insufficiency (CrCl<50ml/min), pregnancy, extreme body weights (<40kg or >150kg), newborns and children [3,4]. As direct measurement of LMWH activity is not feasible, anti-Xa level is often used as a surrogate marker. Nevertheless, there is no available evidence supporting anti-Xa monitoring for patients who have high bleeding risk from other causes such as trauma, liver disease, spontaneous hematomas, or even intracranial bleed, etc. In addition, there is no strong recommendation on the therapeutic target range if anti-Xa were to be checked. Some recommends targeting peak anti-Xa levels at 0.2-0.5IU/ml, 0.5-1.0IU/ml, 1.0-2.0IU/ml for prophylactic, twice daily and once daily LMWH dosing respectively, however, these recommendations are mainly based on experience [5,6]. While it is important to manage thrombosis and its complications, safe use of LMWH is of equal concern. Hence, we would like to gain more insights on the use of anti-Xa monitoring in other high bleeding risk patients and safer target range to minimize both thrombosis and bleeding risks.

3. Case Presentation

3.1. Case 1

Mdm. C, a 67-year-old Chinese female, had undergone right craniotomy and excision of the right frontal tumor in Oct 2021. She developed status epilepticus secondary to subacute hematoma at the craniotomy site in Nov 2021. During the same admission, she was diagnosed with chronic lower limb deep vein thrombosis (DVT) and bilateral pulmonary embolism, for which anticoagulant was indicated. However, she was at high bleeding risk given recent

craniotomy and complication of subacute hematoma. Therefore, the decision was made to start her on SC Enoxaparin 1mg/kg BD (body weight 60.5kg) with anti-Xa monitoring to guide appropriate dosing. The peak anti-Xa level was targeted at 0.5U/ml to 0.75U/ml, which was at the lower end of the recommended range. As such, we aimed to manage the thrombosis without increasing the bleeding risk on the background of high bleeding risk.

3.2. Outcome and Follow Up

Mdm. C was started with SC Enoxaparin 60mg BD on 29/11/2021. (Table 1) shows the peak anti-Xa levels and dose adjustment accordingly. The dose adjustment was guided by the Nomogram developed by Monagle, et al., (2001) [7] as shown in (Table 2). The first dose reduction was 50% of the previous dose without holding off the next dose. This dose adjustment was more than the recommended practice, partly because of the high bleeding risk and a lower normal therapeutic range of 0.5-0.75IU/ml was targeted. Additionally, the Nomogram was derived from a study done with pediatric patients, the applicability in adult population is questionable. Clinical assessment remains the key guiding principle for LMWH dose adjustment. Subsequently, there were two more peak anti-Xa levels checked after dose reduction, which were very close to the target range of 0.5U/ml to 0.75U/ml. There was no further dose adjustment thereafter. Patient was maintained on SC Enoxaparin 30mg BD till discharge. There was no bleeding event as well as recurrent thrombotic event.

Table 1:

Enoxaparin Dose	Time of Blood Taken	Peak Anti-Xa Level	Dose Adjustment
60mg BD	4 hours post 3rd dose	1.69IU/ml	Reduced to 30mg BD
30mg BD	Strictly 3-4 hours post dose	0.76IU/ml	No change
30mg BD	Strictly 3-4 hours post dose	0.72IU/ml	No change

Table 2:

Anti-Xa activity (units/ml)	Hold Next Dose	Dosage Change
<0.35	No	↑25%
0.35-0.49	No	↑ 10%
0.5-1.0	No	No
1.1-1.5	No	↓ 20%
1.6-2.0	3h	↓30%
>2	yes	↓ 40%

[a]consider rechecking anti-Xa prior to next dose to ensure anti-Xa < 0.5 units/ml

[b]Nomogram not to be used for 1.5mg/kg OD dosing

3.3. Case 2

Mr. W, a 58-year-old Chinese male, had a large (7.2x7.8x9.5cm) heterogenous mass in the liver, which was concerning for hepatocellular carcinoma. A staging CTTAP showed bilateral pulmonary embolism without right heart strain. There was thrombosis seen in the right and middle hepatic veins, extending into the inferior vena cava, portal vein and its branches and the superior mesenteric veins. He was initially treated with SC Enoxaparin 1mg/kg BD (Body Weight 58.8kg). Unfortunately, he developed back pain with acute Hb drop two weeks later, which was worrisome for retroperitoneal hemorrhage given large liver mass on anticoagulant. Enoxaparin was held off temporarily. A CTAP reported new and worsening hemoperitoneum likely secondary to hepatic tumor rupture and intra-tumoral bleeds. He underwent VIR guided angioembolization of the posterior sectoral branch of the right hepatic artery.

3.4. Outcome and Follow Up

Mr. W was reassessed for suitability of resuming Enoxaparin one week later when his Hb and hemodynamics were stabilized. SC Enoxaparin was resumed at 60mg BD with anti-Xa peak level monitoring. A lower therapeutic range of 0.5IU/ml to 0.6IU/ml was targeted in view of recent tumor bleed. (Table 3) shows the peak anti-Xa levels and dose adjustment. Mr. W had his first peak anti-Xa level taken four to five hours after 3rd dose of Enoxaparin. It turned out to be 0.61IU/ml. Though the peak level was very close to the target level, as blood was taken slightly past the peak concentration timeline as shown in (Graph 1), true peak level was expected to be higher than 0.61U/ml. Therefore, SC Enoxaparin dose was reduced to 40mg BD. The second and third peak anti-Xa level were taken more than four hours after Enoxaparin administration. Both peak anti-Xa levels were very close to the target range. Hence, there were no dose adjustments, aiming to keep a lower normal therapeutic range between 0.5IU/ml to 0.6IU/ml. Unfortunately, his liver tumor markedly increased in size in a few weeks' time and had a second intra-tumoral bleeding. Due to exceedingly high bleeding risk, Enoxaparin was held off.

There are two learning points to highlight in this case. First, a true peak anti-Xa is technically difficult to obtain in the busy ward setting. Hence, interpretation of the results needs to be cautious.

Second, despite careful monitoring with narrower LMWH therapeutic range, patients with extremely high bleeding risk remain vulnerable. Balance between risk and benefits of anticoagulant becomes more difficult to achieve in this group of patients.

3.5. Case 3

Mr. L, a 67-year-old Chinese male, had multiple co-morbidities including Hypertension, Hyperlipidemia, Atrial Fibrillation, ischemic strokes, ischemic heart disease, mitral regurgitation s/p Mitral Valve Replacement on Warfarin. He was admitted to the hospital for a large spontaneous left inguinal hematoma. His International Normal Ration (INR) on admission was 3.4. His Hemoglobin was 7, which significantly dropped from 16. Warfarin was held off given supratherapeutic INR and low Hb. His coagulopathy was corrected with 4-factor PCC and Vitamin K.

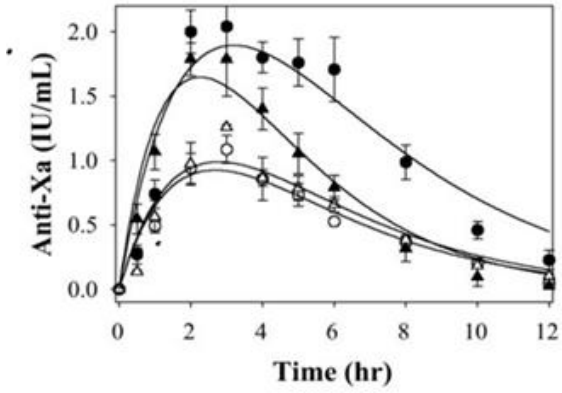
3.6. Outcome and Follow Up

He was closely monitored both clinically and biochemically. Only on Day 17 of admission, he was deemed safe to restart anticoagulant. SC Enoxaparin 60mg BD (Body Weight 67kg) was started with peak anti-Xa level monitoring in view of recent atraumatic hematoma with significant Hb drop while on Warfarin. The target therapeutic range was 0.5IU/ml to 0.7IU/ml. (Table 4) shows the peak anti-Xa levels and dose adjustment.

Enoxaparin dose adjustment was guided by the Nomogram as shown in (Table 3). Strangely, the peak anti-Xa level was higher despite decreasing Enoxaparin dose from 50mg BD to 40mg BD. This raised the concern on factors that could potentially affect the anti-Xa levels.

Table 3:

Enoxaparin Dose	Time of Blood Taken	Peak anti-Xa Level	Dose Adjustment
60mg BD	4-5 hours post 3rd dose	0.61IU/ml	Reduced to 40mg BD
40mg BD	More than 4 hours post dose	0.45IU/ml	No change
40mg BD	More than 4 hours post dose	0.47IU/ml	No change



Graph 1: Pharmacokinetics of enoxaparin, dalteparin, rdLMWH-1, and rdLMWH-2. The anti-Xa activity of enoxaparin(o), dalteparin(Δ), rdLMWH-1(•), or rdLMWH-2(▲) was measured after s.c. administration at 3 mg/kg.

Table 4:

Date	Dose of Enoxaparin	Anti-Xa level	Dose Adjustment
18-11-2021	60mg BD	1.19IU/ml	Reduced to 50mg BD
22-11-2021	50mg BD		
23-11-2021	Coffee ground aspiration		Stopped
24-11-2021	50mg BD	0.75IU/ml	Reduced to 40mg BD
26-11-2021	40mg BD	1.01	Reduced to 30mg BD
29-11-2021	30mg BD	0.58	No change
02-12-2021	30mg BD	0.73	No change
05-12-2021	30mg BD	0.75	No change
	Maintained at 30mg BD		

4. Discussion

All these three cases did not fulfil standard criteria that warrant peak anti-Xa level monitoring. However, all of them had high bleeding risk due to various reasons, such as intracranial surgery with complication of hematoma, large liver tumor and spontaneous intramuscular hematoma. Secondly, all of them were given standard Clexane dose of 1mg/kg BD, of whom two had supra-therapeutic peak anti-Xa level at first check, even though they were prescribed based on standard dosing regimen. One of them, unfortunately, developed a second tumor bleeding despite keeping a lower anti-Xa target level. Therefore, we hope to get some insight from the current evidence to help manage this group of patients safer. Some of the questions that we wish to be addressed include: 1) should peak anti-Xa level be monitored in future practice? 2) How safe is peak anti-Xa therapeutic range of 0.5-1.0IU/ml? 3) What are other independent factors associated with bleeding? 4) Is standard LMWH dosing regimen safe for all patients?

While current evidence only supports anti-Xa monitoring in some special populations as mentioned at the beginning of this article, concern of bleeding remains in some other groups of patients when receiving LMWH. Some authors recommend peak anti-Xa level monitoring in high bleeding risk population to ensure appropriate dosing of LMWH and avoid adverse events [4,8, 9]. They also urged samples for peak anti-Xa level check should be taken strictly 4 hours following administration of LMWH to avoid inaccurate results, inappropriate dose adjustments and increased costs if repeated samples needed [10,11]. A meta-analysis done by Wu et al. (2020) [12] suggested trough anti-Xa monitoring may be more appropriate for patients receiving LMWH as venous thromboembolism prophylaxis. While LMWH dose adjustment could be guided by the Nomogram, it should not replace the clinical judgement. Therapeutic anti-Xa range of 0.5-1.0IU/ml is based on consensus recommendation and experience, lacking large scale prospective study. The relationship between LMWH activity and clinical outcomes continues to be controversial4. Montalescot et al. (2004) [13] reported low anti-Xa activity as an independent predictor of 30-day mortality for patients with Acute Myocardial Infarction. They recommended to achieve minimum peak anti-Xa level of 0.5IU/ml whenever possible. Valve thrombosis and cardioembolic events have also been reported in patients with low peak anti-Xa levels [14]. Nieuwenhuis et al. (1991) [15] concluded that increased bleeding risk observed when mean anti-Xa greater than 0.8IU/ml. Based on limited observation with the three cases reported, a lower normal therapeutic range of 0.5-0.75IU/ml seems a reasonable consideration for patients with high bleeding risk.

In a prospective double-blind trial, Nieuwenhuis et al. (1991) [15] studied 194 patients who were treated for acute venous thromboembolism with Heparin or LMWH. A Univariate analysis was done to identify independent factors associated with bleeding. Results showed 1) WHO performance score, 2) Body surface area, 3) history of bleeding tendency such as intracranial bleed, hemorrhagic pericarditis, hematuria, intestinal bleeding, post op bleeding etc., 4) recent trauma or surgery are important prognostic factors for bleeding. WHO performance score ranges from 0 to 4, 0 being fully active and 4 being completely disabled. Patients with WHO Grade 4 had an eightfold increase in bleeding risk compared with WHO Grade 1. Patients with a total body surface area less than 2m2 were observed to have a 7.3-fold higher risk of bleeding. The study proposed future study may consider whether choosing appropriate initial dose adapted to body surface area or weight to improve safe use of LMWH. Age and sex are not consistent risk factors for bleeding. The relationship between cancer and bleeding is unclear, which could be due to patient selection, specifically the type and stage of cancer. Standard dosing regimen is safe for the majority of low bleeding risk patients, however, there is no one size fits all. Sacha, Greenlee & Ketz (2016)4 reported standard LMWH dose for patients with extreme body weight had inconsistent therapeutic levels. Obese patients achieved therapeutic anticoagulation with lower than recommended doses; whereas underweight patients were often sub therapeutic on the recommended doses. In addition, patients with renal dysfunction tended to have therapeutic to subtherapeutic anti-Xa levels. Hence, it concluded that Enoxaparin has unpredictable pharmacokinetics in these three groups of high bleeding risk patients, which reinforced the need for anti-Xa monitoring to help with appropriate dosing.

5. Conclusion

LMWH is safe to use in most patients. Peak anti-Xa level could be considered to monitor LMWH activity in high bleeding risk population at appropriate time to avoid inaccurate results with inappropriate dose adjustment. Though a therapeutic range of0.5-1.0IU/ml is recommended based on consensus, a lower nor- mal range of 0.5-0.75IU/ml could be a reasonable consideration inhigh bleeding risk patients. A lower starting dose of LMWH could be another way to minimize the bleeding risk with peak anti-Xa monitoring. This should always be coupled with clinical judgement. Large scare prospective studies are needed to prove these recommendations.

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