Case Report

SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
Volume 10: 1–5
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DOI: 10.1177/2050313X221118200
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Critically ill patients with edema and ascites may experience subtherapeutic anti-factor Xa levels following abdominal subcutaneous enoxaparin treatment

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Abstract

Enoxaparin is a low molecular weight heparin that is principally prescribed for the treatment and prevention of thromboembolic disorders. In clinical practice, the abdominal site for subcutaneous enoxaparin administration is most preferable because of its simplicity and safety. However, subcutaneous enoxaparin bioavailability in critically ill patients with ascites is uncertain. According to this case report, the bioavailability and absorption of subcutaneous enoxaparin was potentially impaired in a critically ill patient with ascites and local edema based on the therapeutic drug monitoring of anti-factor Xa levels.

Keywords

Subtherpeutic anti-factor Xa levels, bioavailability, ascites, subcutaneous enoxaparin

Date received: 9 December 2021; accepted: 20 July 2022

Introduction

Enoxaparin is a low molecular weight heparin (LMWH) that is used to treat and prevent thromboembolic disorders.[1] The LMWHs exert their antithrombotic activity by binding to and accelerating the activity of antithrombin III. The activating antithrombin III, coagulation factor Xa, and factor IIa (thrombin) are inhibited. LMWHs also influence the regulation of the tissue factor (TF) pathway by releasing tissue factor pathway inhibitor (TFPI) from the endothelium. Furthermore, LMWHs inhibit the generation and activity of factor VIIa in an Antithrombin (AT)-dependent manner. Therefore, thrombin inhibition prevents fibrin and clot formation. In addition, the LMWHs administered in the recommended dose provide a weaker effect on platelet activation. For this reason, LMWHs are associated with a lower incidence of heparin-induced thrombocytopenia (HIT) compared to unfractionated heparin (UFH). The LMWHs such as enoxaparin and dalteparin have no clinical effect on prothrombin time or activated partial thromboplastin time (aPTT) Anti-Xa activity is used as a biomarker for treatment effects of LMWHs; however, routine monitoring is generally not recommended.[2–5] The LMWHs offer more advantages over UFH, including more predictable pharmacokinetic responses, improved subcutaneous (SC) bioavailability, longer half-life, and lower incidence of HIT.[6] Enoxaparin significantly reduces the incidence of venous thromboembolism in hospitalized patients without increasing the risk of major bleeding.[7] A systematic review and meta-analysis reported that LMWH was as safe and efficacious as UFH in patients undergoing chronic hemodialysis.[8]

The SC bioavailability of LMWHs is entirely absorbed (almost 100%) and concentrated primarily in plasma with minimal distribution in adipose tissue. The volume of distribution of enoxaparin is approximately 4–5 L, which is similar to the normal blood volume.[9,10] However, because LMWH elimination is mainly dependent on renal function, renal impairment might increase the risk of bleeding or a few major bleeding events, such as retroperitoneal and intracranial bleeding. Therefore, the anti-factor Xa (anti-Xa) level should be monitored to assess the degrees of anticoagulation

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in enoxaparin-treated hospitalized patients with renal defects. For a safe and effective anticoagulation management, this pharmacodynamic marker must be precisely obtained. The peak anticoagulant effect (represented as the anti-Xa level) was pragmatically monitored at 4 h after administering the enoxaparin. The therapeutic peak of anti-Xa was estimated to be between 0.5 and 1 IU/mL.[11] The general SC administration area included the abdomen, arm, and thigh, and the literature reported that the abdomen was the most preferred site for SC enoxaparin because of its lower pain intensity and large region for drug rotation.[12] The side effects of heparin preparation through the SC administration may result in bruising, pain, induration, and hematoma at the injection site which might restrict the area that could be rotated for future SC administration.[13,14]

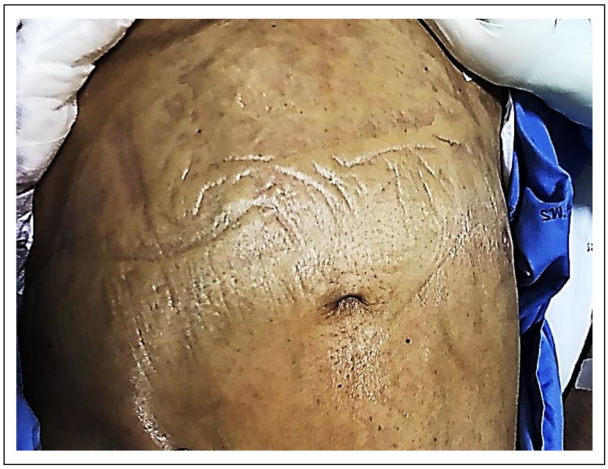

Figure 1. Abdominal subcutaneous tissue edema.

Case report

A 59-year-old Thai man with a dry weight of 43.6 kilograms (kg) was transferred from the medical intermediate unit to the medical intensive care unit on the fourth day of admission because he suffered septic shock with candidemia requiring vasopressor (norepinephrine) and intensive monitoring to improve the hemodynamic instability. He came to the hospital with acute progressive dyspnea and new-onset ascites with a low albumin gradient (Serum to Ascites Albumin Gradient: SAAG < 1.1 g/dL) and high protein. He had the following underlying diseases: type 2 diabetes, hypertension, old pulmonary tuberculosis, end-stage renal disease with no residual urine output requiring hemodialysis three times a week, triple vessel disease with left ventricular ejection fraction (LVEF) 27%, and peripheral artery disease (PAD) with chronic limb ischemia with dry gangrene status post a left percutaneous transluminal angioplasty stent with femoral artery endarterectomy. On the third day of admission, he suffered from dyspnea and was referred for an emergency multidetector computed tomography (MDCT) angiography to evaluate the suspected acute pulmonary embolism. It was reported that a small thrombus ($1.9 \times 0.7\,cm^2$) was seen in the right atrium (RA) adjacent to the tip of the central venous catheter. Then, he was prescribed an enoxaparin sodium prefilled syringe (Clexane® 4000 IU (40 mg)/0.4 mL, Sanofi, Paris, France) 40 mg SC once daily (OD) with bodyweight 46.8 kg for RA thrombus treatment. The recommended dose of enoxaparin is generally determined by bodyweight and renal function. The administration was at the same time each day (5 p.m.) to avoid hemodialysis treatments, which were normally scheduled in the morning (8–9 a.m.). In this case, the anti-Xa level was evaluated 4 h after the dose at 9 p.m. on a non-hemodialysis day to assess the efficacy and safety of enoxaparin. In addition, the anti-Xa levels were monitored because the patient had impaired renal function and needed an optimal enoxaparin therapy for a right atrial thrombus. The anti-Xa level was measured 4 h after the sixth once-daily dose of 40 mg enoxaparin, which was administered to the abdominal wall, as illustrated in Figure 1. The anti-Xa level was 0.72 IU/mL, which was within therapeutic levels (0.5–1.0 IU/mL) for a right atrial thrombus. The clinician provided enoxaparin 40 mg SC OD, with the SC injection at the abdominal wall with local edema. During his ICU hospitalization, the patient had peripheral edema, developed ascites, and gained weight (6 kg) due to ascitic fluid accumulation, hence necessitating an abdominal paracentesis. Because the patient had an operation to change tunneled-cuffed catheters (TCC) on day 11 following a suspected infected TCC, the enoxaparin was held for 4 days from day 10 to 13. After surgery, the patient experienced bleeding and clots in the endotracheal tube, so the clinician decided to withhold the enoxaparin for another two days. Although anti-Xa was within the therapeutic range, there was a risk that bleeding could be partially attributable to LMWH. Yet, LMWH-related bleeding is generally systemic, that is, bleeding affecting multiple sites rather than an isolated airway. In this case, the more likely causes of bleeding from endotracheal tube were airway mucosal injuries associated with long-standing intubation, localized inflammation of trachea and bronchi, and the acquired platelet dysfunction from renal failure. Because of a persistent thrombus in the RA, the patient was further examined by a cardiologist with a repeated echocardiogram. The cardiologist recommended restarting enoxaparin 40 mg SC OD as before and monitoring anti-Xa levels on a regular basis. After the fifth dose of enoxaparin, the peak anti-Xa level was 0.3 IU/mL, which was subtherapeutic. In order to achieve the therapeutic peak level (0.5–1.0 IU/mL), the enoxaparin dose was then increased to 60 mg SC OD, which was determined as 1.17 mg/kg/dose (current bodyweight of 55 kg) Yet, the peak anti-Xa level lowered to 0.25 IU/mL from the augmented enoxaparin dose. Because the anti-Xa level declined as the dose increased and was considered subtherapeutic, ascites at the abdominal wall were suspected to interfere with the SC enoxaparin absorption. As a result, the patient's treatment

continued with enoxaparin 60 mg SC OD as originally prescribed while switching the SC injection site from the abdominal wall to the deltoid to avoid any potential counter-intervention from the ascites. Figure 2 shows that the enoxaparin 60 mg SC OD administered to the deltoid arms without edema resulted in peak anti-Xa levels of 0.45 and 0.51 IU/mL, respectively. The anti-Xa peak levels were nearly within the therapeutic range (0.5–1 IU/mL) The physician chose to maintain the enoxaparin dose and did not increase it although the anti-Xa level appeared to be slightly subtherapeutic. This was due to the fact that the patient was still on hemodialysis and had previously experienced endotracheal tube bleeding.

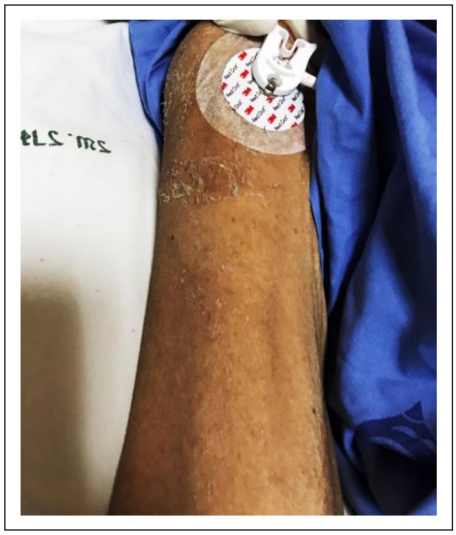

Figure 2. Deltoid area for SC enoxaparin injection.

The dose, duration, anti-Xa level, site of enoxaparin injection, vasopressor dose, and relationship with hemodialysis were indicated in Table 1. The anti-Xa level at the deltoid site tended to increase twofold when compared to that at the abdominal wall. As a result, for this patient with massive ascites, the deltoid region was likely a more suitable SC site to provide an improved bioavailability of enoxaparin.

Discussion

The patient had massive ascites, an end-stage renal disease, and a right atrial thrombus necessitating a hemodialysis and anticoagulation. He was prescribed the enoxaparin for the RA thrombus treatment. The dosage adjustment and the anti-Xa level monitoring were applied to ensure safety and optimal efficacy of enoxaparin.

According to this scenario, the UFH is more appropriate in patients with renal failure compared to LMWH. Nevertheless, the enoxaparin was considered the anticoagulation of choice for this patient. The reasons enoxaparin was selected in this patient are as follows: first, the potential interference of aPTT monitoring related to liver dysfunction as a result of right-side heart failure ascribable to a RA thrombus; second, the occurrence of fungemia which could cause the disseminated intravascular coagulation (DIC) and a bleeding risk; and finally, the avoidance of frequent blood samplings which would be labor-intensive and time-consuming amid the medical personal shortage during the COVID-19 pandemic. In addition, warfarin was not recommended in this patient given the risk of several drug interactions (e.g. fluconazole, midazolam) and hypoalbuminemia associated with warfarin overdose. The enoxaparin had previously been verified in

Table 1. The dose, duration, anti-Xa level, site of enoxaparin injection, vasopressor dose, and relationship with hemodialysis.

Hospital day	3	5	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Subcutaneous site		Abdominal wall				Hold due to TCC removal					Abdominal wall								
Enoxaparin dose		40 mg SC q 24 h									40 mg SC q 24 h					60 mg SC q 24 h			
Anti-Xa level				0.72										0.3					0.25
Average norepinephrine doses (mcg/kg/min)		0.07		0.12			0.07				0.07					0.1			0.1
Abdominal paracentesis							✓				✓			✓					
Hemodialysis day			✓		✓		✓				✓					✓	✓		

Hospital day	24	25	26	27	28	30	40	42	44	46	50	56	60	70
Subcutaneous site							Deltoid region							
Enoxaparin dose							60 mg SC q 24 h							
Anti-Xa level				0.45				0.51						0.48
average norepinephrine doses (mcg/kg/min)				0.04							0.02			
Abdominal paracentesis							✓			✓				
Hemodialysis day			✓			✓	✓			✓	✓	✓		

TCC: transitional cell carcinoma.

the treatment of right ventricular thrombi and proven to provide better clinical outcomes over UFH.[15] Enoxaparin was found to be as safe and effective as UFH in patients undergoing chronic hemodialysis from a systematic review and meta-analysis,[8] and also as safe and efficacious as intravenous UFH for submassive pulmonary embolism treatment.[9]

In this case report, the peak anti-Xa levels from the enoxaparin 60 mg SC OD were lower than that from the initial enoxaparin 40 mg SC OD despite the dosage increase. It implied that the increasing dose of enoxaparin could not enhance therapeutic anti-Xa levels at the abdominal wall administration site, and that injecting enoxaparin subcutaneously into such area in a patient with ascites might actually result in subtherapeutic anti-Xa levels. In this scenario, the deltoid region was a more appropriate site for SC enoxaparin administration as evidenced by the sufficient anti-Xa levels within a therapeutic range for a successful treatment by enoxaparin. The fluctuation of the anti-Xa levels in this patient was attributable to a few factors. First and foremost, the vasopressor and the hemodynamic instability causing reduced blood flow in the local SC tissue affected the bioavailability of SC LMWH. The previous studies indicate that patients receiving vasopressors had lower plasma concentrations of anti-Xa activity than those not on vasopressors and postoperative controls.[16] For this reason, critically ill patients who take vasopressors may require higher doses of LMWH or a different mode of drug administration to attain adequate thrombosis prophylaxis. The previous study reported that the intravenous administration of LMWH has shown to produce a higher peak anti-Xa level compared to the SC LMWH administration in critically ill patients who received the concomitant vasopressor and LMWH.[17] Second, SC edema might have impaired the absorption of SC drug injection as was previously reported in the insulin given by edema SC in diabetic patients.[18] However, it should be noted that the pilot study has shown that there was no clinically relevant difference in anti-Xa activity after SC administration of LMWH between patients with and without SC edema.[19] The pharmacokinetics and pharmacodynamics of enoxaparin have been tested in multiple trauma patients. The anti-Xa activity was significantly lower in edematous trauma patients as defined by peripheral edema and increased body weight of more than 10 kg.[20] The site and route of injection in patients with SC edema must be considered in this specific clinical condition. In spite of the lack of sufficient definite evidence that ascites may interfere with the enoxaparin absorption, which could explain why the anti-Xa levels were subtherapeutic in patients who were given enoxaparin at the abdominal wall, the direct comparison of anti-Xa level at the different sites of LMWH SC injection (for instance the abdominal wall and the deltoid) is essential and needs to be further studied in a prospective way. In this report, the author hypothesized that SC enoxaparin was transported into the interstitial space of the hypoderm which contains few arterioles and venues, and therefore the unabsorbed drugs were concentrated at the injection site in ascites patients with hypoalbuminemia. This finding implies that the site of SC enoxaparin injection should be considered to accommodate patients with ascites problems. According to the study, abdomen should not be used as the only preferable SC site for enoxaparin injections in patients with edematous state, including ascites. Further research is needed to provide a more consistent, scientific, conclusive, and logical approach to the clinical usage of enoxaparin at the SC site for patients with ascites.

Conclusion

In general clinical practice, abdominal site for SC enoxaparin administration is most preferable due to a number of advantages including its convenience and safety. However, according to this case report, the bioavailability and absorption of enoxaparin injected subcutaneously at the abdomen wall was potentially impaired in a critically ill patient with ascites and local edema based on the therapeutic drug monitoring of anti-Xa levels.

Acknowledgements

The author(s)would like to thank you the patient in this case for his contribution and the author(s) wish to thank Authorea for preprinting this manuscript.

Author contributions

Vichapat Tharanon: informed consent, collected, analyzed and interpreted data, wrote and revised manuscript.
Theerasuk Kawamatawong: analyzed and interpreted data, wrote and revised manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval

Ethical approval to report this case was obtained from the Institutional Review Boards of Mahidol University (MURA2021/586). The date of approval is 19 July 2021.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

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