CASE REPORT

Enoxaparin-induced hepatotoxicity: an under-recognised complication of enoxaparin therapy

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SUMMARY

Low-molecular-weight heparins including enoxaparin are commonly used for anticoagulation as prophylaxis and treatment for deep vein thrombosis (DVT). Prescribers of enoxaparin monitor for common side effects, such as bleeding and thrombocytopenia, but hepatotoxicity, a less common and under-reported adverse effect, may be overlooked. This report describes a case of enoxaparin-induced hepatotoxicity in a 57-year-old man who was started on the drug for a DVT. Within 3 days of taking enoxaparin, elevated transaminases were noted, and the drug was discontinued after 6 days. Similar to other published reports, the patient's transaminases peaked 1 day after discontinuation of the drug and then trended down to normal over 32 days.

BACKGROUND

This report describes the case of a 57-year-old man who started administering enoxaparin for a deep vein thrombosis and subsequently developed elevated liver transaminases. Though there are other reports of adverse hepatic effects from low-molecular-weight heparins, this seems to be an under-reported event, especially given the widespread use of this type of medication for anticoagulation.^{1–7} We hope to increase awareness among the medical community of hepatic injury as a side effect of enoxaparin, a commonly used anticoagulant medication.

CASE PRESENTATION

A 57-year-old Caucasian man presented to his general practitioner with discomfort and swelling in his right calf which had developed over several days. The week prior to presentation, he had driven in his automobile for 6 hours to visit family. His medical history included hyperlipidaemia, hypertension and obesity. The patient was taking no medications at the time. The patient did not use tobacco products, caffeine, alcohol or recreational drugs. He was employed as a maintenance worker.

On physical examination, the patient's vital signs included a pulse of 64 bpm, a blood pressure of 164/104 mm Hg and temperature and respiratory rate within the normal limits. He reported discomfort in his right leg and was found to have swelling of the mid-right calf measuring 43 cm in diameter. No erythema or palpable cords were appreciated. He was referred for lower extremity venous duplex ultrasound, which indicated an acute occlusive deep venous thrombosis of the right posterior tibial veins in the right calf. The patient was started on 1 mg/kg (100 mg) enoxaparin subcutaneously two times per day and 10 mg of warfarin daily. He was also started on lisinopril to treat hypertension.

Three days after starting enoxaparin and warfarin, liver enzyme elevation was noted (see [table 1](#)). Liver function tests had been obtained to establish a baseline in the setting of obesity and hyperlipidaemia. Alanine aminotransferase (ALT) was 88 U/L (7–40 U/L), and aspartate aminotransferase (AST) was 59 U/L (12–45 U/L). His direct and total bilirubin and alkaline phosphatase were within the normal limits, and by patient report, he was feeling well. Six days after starting enoxaparin, his ALT was 176 U/L and AST was 98 U/L. The patient's enoxaparin was discontinued. He continued taking warfarin and lisinopril. Repeat transaminases 1 day after discontinuing the enoxaparin showed a peak ALT of 257 U/L and AST of 135 U/L.

INVESTIGATIONS

α -1 Antitrypsin, ANA-antinuclear antibodies, hepatitis B core, surface antibody and surface antigen, and hepatitis C antibody titres were within the normal limits. Hepatic imaging was not performed because liver enzymes began trending down within 2 days of discontinuing the enoxaparin. Normal laboratory results in conjunction with the patient's history and physical examination helped exclude viral fever, hepatitis B and C, liver cancer and alcohol use as other causes of transaminitis.

DIFFERENTIAL DIAGNOSIS

Enoxaparin appeared to be the causative agent, but we considered other possible aetiologies for this patient's transaminitis. Acute viral hepatitis is a common cause of transaminitis, but this patient's hepatitis B and C serologies were within normal limits, making this unlikely. Non-alcoholic fatty liver disease, also known as steatohepatitis, was another possibility given the patient's history of obesity and hyperlipidaemia.⁸ However, his liver enzymes rose acutely rather than steadily over time, making a chronic process less likely. Budd–Chiari syndrome, or hepatic vein thrombosis, is a rare cause of elevated transaminases, and this patient lacked the typical signs and symptoms, including abdominal pain, jaundice and hepatosplenomegaly. The patient was taking lisinopril and warfarin, which have also been associated with transaminitis.⁸ However, the patient's transaminase values resolved to normal while still taking these medications making them less likely the causative agents.

TREATMENT

When the elevated transaminases were discovered, enoxaparin was withdrawn. The patient and liver function tests were followed over the next 5 weeks.

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Table 1 Pertinent laboratory values

	Baseline, 1 year prior		Day 3	Day 6		Day 7	Day 8	Day 15	Day 18	Day 32
ALT (7–40 U/L)	27	Lovenox started	88	176	Lovenox discontinued	257	136	64	46	33
AST (12–45 U/L)	22		59	98		135	29	23	20	22
Alkaline phosphatase (30–115 U/L)	60		66	66		70	60	68	66	64
Total bilirubin (0–1.2 mg/dL)	0.6		0.6	0.6		0.5	0.5	0.5	0.6	0.8
Direct bilirubin (0–0.4 mg/dL)	0.1		0.1	0.1		0.1	0.1	0.1	0.1	0.1

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2 A comparison of published cases of enoxaparin-induced liver injury

Case	AST (U/L) level and timing	ALT (U/L) level and timing	Alkaline phosphatase (U/L) level	Other abnormalities	Time to resolution
Carlson ³	147 at 7 days	93 at 7 days		Abdominal pain	18 days
Baker ¹	228 at 3 days	465 at 4 days	191 at 4 days	Nausea and vomiting	3 months
Hui 26-year-old woman during challenge ²	110	170	313 at 1 month	Liver biopsy showed ballooning degeneration, scattered necrosis, macrovesicular fatty changes	2 months
Hui 33-year-old man ²	103 at 10 days	283 at 10 days	No change	Decreased serum complement 3 activity	3 months
Arora 65-year-old man ⁴		992		Nausea, jaundice, anorexia	
Arora 75-year-old man ⁴		600 at 1–2 days			
Our case	135 at 7 days	257 at 7 days	No change	No symptoms	32 days

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

OUTCOME AND FOLLOW-UP

The patient's transaminases trended down and were back to baseline, as compared to values from 1 year prior, on day 32. On follow-up physical examination 8 days after initial presentation, he had no signs of liver failure and right leg swelling had resolved.

Over this period, the patient's albumin remained stable at 4.3–4.4 g/dL (3.5–5.0 g/dL). No kidney dysfunction was evident as demonstrated by a blood urea nitrogen range of 16–20 mg/dL (10–26 mg/dL), creatinine 0.9–1.0 mg/dL (0.4–1.4 mg/dL) and eGFR >60 mL/min.

DISCUSSION

Anticoagulant-induced liver injury was first documented more than 40 years ago.^{1 6} Unfractionated heparin compounds have a described association with liver injury.⁷ There have been several published reports of elevated transaminases resulting from enoxaparin use^{1–7} (see table 2). This is an uncommon event, and evidence from FDA Adverse Event Reporting System has indicated 4% of reported enoxaparin adverse events involved hepatic toxicity.⁹ The Naranjo adverse drug reaction probability scale indicates enoxaparin as the probable source of adverse reaction (score of 5) in our case¹⁰ (see table 3).

The patient presenting with enoxaparin-induced liver injury (EILI) is likely to be asymptomatic, but symptoms may include abdominal pain or nausea.^{1 3 5} Hepatic laboratory analyses reveal elevations in transaminases to three times the upper limit of normal or greater and usually occur within a week of starting enoxaparin.³ Ultrasonography of the liver was obtained in several reported cases and was unrevealing.² Transaminases typically peak within 7–10 days and begin trending down to normal on cessation of the drug. Several theories exist as to the pathophysiology of liver injury, and the near universal ALT elevation in EILI suggests a direct toxic effect on hepatocytes.¹¹

Table 3 Naranjo adverse drug reaction scale¹⁰

Scoring: >9 definite, 5–8 probable, 1–4 possible, 0 doubtful	
1. Are there previous conclusive reports of this reaction?	Yes (+1)
2. Did the adverse reaction appear after the suspected drug was administered?	Yes (+2)
3. Did the adverse reaction improve when the drug was discontinued?	Yes (+1)
4. Did the adverse reaction reappear when the drug was re-administered?	Do not know (0)
5. Are there alternate causes that could, on their own, have caused the reaction?	Do not know (0)
6. Did the reaction appear when a placebo was given?	Do not know (0)
7. Was the drug detected in the blood or other fluids in known toxic concentrations?	Do not know (0)
8. Was the reaction more severe with increased doses/less severe with decreased doses?	Do not know (0)
9. Did the patient have a similar reaction to the same/similar drug in previous exposures?	No (0)
10. Was the adverse reaction confirmed by any objective evidence?	Yes (+1)
Total score	5

Harril *et al*¹¹ suggested there may be a specific hepatic intracellular biomarker, miR-122, which causes hepatocyte necrosis.⁵

Bleeding and its complications may be associated with anticoagulant use, and while healthcare providers may monitor for efficacy of anticoagulation, transaminase testing is not routinely performed. Our case demonstrates an association between use of enoxaparin and elevated liver enzymes. With this in mind, physicians may opt to monitor serum transaminase levels in patients initiated on enoxaparin and discontinue the medication if elevation in liver enzymes occurs. Knowledge of this adverse effect may reduce the amount of invasive workups usually

prompted by deranged liver function tests. Enoxaparin-induced hepatotoxicity is likely an under-reported adverse effect, and greater awareness may prevent possible hepatic injury due to this widely used drug.

Competing interests None declared.

Patient consent Patient consent was obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ Healthcare providers may monitor for efficacy of anticoagulation and signs of blood loss when prescribing enoxaparin, but transaminase testing is not routinely performed.
- ▶ In patients initiated on enoxaparin, particularly in those with known hepatic disease, physicians may opt to assess baseline liver function and to monitor liver function tests over the duration of treatment.
- ▶ Enoxaparin-induced hepatotoxicity is an under-recognized adverse effect and one that, if monitored, might prevent possible hepatic injury and reduce the amount of invasive workups usually prompted by deranged liver function tests.

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