



Enoxsarin Induced Fever after Orthopedic Surgery

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ABSTRACT

A fever above 38°C is a common complication in the first few days after major surgery. Drug-induced fever is the most common cause of fever among the noninfectious causes of postoperative fever. Antimicrobial drugs and heparin, widely used for venous thromboembolism prophylaxis after major orthopedic surgery, are the drugs most commonly associated with postoperative fever. This case study, showing that enoxsarin may be the drug responsible for unexplained fever, may help significantly reduce patient morbidity and the additional costs of investigating the underlying causes of fever. At this stage, the approaches of the clinical pharmacist to provide counseling services to the patient and the healthcare professional in the treatment of medications, the detection of side effects of medications and the suggestion of a solution are important.

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Introduction

Body temperature is one of the most important vital signs that should be monitored in all patients. Recognition of drug-induced fever is clinically important and carries undesirable consequences such as failure to establish a healthy etiologic relationship, additional testing, unnecessary treatment, and prolonged hospitalization. A fever above 38°C is a common complication in the first few days after major surgery (1,2). Drug-induced fever is the most common cause of fever among the noninfectious causes of postoperative fever (3,4). Drug-induced fever can usually occur hours or days after starting a new medication (5). However, it can occur at any time, including days or months later. If fever persists for more than 96 hours after drug discontinuation, drug suspicion is unlikely to be the cause (6).

Enoxsarin is a low molecular weight heparin commonly prescribed for the prophylaxis of venous thromboembolism in patients who have undergone postoperative hip/knee replacement or abdominal surgery. In the literature, repeated fever has been indicated as one of the possible side effects of enoxsarin use, but the exact incidence is not yet known due to lack of data. The use of heparins for thromboprophylaxis, especially in postoperative patients,

causes fever; it is a condition that complicates its diagnosis because it can be attributed to postoperative fever (7).

This prospective study is a single centre non-consecutive, a case of postoperative fever will be presented due to the use of enoxsarin. The patient was informed verbally that his condition would be presented as a case report.

Case Study

A 71-year-old obese man was hospitalized with severe pain and restricted movement in both knees. Bicomponent osteoarthritis was identified in both knees on exploratory and supplemental testing. One week after diagnosis, he underwent surgery for a bilateral total knee arthroplasty. The patient has no comorbidity. The patient has been on chronic oral aspirin 100 mg/day for more than 10 years. The patient's history of drug allergy was questioned, and we were informed that he did not have any drug allergy. The result of the COVID-19 PCR test performed on the patient confirmed that the patient was COVID-19 negative. On the day of surgery, enoxsarin was administered subcutaneously at a dose of 6,000 IU/0.6 mL 1x1 for prophylaxis of postoperative thromboembolism. One hour after the application, the patient showed a fever of 38.5 °C. Given the increase in fever, the internist followed the

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patient. Urine culture, blood culture, and chest X-ray for postoperative infection testing were evaluated, with no focus found that could cause fever. There is no evidence of upper respiratory tract infection or respiratory infection in the patient. Results of the postoperative full blood count, normal kidney function, no leukocytosis. The surgical wound is clean and there is no infection.

To control the fever, sodium metamizole was administered orally at a dose of 500 mg 2x1 and the fever was reduced. The patient's fever increased 1 hour after administration of enoxaparin during the 4 days he was hospitalized and fever decreased after administration of metamizole sodium. Medications administered from the day of surgery to patient discharge are listed in Table 1.

Table 1. Medications administered during hospitalization.

	Day 1	Day 2	Day 3	Day 4
Drugs/Doses				
	Gentamicin sulfate 160 mg/2 mL; 1x1 IV	Gentamicin sulfate 160 mg/2 mL; 1x1 IV	As a result of the consultation, the use of Gentamicin sulfate was discontinued, since it was thought that aminoglycoside antibiotics might cause fever.	
	Enoxaparin sodium 6000 IU/0.6mL 1x1 SC	Enoxaparin sodium 6000 IU/0.6mL 1x1 SC	Enoxaparin sodium 6000 IU/0.6mL 1x1 SC	Enoxaparin sodium 6000 IU/0.6mL 1x1 SC
	Pantoprazole sodium 40 mg IV solution for injection 2x1 IV	Pantoprazole sodium 40 mg IV solution for injection 2x1 IV	Pantoprazole sodium 40 mg IV solution for injection 2x1 IV	Pantoprazole sodium 40 mg IV solution for injection 2x1 IV
	Dexketoprofen trometamol 50 mg; 2X1 IV	Dexketoprofen trometamol 50 mg; 2X1 IV	Dexketoprofen trometamol 50 mg; 2X1 IV	Dexketoprofen trometamol 50 mg; 2X1 IV
	Cefazolin sodium 1000mg/4mL; 3X1 IV	Cefazolin sodium 1000mg/4mL; 3X1 IV	Cefazolin sodium 1000mg/4mL; 3X1 IV	Cefazolin sodium 1000mg/4mL; 3X1 IV
			Calithromycin 500mg/10mL 2X1 IV	Calithromycin 500mg/10mL 2X1 IV

The condition of the patient, who was discharged 4 days after the operation, is stable. The drugs prescribed for use at home when the patient is discharged are as follows;

Enoxaparin sodium 6000 IU/0.6 mL 1x1 Subcutaneous

Pantoprazole sodium 40 mg 1x1 Oral

Dexketoprofen trometamol 25 mg 2x1 Oral

Paracetamol 500 mg 2X1 Oral

Amoxicillin (875 mg) /clavulanic acid (125 mg) 2x1 Oral

After discharge, the patient applied enoxaparin at home for 4 days and 1 hour later the fever rose again and the fever decreased after administration of paracetamol. The patient was re-examined and no source of infection was found.

On the 8th day, only 5 reports on induced heparinized fever were found as a result of a comprehensive review of literature after consultation with the surgeon and clinical pharmacists who performed the operation.

The literature search was performed by searching the key terms enoxaparin-induced fever, enoxaparin-associated fever, enoxaparin-drug fever, drug-heparin fever, heparin-induced fever, and heparin-associated fever in MEDLINE, PubMed, Web of Science, Up to Date, Science Direct and Scopus databases. A decision was made to discontinue enoxaparin based on the presence of enoxaparin-induced fever, albeit in very limited numbers, in the literature.

After discontinuation of enoxaparin, aspirin was started as an antiplatelet therapy, after this change the fever did not rise again and the patient became stable. When the patient came to the hospital for follow-up after 1 month, the patient's condition was stable, and no complications related to the surgery were encountered.

Discussion

The use of heparins for thrombosis prophylaxis, especially in postoperative patients, leads to fever; it is a condition that complicates its diagnosis due to the possibility of being attributed to postoperative fever (7). Although the incidence of heparin-induced fever is unknown in the literature, 5 case reports were obtained as a result of our investigation.

In one case, a 66-year-old obese female patient developed fever versus enoxaparin administered for venous thromboembolism prophylaxis after undergoing right total knee replacement surgery (7).

In another case, a baby born after 26 + 3 weeks of pregnancy developed after recognizing coagulation disorders after detecting coagulation disorders with dalteparinin's fever (8).

In a different case, a 32-year-old patient with Guillain-

Barré syndrome was diagnosed with deep vein thrombosis on routine ultrasound and developed fever after heparin therapy (9).

Findings of another case, a 50-year-old man who underwent external fixation after a tibial plateau fracture developed fever to postoperatively administered enoxaparin. The patient's allergy to pork products was identified as the cause of the enoxaparin-induced fever (10).

Obtain results of another case, a 23-year-old patient was hospitalized with a burn covering approximately 32% of her body surface area due to the friction she suffered in a motorcycle accident, and underwent a right knee arthroscopy and skin graft. After the operations, fever occurred in response to thromboprophylactic administration of heparin (11).

Drug-induced fever is the most common cause of fever among the non-infectious causes of postoperative fever. Skin reactions and hypotension may accompany fever (3). In our case, fever was not accompanied by any skin reaction and/or hypotension in our patient.

The treatment of imprisonment with the hurting drug is the safest form of diagnosis and treatment. The drug should be discontinued, starting with the drug most likely to cause fever. If the fever rises after the suspect drug is re-administered to the patient, the diagnosis is confirmed and the drug is permanently discontinued to be replaced with the responsible alternative drug (4).

Because antimicrobial drugs are most commonly used in the postoperative period, they are the drugs thought to be most commonly associated with postoperative fever (4). Based on these findings, our patient's use of gentamicin sulfate was discontinued and instead clarithromycin was administered, but the fever did not decrease.

After a thorough evaluation of all medications used in our patient, the possibility that enoxaparin caused drug-induced fever was emphasized, enoxaparin use was discontinued and aspirin started, and it was decided that the fever was enoxaparin-related, based on the fact that the fever did not return after changing the medication.

Conclusion

Recognition of drug-precipitated fever is clinically important, and it results in unwanted effects including failure to set up a wholesome etiological relationship, greater tests, needless treatment, and extended hospitalization.

This case study, showing that enoxaparin may be the drug responsible for unexplained fever, can significantly reduce patient morbidity and the additional costs of investigating the underlying causes of fever. Drug treatment personnel, recognizing drug side effects and proposing a solution are important.

As a result of the literature review, it is thought that more

research should be done on heparin-associated fever; clinicians should be alert to the possibility of enoxaparin-induced fever.

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