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# Low Molecular Weight Heparins

Updated: November 13, 2017.

# OVERVIEW

## Introduction

The low molecular weight heparins enoxaparin, dalteparin and tinzaparin are purified fragments of natural heparins that have anticoagulant activity and are used to treat patients at high risk of venous thrombosis. The low molecular weight heparins are associated with serum enzyme elevations during therapy that are usually asymptomatic and resolve rapidly upon stopping; the low molecular weight heparins have not been implicated in cases of acute, clinically apparent, idiosyncratic liver injury.

## Background

Low molecular weight heparins are prepared from natural heparins isolated from porcine intestine or bovine lung by controlled depolymerization of the large natural heparin molecule (which has varying molecular weights averaging ~15,000 daltons) into smaller fragments and subsequent fractionation to obtain homogenous heparin fragments with biological activity and molecular weight averaging 4,000-5,000 daltons (range, 2,000-9,000 daltons). The low molecular weight heparins have the advantage of more favorable pharmacokinetics and fewer side effects, which allow for once daily administration and outpatient use. The onset of anticoagulation may be slower with low molecular weight compared to standard heparin, but the degree of anticoagulation is easier to maintain and manage. The mechanism of action of low molecular weight heparins is similar to that of standard heparin and involves binding to antithrombin III and inhibition of activated coagulation factors including thrombin and Factor IX. Current indications include prevention of deep vein thromboses in high risk individuals (such as after surgery or during immobilization), prevention of ischemic complications in patients with unstable angina (in combination with aspirin), and active treatment of deep vein thrombosis with or without pulmonary embolism (in combination with warfarin). Common side effects of the low molecular weight heparins include dizziness, fatigue, headache, indigestion, nausea, bleeding, ecchymoses, rash and urticaria. The dose regimen of the low molecular weight heparins varies by product, concentration units (mg vs anti-Factor IX IU) and indication. The typical regimen of treatment is once daily for 7 to 14 days, but longer term treatment is sometimes used in high risk situations including during cancer chemotherapy where there is a high risk of venous thomboses.

Enoxaparin (ee nox' a par' in) was the first small molecular weight heparin (average 4,500 daltons) to be approved for use in the United States (1993) and is available in liquid solution in several forms (ampoules, syringes) generically and under the brand name Lovenox.

Dalteparin (dal' te par' in) (average 5,000 daltons) was approved in the United States in 1994 and is available in liquid solution in single or multidose vials under the brand name Fragmin.

Tinzaparin (tin" za par' in) (average 4,500-5,500 daltons) was approved for use in the United States in 2000 and has more restricted indications. Tinzaparin is available as solution for injection in multidose vials under the brand name Innohep.

## Hepatotoxicity

The low molecular weight heparins have been associated with serum aminotransferase elevations in 4% to 13% of patients, but values greater than 5 times the upper limit of normal (ULN) are not common and occur mostly among patients receiving the highest doses. These elevations generally arise within 3 to 7 days of starting therapy and are usually mild, do not cause symptoms, and resolve rapidly once therapy is stopped. The enzyme elevations may improve with dose adjustment and sometimes resolve despite continuation of treatment using the same dosage. Recurrence of liver injury with restarting therapy is not invariable and the clinical implications of these abnormalities are not clear. The relative rates of serum enzyme elevations among the different low molecular weight heparins has not been clearly defined, but the abnormalities can occur with all of the currently available products, although perhaps at a lower rate than with standard heparin. Neither standard nor the low molecular weight heparins have been convincingly implicated in cases of acute, clinically apparent idiosyncratic liver injury with jaundice.

Likelihood score: E (although a frequent cause of asymptomatic serum enzyme elevations, the low molecular weight heparins are unlikely causes of clinically apparent liver injury).

## Mechanism of Injury

The low molecular weight heparins, like standard heparin, are likely to have a direct toxic effect on hepatocytes accounting for the frequency of serum enzyme elevations during therapy, particularly with higher doses. The mechanism of this injury is not known but has been reproduced in animal models.

## Outcome and Management

The serum aminotransferase elevations that occur during low molecular weight heparin therapy are usually self-limited and do not require dose modification or discontinuation of therapy. No convincing instances of clinically apparent or severe acute liver injury have been linked to the low molecular weight heparins in the published literature.

References to the safety and hepatotoxicity of the low molecular weight heparins are provided together at the end of the overview section on heparins.

Drug Class: Antithrombotic Agents, Anticoagulants

Other Drugs in the Subclass: Heparins, Heparin

# CASE REPORT

## Case 1. Asymptomatic aminotransferase elevations during enoxaparin therapy.

[Modified from: Hahn KJ, Morales SJ, Lewis JH. Enoxaparin-indued liver injury: case report and review of the literature and FDA Adverse Event Reporting System (FAERS). Drug Saf 2015: 2:17. PubMed Citation].

A 45 year old man with a dural venous thrombosis was anticoagulated starting with a heparin drip that was converted to a low molecular weight heparin, enoxaparin in a dose of 1 mg per kilogram subcutaneously twice daily. Before anticoagulation his liver tests were completely normal (Table). After 4 days of enoxaparin therapy serum aminotransferase levels were found to be elevated, although he had no symptoms of liver disease. He

denied a history of liver disease, drug allergies, alcohol abuse and risk factors for viral hepatitis. His other medications were not provided. A physical examination was evidently unrevealing. Laboratory testing showed an ALT 569 U/L, AST 340 U/L, Alk P 89 U/L [R ratio=20], bilirubin 0.7 mg/dL [direct 0.1 mg/dL] and INR 1.1. Tests for hepatitis A, B and C and for EBV and CMV infection were negative as were routine autoantibodies. Abdominal ultrasound showed no evidence of biliary obstruction or other abnormalities. Enoxaparin was continued for several days, but ALT and AST levels continued to rise and the low molecular weight heparin was discontinued on day 7. Thereafter, serum enzymes elevations improved and they were near normal 2 weeks later. He was never jaundiced or symptomatic. He was later found to have adenocarcinoma of the colon which was considered a possible cause of a hypercoagulable state accounting for the dural venous thrombosis.

## Key Points

| | |
|---|---|
| Medication: | Enoxaparin (1 mg/kg twice daily) |
| Pattern: | Hepatocellular (R=20) |
| Severity: | 1+ (enzyme elevations without jaundice) |
| Latency: | 4 days |
| Recovery: | Almost complete by 2 weeks |
| Other medications: | Not mentioned |

## Laboratory Values

| Days Since Starting | ALT (U/L) | Alk P (U/L) | Bilirubin (mg/dL) | Other |
|---|---|---|---|---|
| Pre | 33 | 78 | 0.3 | Admission |
| 1 | | | | Enoxaparin started |
| 5 | 579 | 89 | 0.7 | |
| 6 | 644 | 104 | 0.5 | |
| 7 | 770 | 103 | 0.4 | Enoxaparin stopped |
| 13 | 273 | 119 | 0.4 | Fondaparinux started |
| 22 | 70 | 97 | 0.5 | |
| **Normal Values** | **<41** | **<126** | **<1.2** | |

## Comment

This patient was found to have elevations in serum aminotransferase levels, without symptoms, jaundice or other liver test abnormalities, 4 days after starting subcutaneous enoxaparin for treatment and prevention of venous thromboses. Serum ALT and AST values continued to rise for the next two days, enoxaparin was stopped and the injury rapidly resolved. Liver injury did not recur upon switching therapy to fondaparinux, an oral anticoagulant that acts by inhibition of factor Xa. Typical of the liver injury that occurs in patients receiving low molecular weight heparins was the rapid onset (within 3 to 5 days of starting), rapid recover (generally within 1 to 4 weeks) and the absence of symptoms and jaundice. Some patients have mild increases in serum bilirubin and alkaline phosphatase, but they usually remain within the normal range. Indeed, without prospective monitoring, the injury may go undetected and resolve, even without discontinuation or dose modification. The injury seems to be partially dose related and the injury is not accumulative. The cause of the liver injury with heparins is unknown, but it resembles similar bouts of "transaminitis" due to high doses of penicillin (such as oxacillin) and bile acid resins (such as cholestyramine).

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Dalteparin – Fragmin®

Enoxaparin – Generic, Lovenox®

Tinzaparin – Innohep®

**DRUG CLASS**

Antithrombotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

# CHEMICAL FORMULAS AND STRUCTURES

| DRUG | CAS REGISTRY NUMBER | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Dalteparin | 9005-49-6 | Unspecified | No Structure |
| Enoxaparin | 679809-58-6 | Unspecified | No Structure |
| Tinzaparin | 9005-49-6 | Unspecified | No Structure |