

Anticoagulants and Transaminase Elevation

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Case 1: Mr F., a 65-year-old man with hypertension and atrial fibrillation, began long-term anticoagulation with warfarin 1 year ago. He presented with a 1-week history of nausea, anorexia, jaundice, and altered mental status. His laboratory workup showed elevated serum transaminases and direct bilirubin. Could warfarin be potentially responsible?

Case 2: Mr S., a 75-year-old man with diabetes and coronary artery disease, presented with an acute anterior myocardial infarction. Echocardiography showed a left ventricular aneurysm with apical akinesis and thrombus. He was started on enoxaparin, and 3 days later, he developed a rise in alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN). Could this laboratory abnormality be related to enoxaparin?

Epidemiology

Drug-induced hepatotoxicity is the most common cause of acute liver failure in the United States and is the most frequently cited reason for withdrawal of an approved drug from the market.¹ It occurs at rates of 1 in 1000 to 1 in 100 000 patients, making it difficult to detect in the premarketing

randomized controlled trials that are required for drug approval.²

Anticoagulant-induced liver injury has been infrequently reported. Case reports have described the association of anticoagulants with asymptomatic elevation of serum transaminases, clinically significant hepatitis, and fatal liver failure.^{3–22} As an increasing number of patients receive long-term anticoagulation for prevention of stroke and venous thromboembolism, the rare adverse event of anticoagulant-induced liver injury is gaining attention.

Ximelagatran is an oral direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin by thrombin. This agent is a prodrug and is converted to its active form, melagatran, via hepatic metabolism.²³ It has a short half-life, requires twice daily administration, and produces a predictable response after oral administration. It does not require anticoagulant-level or drug-level monitoring, and it has virtually no drug-drug or drug-food interactions.^{24–26}

The Federal Drug Administration (FDA) did not approve ximelagatran after review of 2 pivotal premarketing efficacy trials, Stroke Prevention Using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III

and SPORTIF V; a 6 times higher rate of serum transaminase abnormalities was found in patients receiving ximelagatran compared with those receiving warfarin.^{27–30} Among the 3700 patients randomized to ximelagatran, there was 1 case of biopsy-documented drug-induced liver failure leading to death (Figure) and a second probable case of drug-induced liver failure leading to coagulopathy, massive hemorrhage, and death.³¹

Clinical Significance of Transaminase Elevation

Levels of transaminases ALT and aspartate aminotransferase (AST) are sensitive indicators of drug-induced hepatocellular injury. Elevations in ALT and AST can occur from conditions other than liver injury, but ALT is relatively more specific because it is synthesized primarily by the liver. The normal range for any laboratory test is mean \pm 2 SD. By definition, 5% of results fall outside the normal range, and 2.5% may be above the ULN.³² Levels of ALT >3 times the ULN are often used as a possible signal for drug-induced hepatotoxicity.^{33,34}

An elevation in transaminase levels in conjunction with a rise in bilirubin level >2 ULN is a more ominous

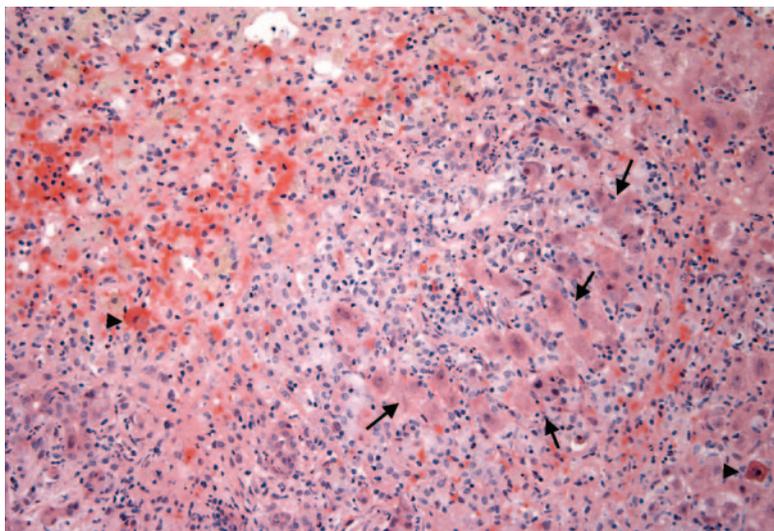
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(*Circulation*. 2006;113:e698-e702.)

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.105.603100



Liver biopsy in an 84-year-old man who had taken the anticoagulant ximelagatran to prevent stroke from permanent atrial fibrillation. The biopsy shows acute massive hepatic necrosis. There is extensive parenchymal architectural collapse with hemorrhage (white arrows), mixed inflammation, and focal clusters of residual hepatocytes (black arrows). There are darkly stained (resulting from nuclear collapse and apoptosis) pyknotic hepatocytes (acidophil bodies) indicated by black arrowheads. No normal hepatic parenchyma remains. On the day of the biopsy, the ALT was 1778 U, and the AST was 1630 U. The total bilirubin was 4.5 mg/dL. The biopsy findings are not etiologically specific but may be due to drug toxicity. He died 5 weeks after this biopsy. (Prepared by Jason L. Hornick, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston, Mass).

marker for drug-induced liver injury. This combination was first noticed in 1978 by Hyman Zimmerman (cited in Reuben³⁵). He described drug-induced hepatic reactions that caused hepatocyte injury sufficient to affect global liver function and, in particular, to cause jaundice as a result of impaired bilirubin transport by the liver. Hepatotoxicity of such severity is likely to lead to patient death in 10% to 15% of cases, especially if the offending drug is not stopped.³⁵ This sequence of adverse events is now called Hy's Law. According to the Clinical White Paper on hepatotoxicity published by the FDA (November 2000), Hy's Law has been the basis for the rejection of several new drugs.³³

Magnitude of the Problem

Transaminase elevation in patients taking anticoagulant agents might be underreported. There are no guidelines that require monitoring of liver function in patients who are prescribed anticoagulants. We lack postmarketing studies and registries that assess the

long-term clinical outcomes of these patients.²

Oral Anticoagulants

Warfarin is the most common oral anticoagulant used in the United States. There have been case reports describing the association of warfarin with fatal liver failure. Warfarin is associated with a 0.8% to 1.2% risk of transaminase elevation >3 ULN.^{27,28,30}

Although there have been no long-term postmarketing trials or prospective registries in the United States, a large retrospective registry consisting of 4390 patients from Germany described the association of liver injury with phenprocoumon, a structurally similar coumarin analogue of warfarin and the most commonly used oral anticoagulant in Europe.³⁶ There was a 2% incidence of hepatitis and 0.2% incidence of liver failure.³⁷ Another German study described 8 patients on phenprocoumon with hepatotoxic adverse effects, 3 of whom developed liver failure, leading to 1 death and 2 liver transplants.³⁷ In some of these

patients, repeat challenge with warfarin resulted in recurrent deterioration of liver function.

With short-term therapy (prophylaxis against venous thromboembolism for <12 days), ximelagatran was not associated with abnormalities in liver function.³⁴ In trials evaluating long-term use, however, it was associated with a 7.9% incidence of transaminase elevation >3 ULN, 1.1% incidence of hepatitis, and a 1 in 2000 risk of dying from liver failure.³⁴

Another oral direct thrombin inhibitor, dabigatran, underwent evaluation in the Boehringer-Ingelheim Study in Thrombosis (BISTRO) I and II trials for prevention of venous thromboembolism after orthopedic surgery. Use of dabigatran for durations of 6 to 10 days resulted in a 1.5% to 3.1% rise in ALT >3 ULN. Elevations in serum alkaline phosphatase were also reported in some patients.^{38,39}

Parenteral Anticoagulants

Unfractionated heparin (UFH) and low-molecular-weight heparins can lead to transaminase elevation. UFH has been associated with transaminase elevation even with low subcutaneous prophylactic dosages, although at a lesser frequency than with higher therapeutic dosages. Transaminase elevations >3 ULN have been reported to occur in 5% of patients receiving UFH and in 4.3% to 13% of patients receiving the currently FDA-approved low molecular weight heparins (enoxaparin, dalteparin, and tinzaparin).⁴⁰⁻⁴² The hepatotoxic effects remained confined to transaminase elevations, reflecting possible hepatocellular injury, and were not associated with cholestasis or jaundice.^{6,14,15}

Recombinant hirudins such as lepirudin have been reported to be associated with a 6% risk of transaminase elevation, although there are no reports associated with argatroban or bivalirudin.⁴³ The indirect factor Xa inhibitor fondaparinux has been associated with >3 ULN elevation of ALT in 2.6% of patients.⁴⁴

Pattern of Liver Function Test Abnormalities and the Usual Course

The most common abnormality is elevation of serum transaminases (ALT and AST). Elevation of alkaline phosphatase has been reported with dabigatran, ximelagatran, and warfarin. Jaundice has been reported only with ximelagatran and warfarin. Prothrombin time and international normalized ratio (INR) are usually normal in clinically stable patients. Elevation in ALT and AST levels occurs within the first week of initiating therapy, although it can occur at any time during the course of treatment. After terminating the anticoagulant agent, transaminases usually improve or return to normal within 2 weeks. Although these laboratory abnormalities are believed to represent true hepatocellular injury, they often reverse even when the drug is continued. It is not clear why some patients adapt and others develop severe liver failure.⁴⁵

Is There a Common Underlying Mechanism?

The specific mechanism of transaminase elevation after anticoagulant use has not been identified and requires further research. Possible mechanisms for heparin include direct toxicity, hepatocyte membrane modification, and immune-mediated hypersensitivity reaction.⁶ Phenprocoumon can be associated with direct damage of hepatocytes by reactive metabolites, which may result in augmented antigenicity and consequent immunoallergic reaction. It can also be associated with high-energy reactions involving cytochrome P-450 enzymes, causing decline of adenosine triphosphate levels, loss of ionic gradients, cell swelling, and rupture.³⁷

How to Diagnose Anticoagulant-Induced Liver Injury

Encountering ALT or AST elevation in patients on anticoagulants can pose difficulty regarding the establishment of a diagnosis and causality. The gold

Clinical Diagnostic Scale

Component Elements	Score Attributed
Temporal relation between drug intake and reaction	
Time from drug intake to onset of first clinical or laboratory manifestation	
4 d to 8 wk (or <4 d in case of reexposure)	3
<4 d or >8 wk	1
Time from withdrawal of drug until onset of manifestations	
0 to 7 d	3
8 to 15 d	0
>15 d (except in case of drugs that persist for a long time; eg, amiodarone)	-3
Time from withdrawal of drug to decrease of ALT or AST <2 ULN	
<6 mo (cholestatic or mixed pattern) or 2 mo (hepatocellular)	3
>6 mo (cholestatic or mixed pattern) or 2 mo (hepatocellular)	0
Exclusion of alternative causes (viral hepatitis, alcoholic liver disease, biliary obstruction, preexisting liver disease, ischemic hepatitis)	
Complete exclusion	3
Partial exclusion	0
Possible alternative cause detected	-1
Probable alternative cause detected	-1
Extrahepatic manifestations (rash, fever, arthralgia, eosinophilia, cytopenia)	
4 or more	3
2 to 3	2
1	1
None	0
Intentional or accidental reexposure	
Positive repeat challenge test	3
Negative or absent repeat challenge test	0
Previous report in literature of cases of hepatotoxicity associated with drug	
Yes	2
No (drugs marketed for up to 5 y)	0
No (drugs marketed for >5 y)	-3

CDS scoring for drug-induced hepatotoxicity⁴⁶ is as follows: >17, definitive; 14 to 17, probable; 10 to 13, possible; 6 to 9, unlikely; and <6, excluded.

CDS score >9 indicates sensitivity of 70% to 88% and specificity of 92% to 99%.

standard for diagnosis is liver biopsy, but it is an invasive and potentially risky procedure.

The first step in the evaluation of an elevated ALT or AST level is to repeat the test. If still abnormal, try to rule out conditions such as alcohol ingestion, hepatotoxic co-medications, chronic hepatitis B and C, autoimmune hepatitis, nonalcoholic fatty liver disease, hemochromatosis, Wilson's disease, α -1 antitrypsin deficiency, and celiac sprue.³²

A clinical diagnostic scale (CDS) has been developed and validated for causality assessment of drug-induced liver damage (Table).^{46,47} CDS covers (1) time from intake to onset of reaction, (2) course of reaction after cessa-

tion, (3) exclusion of alternative reasons for liver damage by using detailed investigations, including liver biopsy, (4) positive response to reexposure, and (5) previous reports of liver injury associated with the drug. Patients with a CDS score >9 are considered to be at possible risk for drug hepatotoxicity. Healthcare providers under these circumstances should file adverse drug reaction reports to relevant drug safety-monitoring authorities.

Recommendations for Patient Management

Screening for liver function test abnormalities before starting anticoagulants is not a routine recommendation but may be considered if there is a known

preexisting liver disorder. Although the traditional wisdom among the hepatologists is that patients with preexisting liver disease do not have a higher risk for drug-induced hepatotoxicity, inasmuch as most reactions are idiosyncratic, recent controversies have challenged that assumption. If no other cause is apparent and if ALT or AST is elevated to >3 ULN in any patient on anticoagulant therapy, close follow-up is recommended.⁴⁸ If the trend shows a persistent rise, switch to another class of anticoagulant agent. If the bilirubin is elevated to >2 ULN and if there is a strong suspicion of the anticoagulant medication being the culprit, discontinue the anticoagulant immediately.

Fulminant hepatic failure can develop within 2 weeks of onset of hepatocellular injury. If there is evidence of encephalopathy with persistent jaundice and coagulopathy (as measured by an INR of 1.5 or greater) even after discontinuation of the anticoagulant, consider transferring the patient to a liver transplantation center.³⁴ Corticosteroid treatment may be used in patients with evident hypersensitive reactions, although controlled trials have not proven the efficacy of such treatment for the hepatotoxic adverse reactions of other drugs.⁴⁹ A cautious repeat challenge can be performed if the association is highly questionable and if no other drug is available for the treatment of a potentially life-threatening disorder.

Conclusion

In summary, anticoagulant-induced transaminase elevation is common and can be the initial marker of toxic liver injury ranging from mild acute hepatitis to massive hepatocellular necrosis with liver failure. Further research is required to better understand the outcomes and underlying mechanisms. There is a need to improve the recognition of this entity by clinicians. Increased awareness will help achieve the correct diagnosis, prevent unnecessary procedures such as liver biopsy, minimize expensive evaluations, and

prevent patients from developing fatal liver failure.

Review of Cases

Case 1

The patient presented with prodromal symptoms suggestive of acute hepatitis and had an ALT level of 992 U/L and direct serum bilirubin level of 2.5 mg/dL. His mental status and liver functions showed further worsening over the next 3 to 4 days. There was no bleeding from any site, and the INR was in the therapeutic range of 1.5 to 2.5. Warfarin was temporarily withheld during the inpatient stay, and liver functions gradually improved. No cause of hepatocellular injury was apparent from the history or laboratory workup. After he was discharged, the patient was restarted on warfarin and had a repeat hospitalization that was due to worsening of liver function. A switch was finally made from warfarin to enoxaparin as monotherapy, and the patient has been doing well since.

Case 2

Serum ALT levels start rising 6 to 8 hours after myocardial infarction, peak at 24 to 48 hours, and can remain elevated above normal levels for up to 6 days. Our patient was initially considered to have ALT elevation (levels=600 IU/L) that was due to acute myocardial infarction and was discharged home. He continued enoxaparin therapy at home because coronary bypass graft surgery was planned within 2 weeks. At the time of admission for coronary bypass graft surgery, the patient still had elevated serum ALT level (650 IU/L), prompting a further workup. A thorough history, examination, and extensive laboratory workup failed to identify any cause for hepatocellular injury. Enoxaparin was considered to be a possible cause and was discontinued. The patient received UFH and had improvement in ALT levels within 48 hours.

Disclosures

Dr Goldhaber receives clinical research funding from Sanofi-Aventis and Astra-

Zeneca and is a consultant for Sanofi-Aventis. Dr Arora reports no conflicts.

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