

Fatty liver and drugs

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Abstract. – Drug-induced liver diseases (DILD) are clinico-pathologic patterns of liver injury caused by drugs or other foreign compounds. Steatohepatitis is a rare form of DILD, and drugs account for fewer than 2% of non-alcoholic steatohepatitis (NASH). Drugs known to be capable of inducing steatosis and steatohepatitis can be divided into three broad groups: those that cause steatosis and steatohepatitis independently (e.g., amiodarone, perhexiline maleate); drugs which can precipitate latent NASH (e.g., tamoxifen); drugs which induce sporadic events of steatosis/steatohepatitis (e.g., carbamazepine). Clinical DILD syndromes include acute viral hepatitis-like injury, acute liver failure, cholestatic hepatitis, liver disease with signs of hypersensitivity, autoimmune hepatitis-like injury, acute venous-outflow obstruction, chronic cholestasis, cirrhosis, steatosis and steatohepatitis. The clinical picture is by no means dependent on the mechanism of injury (direct hepatotoxicity, idiosyncratic reactions, hypersensitivity reactions). Reliable diagnosis of drug-induced liver disease requires demonstration of close correlation between the patient history and clinical, laboratory, and histological data.

Key Words:

Steatohepatitis, Drugs, Hepatotoxicity, Cirrhosis.

Introduction

Drug-induced liver diseases (DILD) are clinic-pathologic patterns of liver injury caused by drugs or other foreign compounds^{1,2}. Their true incidence is unknown, but it has been estimated that, in the United States, severe adverse drug reactions (ADR) are responsible for close to 5% of all hospital admissions, and they are ranked from fourth to sixth among the leading causes of death³. In the 1970s, ADR were responsible for 2% to 5% of the hospital admissions for jaundice

in the United States, and in Europe they were the cause of 10% of all hospitalizations for hepatitis in the 1980⁴.

Steatohepatitis is a rare form of ADR, and fewer than 2% of all cases of non-alcoholic steatohepatitis (NASH) are attributed to drugs^{1,5}. Proof of the causative role of a drug or foreign compound in the development of steatohepatitis requires demonstration of a close temporal relationship between disease onset and drug ingestion, as well as the absence of liver disease before drug ingestion and recovery after drug withdrawal. Many of the reported associations between drugs and NASH are based on tenuous temporal relationships, and re-challenge data are rare; in some cases, the role of the drug is rendered additionally problematic by a high prevalence of NASH in the background population⁶.

In general, drug-induced steatohepatitis bears a closer resemblance to alcoholic liver disease than it does to the NASH associated with diabetes and the insulin resistance syndrome. Progression from fibrosis to cirrhosis can occur much more rapidly, within the space of weeks or months, whereas cirrhosis is extremely rare in NASH-NAFLD patients and when it does occur it develops slowly over decades⁷.

The drugs known to provoke steatosis and steatohepatitis can be divided into three basic groups:

1. Drugs that can cause steatosis and steatohepatitis independently. These agents share a well characterized mechanism of hepatotoxicity. Examples include amiodarone, perhexiline maleate, and diethylaminoethoxyhexestrol.
2. Drugs that can precipitate latent forms of NASH. An example is tamoxifen, the non-steroidal drug used as an adjuvant in the treatment of breast cancer⁸.

3. Drugs that provoke sporadic cases of steatosis/steatohepatitis without any substantial pathological evidence of the mechanism of liver injury involved. For example, we recently observed a case of NASH that was associated with chronic use of carbamazepine⁹.

Pathogenesis

As noted above, drug-induced steatosis and steatohepatitis share many features with alcoholic liver disease, including the presence of significant inflammatory-cell infiltration with ballooning degeneration and the presence of Mallory bodies. Fat accumulates in parenchymal liver cells as a result of abnormal fatty acid metabolism, increased delivery of free fatty acids to the liver, increased mitochondrial synthesis of fatty acids, or impaired secretion of lipoproteins.

Several commonly used drugs can damage liver-cell mitochondrial function by interfering with fatty acid metabolism and mitochondrial respiration. High blood levels of some drugs can directly inhibit respiratory-chain enzymes (including those involved in beta-oxidation of fatty acids). The results are a decreased proton gradient, reduced cellular ATP, and depletion of NADH, which exerts an additional negative effect on beta-oxidation¹⁰. Excessive mitochondrial generation of reactive oxygen species (ROS) can easily provoke fat deposition with the formation of lipid peroxides, which can further impair respiratory chain enzyme activity and membrane transport capacity.

Free radicals or reactive oxygen species generated in tissues are effectively scavenged by the antioxidant defense system, which includes antioxidant enzymes, such as glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase. When the activity of this defense system decreases or when ROS production increases, oxidative stress may occur¹¹. Lipid peroxidation can cause hepatocyte death directly, by provoke ballooning degeneration and necrosis, or indirectly, through the generation of malondialdehyde and 4-hydroxynonenal. The latter compounds are in fact both capable of cross-linking structural proteins in the hepatocytes.

They are also potent chemoattractants of polymorphonuclear cells and hepatic stellate-cell stimulators¹².

Other studies have implicated the peroxisome proliferator-activated receptor- α , a ligand-dependent transcription factor that modulates both the microsomal and peroxisomal pathways of lipid oxidation and is involved in intracellular fatty-acid disposal. Peroxisomes contribute to the beta-oxidation of very long-chain fatty acids by increasing production of the free oxygen radical H_2O_2 ^{7,13}. We recently observed a case of massive steatosis following use of mefloquine, in which the injury seemed to be the result of a toxic effect on peroxisome activity¹⁴.

Each of these cascades of events may be sufficient to trigger the development of drug-induced steatohepatitis, but the actual risk also depends on nutritional, genetic, and environmental factors.

Two of the drugs that have been most frequently associated with fatty liver or steatohepatitis are amiodarone and tamoxifen.

Amiodarone

Amiodarone is a highly effective drug for the treatment and prevention of atrial and ventricular arrhythmias, but it is known to produce both thyroid and hepatic side effects. It is a well characterized hepatic mitochondrial toxin, which inhibits enzyme complexes in the electron transport chain, impairs β -oxidation, and uncouples oxidative phosphorylation. Asymptomatic elevation of serum transaminases, associated in some cases with mild cholestasis, is observed in 4-80% of patients treated with amiodarone¹⁵. (The wide variability of these figures is related to the clinical characteristics of the series being analyzed).

In contrast, symptomatic amiodarone hepatotoxicity develops in only 1-3% of all patients who use the drug. It can be quite severe, leading to acute hepatitis; chronic treatment can lead to the development of chronic liver disease with severe fibrosis and cirrhosis¹⁶.

Liver histology reveals steatohepatitis resembling alcohol hepatitis, characterized by Mallory bodies, ballooning degeneration, and inflammatory PMN infiltrates. Cases of microvesicular steatosis have also been reported¹⁷. The liver injury usually regresses

when the drug is discontinued, but full recovery may take weeks or months due to the drug's long terminal half-life¹⁸.

Tamoxifen

Tamoxifen is a non-steroidal antiestrogenic drug that is being used worldwide as adjuvant/palliative therapy for women with breast cancer. It is well known that the drug can cause hepatic steatosis but steatohepatitis is much more rare. Mild elevations of serum transaminases are commonly observed with rapid recovery after drug discontinuation¹⁹.

Again, the pathological picture generally resembles that of alcoholic hepatitis, but fibrosis or cirrhosis has also been reported²⁰.

A recent study has shown that tamoxifen causes steatohepatitis in a substantial percentage of cancer patients with pre-existing liver steatosis, particularly those with higher BMIs and high glucose and lipid levels at baseline.

The risk for potential progressive steatohepatitis associated with chronic use of tamoxifen must naturally be weighed against its beneficial effect for the woman with breast cancer. In any case, improved metabolic control can ameliorate the fatty liver disease caused by this drug, as demonstrated by a recent study on fibrate therapy²¹.

In conclusion, reliable diagnosis of drug-induced liver disease requires demonstration of close correlation between the patient history and clinical, laboratory, and histological data (if a biopsy has been performed). This is particularly true in a patient who already has fatty liver at the time of the ADR.

References

- 1) FARRELL GC. Drug-induced liver disease. Edinburgh: Churchill Livingstone, 1994.
- 2) GASBARRINI G, GRIECO A, MIELE L, et al. Epatite da farmaci (Drug induced liver disease). *Ann Ital Med Int* 2001; 16(Suppl. 4): 1S-80S.
- 3) LAZAROU J, POMERANZ BH, COREY PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; 279: 1200-1205.
- 4) LEWIS JH, ZIMMERMAN HJ. Drug-induced liver disease. *Med Clin North Am* 1989; 73: 775-792.
- 5) STRAVITZ RT, SANYAL AJ. Drug-induced steatohepatitis. *Clin Liver Dis* 2003; 7: 435-451.
- 6) BELLENTANI S, TIRIBELLI C, SACCOCCIO G, et al. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. *Hepatology* 1994; 20: 1442-1449.
- 7) FARRELL GC. Drugs and steatohepatitis. *Semin Liver Dis* 2002; 22: 185-194.
- 8) ELEFSINIOTIS IS, PANTAZIS KD, ILIAS A, et al. Tamoxifen induced hepatotoxicity in breast cancer patients with pre-existing liver steatosis: the role of glucose intolerance. *Eur J Gastroenterol Hepatol* 2004; 16: 593-598.
- 9) GRIECO A, ALFEI B, DI ROCCO P, et al. Non-alcoholic steatohepatitis induced by carbamazepine and variegate porphyria. *Eur J Gastroenterol Hepatol* 2001; 13: 973-975.
- 10) DESCHAMPS D, DEBECO V, FISCH C, FROMENTY B, GUILLOUZO A, PESSAYRE D. Inhibition by perhexiline of oxidative phosphorylation and the beta-oxidation of fatty acids: possible role in pseudoalcoholic liver lesions. *Hepatology* 1994; 19: 948-961.
- 11) BERSON A, DE BECO V, LETTERON P, et al. Steatohepatitis-inducing drugs cause mitochondrial dysfunction and lipid peroxidation in rat hepatocytes. *Gastroenterology* 1998; 114: 764-774.
- 12) FROMENTY B, PESSAYRE D. Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity. *Pharmacol Ther* 1995; 67: 101-154.
- 13) CHITTURI S, FARRELL GC. Etiopathogenesis of nonalcoholic steatohepatitis. *Semin Liver Dis* 2001; 21: 27-41.
- 14) GRIECO A, VECCHIO FM, NATALE L, GASBARRINI G. Acute fatty liver after malaria prophylaxis with mefloquine. *Lancet* 1999; 353: 295-296.
- 15) VORPERIAN VR, HAVIGHURST TC, MILLER S, JANUARY CT. Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol* 1997; 30: 791-798.
- 16) POUCELL S, IRETON J, VALENCIA-MAYORAL P, et al. Amiodarone-associated phospholipidosis and fibrosis of the liver. Light, immunohistochemical, and electron microscopic studies. *Gastroenterology* 1984; 86(5 Pt 1): 926-936.
- 17) JONES DB, MULLICK FG, HOOFNAGLE JH, BARANSKI B. Reye's syndrome-like illness in a patient receiving amiodarone. *Am J Gastroenterol* 1988; 83: 967-969.
- 18) SIMON JB, MANLEY PN, BRIEN JF, ARMSTRONG PW. Amiodarone hepatotoxicity simulating alcoholic liver disease. *N Engl J Med* 1984; 311: 167-172.
- 19) PRATT DS, KNOX TA, ERBAN J. Tamoxifen-induced steatohepatitis. *Ann Intern Med* 1995; 123: 236.
- 20) VAN HOOFF M, RAHIER J, HORSMANS Y. Tamoxifen-induced steatohepatitis. *Ann Intern Med* 1996; 124: 855-856.
- 21) SAIBARA T, ONISHI S, OGAWA Y, YOSHIDA S, ENZAN H. Bezafibrate for tamoxifen-induced non-alcoholic steatohepatitis. *Lancet* 1999; 353: 1802.