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MINIREVIEW

Drug-Induced Liver Injury

*Cholestatic Injury, Acute and Chronic**

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Cholestasis is the failure of bile to reach duodenum due to three different mechanisms: a. alteration of bile secretion by hepatocytes into the canaliculus with or without liver cell damage; b. obstruction of the intrahepatic bile ducts caused by diseases of ductules or small/medium bile ducts; c. obstruction of extrahepatic bile ducts. This short review focuses on drugs which may induce cholestasis by any of these mechanisms. (Pathology Oncology Research Vol 3, No 4, 260–263, 1997)

Key words: cholestasis, drug-induced

Introduction

Cholestasis is the failure of bile to reach the duodenum. Bile is normally secreted by the hepatocytes into the canaliculus, an intercellular space between adjacent hepatocytes. Bile is drained at the periphery of the hepatic lobule by the ductules (or cholangioles), lined by cuboidal biliary epithelial cells and unaccompanied by arterial or venous branches. From the ductules, bile is collected by portal (interlobular) bile ducts, accompanied by arterial and portal venous branches. Bile ducts are referred to, according to their diameter, as small (less than 100 μm), medium (approximately 100 μm) and large (more than 100 μm).[1]

Cholestasis may be due to three different mechanisms.[2]

1. The alteration of bile secretion by hepatocytes into the canaliculus. In this case, cholestasis may be/or not associated with some degree of liver cell damage. Hepatitis is described as "cholestatic" when cholestasis dominates the picture.

2. The obstruction of the intrahepatic bile ducts. This is usually due to diseases of the ductules or of the small or medium bile ducts (primary biliary cirrhosis, primary sclerosing cholangitis, obstruction by tumor or by lymphoma).

3. The obstruction of extrahepatic bile ducts by a tumor or a stone.

Drugs may induce cholestasis by any of these three mechanisms.[3,4] The most usual type is hepatocellular cholestasis, pure or due to cholestatic hepatitis. Less frequently, drugs may cause cholestasis by obstruction of the ductules or small bile ducts. Some drugs may cause obstructive lesions of the extrahepatic bile ducts.

Cholestasis may be acute (less than six months' duration), or prolonged (more than six months).

Acute Cholestasis

Pathology

In pure cholestasis, the hepatocytes bear brownish granules in cytoplasm. Canaliculi are dilated and contain bile pigment material. Enlarged Kupffer cells may also contain bile pigment. This predominates in the centrilobular zone. In cholestatic hepatitis, the features of cholestasis are associated with a variable amount of liver cell necrosis and with inflammatory infiltration by mononuclear cells and sometimes eosinophils. In some cases, the portal inflammation is marked.[5,7]

Upon electron microscopic examination, the canalicular lumen is dilated, the microvilli diminish or disappear, and a thick network of pericanalicular microfilaments develops.

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Drugs causing acute hepatocellular necrosis[6,7]

A. Sex hormones

Cholestasis occurs in women taking *oral contraceptives* with an estimated prevalence of approximately 1:10.000 in Europe and North America and in 1:4000 in Chile and Scandinavia. The prevalence may be lower because of the low oestrogen content of the pills now used. There is an association between oral contraceptive-induced cholestasis and cholestasis of pregnancy. Patients with benign recurrent cholestasis, Dubin-Johnson syndrome or an underlying liver disease, such as primary biliary cirrhosis, may also be more likely to develop this condition. It appears that cholestasis develops predominantly in genetically predisposed women.

In high therapeutic doses, *androgens* may induce cholestatic jaundice. Steroids with a C-17 methyl or alkyl group are more prone to induce cholestasis than non-C-17 substituted ones, but the latter may also induce liver function test abnormalities or jaundice. *Sex hormone antagonists* may induce abnormalities of liver function tests and, in few patients, jaundice.

B. Psychopharmacological agents

Phenothiazines and, more specifically *Chlorpromazine*, may cause cholestatic hepatitis: the incidence of jaundice is approximately estimated at 0.1 %. Jaundice appears within the first five weeks of therapy. Signs of hypersensitivity (fever, hypereosinophilia) occur in up to 70% of patients and a skin rash in 3-5% of cases. The typical histological picture includes cholestasis, little hepatocellular injury and a portal inflammatory infiltrate. Eosinophilic infiltration is seen in 25-50 % of cases. Cholangitis occurs in 25% of cases. The mechanism appears to involve a hypersensitivity reaction to the drug or one of its metabolites, coupled with direct toxicity. Approximately one-third of patients recover within four weeks after cessation of treatment; another third recover in four to eight weeks, and the remainder may have a prolonged course.

Other phenothiazines have also been reported to cause cholestasis: Fluphenazine, Prochloroperazine, Promazine, Thioridazine, etc. Cross-sensitivity between chlorpromazine and other phenothiazines has been observed.

Several cases of cholestatic injury have been attributed to some *Benzodiazepines:* chlordiazepoxide, diazepam, fluazepam, etc. However, benzodiazepines cause rarely hepatic injury.

Barbiturates: Phenobarbital has rarely been incriminated despite its widespread use. Several *tricyclic antidepressants* including desipramine, imipramine, iprindole and amitryptiline may cause cholestatic hepatitis. The histopathology may be similar to that seen with phenothiazines, including chronic cholestasis.

Some cases of jaundice have been reported in patients taking *amineptine.*

C. Antimicrobial and antiparasitic agents

Several antibiotics may cause cholestasis; the differential diagnosis with cholestasis related to the bacterial infection itself may be difficult: jaundice due to bacterial infections occurs within a few days after the beginning of infection; jaundice due to antibiotics occurs at a later time.

Erythromycin may induce jaundice in some patients, by a mechanism of hypersensibility with some degree of toxicity.

The *triacetyloleandomycin* is known to induce cholestatic jaundice. The incidence seems to be much higher when it is used in association with oral contraceptives. *Penicillins, cephalosporins, antituberculosis agents, sulphonamides, nitrofurantoin* have been rarely been incriminated as a cause of cholestatic injury. *Antifungal* agents (griseofulvin, ketoconazole) and *antihelmintic* drugs (thiobendazole) have been reported to cause cholestasis.

D. Antirheumatic and antigout drugs

Non-steroids, antiinflammatory drugs (sulindac, piroxicam, phenylbutazone and its derivatives) may cause cholestasis. *Gold salts* have been associated with cholestasis in numerous cases. The mechanism appears to be hypersensitivity. *Penicillamine* has been incriminated as a cause of several cases of jaundice. *Allopurinol* may occasionally induce cholestasis.

E. Oral hypoglycaemic drugs

Chlorpropamide causes cholestatic hepatitis in 0.5% to 1.5% of recipients. Other antidiabetic drugs *(tolbutamide, glibenclamide,* etc) are associated with some cholestatic diseases.

F. Antithyroid drugs

Jaundice has been described after treatment with several thiourea derivatives. In most cases, rash and fever suggest a hypersensitivity mechanism.

G. Cardiovascular, hypotensive and anticoagulant agents

Ajmaline and its derivatives can induce jaundice. It is usually associated with hypereosinophilia. The presumed mechanism is hypersensitivity. Occasionally, the *calcium-channel antagonists, captopril, methyldopa, hydralazine* and some drugs used as anticoagulant therapy can induce cholestasis.

H. Anticancer drugs and immunosuppressants

Azathioprine rarely causes cholestatic jaundice. Histology may show associated mild liver injury and sinusoidal dilatation. Other anticancer drugs *(cytosine arabinoside)* have been associated with cholestasis. With the widespread use of *cyclosporin* in patients with organ transplantation, several cases of cholestasis have been reported.

Acute Ductular and Ductal Cholestasis

They are characterized *pathologically* by acute cholangitis and/or cholangiolitis.[4,7]

- Cholangitis refers to oedema and acute inflammatory changes in and around portal bile ducts. When the lesions are marked, bile ducts are dilated and epithelial cells are swollen or necrotic. Inflammatory infiltrate is usually polymorphous and contains lymphocytes, neutrophils and eosinophils.
- Cholangiolitis refers to inflammation of the ductules and is characterized by ductular proliferation with oedema and infiltration by polymorphonuclear leucocytes in and around the ductules.

In some cases, acute cholangitis and/or cholangiolitis were associated with other liver lesions: granulomatous hepatitis, hepatocyte necrosis or feathery degeneration of hepatocytes.

Drugs causing acute ductular and ductal cholestasis

Acute cholangitis and cholangiolitis have been ascribed to the administration of a few drugs: *Ajmaline, Amitryptyline, Barbiturate, Carbamazepine, carbutamide, Chlorpromazine, Cimetidine, Cyproheptadine, Haloperidol, Imipramine, Chlorpropamide, Phenytoin, Thiabendazole, Tolbutamide, Troleandomycin.*

The main clinical manifestations are pruritus and jaundice. Associated features include hypersensitivity manisfestations such as cutaneous disorders or blood hypereosinophilia. The outcome of drug-induced acute cholangitis is generally good, with recovery after discontinuation of the causative drug. In some patients, however, acute cholangitis is followed by prolonged cholestasis. The mechanism of acute cholangitis and cholangiolitis involving small bile ducts is unknown. The association with granulomas and the frequent presence of hypersensitivity manifestations are suggestive of an immunoallergic mechanism.

Prolonged Cholestasis

In most cases, drug-induced acute cholestasis or mixed-pattern hepatitis is followed by a prompt recovery within a few weeks. In a few patients, however, the liver disease is protracted.

Drug-induced prolonged cholestasis may be defined by the persistence of jaundice for more than six months or the persistence of biochemical disorders consistent with anicteric cholestasis (high serum alkaline phosphatase and gamma-glutamyl transferase activities) for more than one year after drug-induced acute hepatitis, despite withdrawal of the causative drug, in the absence of past history of chronic disease of the liver and biliary tract. This definition is restrictive and somewhat arbitrary. This definition excludes cases in which the initial acute drug-induced liver injury is not well characterized and those in which asymptomatic, pre-existing liver disease cannot be eliminated.

Prevalence

Prolonged cholestasis following acute hepatitis has been reported with about twenty drugs. *Chlorpromazine* has been involved in more than thirty cases of jaundice lasting for more than one year. Prolonged cholestasis occurs in 7% of patients with chlorpromazine-induced acute hepatitis. The other main causative drug is *ajmaline*. For other drugs, only one or two cases of prolonged cholestasis have been reported: *Aceprometazine, Amitriptyline, Barbiturate, Carbamazepine, Carbutamide, Cimetidine, Cyproheptadine, haloperidol, Imipramine, Methyltestosterone, Phenytoin, Prochloperazine, Thiabendazole, Tiopronin, Tolbutamide, Triacetyl-oleandomycin, etc.*

Clinicopathologic features[4,8]

Analysis of the reported cases shows that two types of prolonged cholestasis can follow drug-induced acute hepatitis: a major form mimicking primary biliary cirrhosis and a minor form characterized by the disappearance of jaundice but the persistence of abnormal liver tests.

The major form is characterized by the persistence of jaundice; in some cases, hepatomegaly and splenomegaly are present. Serum alkaline phosphatase and gamma-glutamyl transferase activities are very high; serum concentration of bilirubin, bile acids and cholesterol are high; serum aminotransferase activities are moderately increased. The pathologic findings are similar to those observed in primary cirrhosis: in portal tracts, findings include the disappearance of interlobular bile ducts, a polymorphous inflammatory infiltration, a ductular proliferation and an extensive fibrosis; in lobules, cholestasis is always present, but inflammatory infiltration and necrosis are usually mild or absent. In some cases, a biliary cirrhosis can develop.

In the majority of patients, the prognosis appears to be relatively good: the patients become asymptomatic and the liver function tests tend to disappear slowly. By contrast in some cases, the syndrome seems to be irreversible.

The minor form is more frequent. Jaundice disappears rapidly; high serum alkaline phosphatase and gamma-glutamyl transferase activities persist. Liver lesions consist of partial disappearance of the interlobular bile ducts, mild inflammatory infiltrate and ductular proliferation. Portal fibrosis is absent. The prognosis is good. Abnormalities of liver tests tend to decrease progressively.

Pathogenesis

The sequential histologic examinations suggest that the disease is related to the progressive destruction of the small bile ducts. An autoimmune mechanism has been proposed on the basis of the following arguments: prolonged cholestasis occurs with drugs that induce acute hepatitis through an immunoallergic mechanism; persisting hypereosinophilia and circulating immune complexes were present in some cases.

Extrahepatic Cholestasis

Jaundice develops in some patients treated by direct administration of *floxuridine (FUDR)* into the hepatic artery for hepatic metastases from carcinoma. Jaundice is caused by sclerosing cholangitis, which develops generally several months after the onset of chemotherapy (in 5 to 25% of treated patients). FUDR-induced sclerosing cholangitis is characterized by multiple and segmental strictures of varying lengths. The pathogenesis may be related to a toxic effect of FUDR on arterioles supplying the upper part of the common bile duct, resulting in ischaemic lesions.

References

1. *Review by an international group*: Histopathology of the intrahepatic tree. Liver 3: 161-175, 1983.
2. *Erlinger S:* What is cholestasis in 1985? J Hepatol 1:687-693, 1985.
3. *Sherlock S:* Drugs and the liver.In: Diseases of the liver and biliary system, 6th edn. Oxford: Blackwell Scientific Publications: pp 295-322, 1991.
4. *Pessayre D, Larrey D:* Drug-induced liver injury. In: Oxford Textbook Of Clinical Hepatology. Oxford University Press: pp 875-902, 1991.
5. *Stricker BHCh, Blok APR, Desmet VJ:* Pathology of drug-induced hepatic injury. In: Drug-induced hepatic injury, 2nd edn. Elsevier: pp 51-70, 1992.
6. *Stricker BHCh, Biour M, Wilson JHP:* Individual agents: drugs. In: Drug-induced hepatic injury, 2nd edn. Elsevier, 1992.
7. *Zimmerman HJ, Ishak KG:* Hepatic injury due to drugs and toxins. In: Pathology of the liver, 3rd edn.Churchill Livingstone: pp 563-633, 1995.
8. *Degott C, Feldmann G, Larrey D, et al:* Drug-induced prolonged cholestasis in adults: A histological semiquantitative study demonstrating progressive ductopenia. Hepatology, 15:244-251, 1992.