Hepatitis vaccination in patients with chronic liver diseases

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Introduction

Infection with the hepatitis A virus (HAV) results in a self-limited disease, which does not become chronic. When acquired in adulthood, serious morbidity and even mortality can occur. Hepatitis B virus (HBV) infection, in contrast, can result in chronic carriership in 5-10% of infected adult patients. Hepatitis C virus (HCV) infection leads to chronicity in a majority of patients. Inactivated hepatitis A vaccine and recombinant hepatitis B (HB) vaccine have been extensively studied and shown to be safe and efficacious in preventing infection. In recent years, several studies investigated the outcome of HAV or HBV infection in patients with chronic liver disease (CLD) and the rationale of vaccinating these patients against HAV and HBV was discussed. This paper will focus on two issues :

1. HAV infection in patients with CLD, which was reviewed during an International Symposium in Phuket, Thailand, 26.04.1999
2. HBV-HCV coinfection, on the occasion of the recent registration of recombinant HB vaccine in Belgium for patients with hepatitis C

1. Hepatitis A

Hepatitis A superimposed on chronic hepatitis B infection

There are several reports on the outcome of hepatitis A in patients with underlying chronic HBV infection.

A large surveillance study of an outbreak of hepatitis A in Shanghai in 1988, affecting 310,746 people, showed a case fatality rate 5.6-fold higher in HBsAg carriers compared with non-carriers (1). Examination of Centers for Disease Control and Prevention (CDC) statistics in the USA has demonstrated an even 58.5-fold increase in the mortality rate in HBsAg carriers (2). This higher case fatality rate compared with the previous study may be explained by the higher mean age of the patients in the USA. Experience from a Japanese institution combined with a review of the Japanese literature showed that severe hepatitis A occurred primarily in patients with chronic hepatitis B and histologically confirmed chronic hepatitis or cirrhosis ; HAV infection in "healthy" HBsAg carriers was not different from infection in a control group of patients without HBV infection (3). In a prospective study of 90 patients with acute hepatitis A in Greece, mean ALT levels were 1.5-2 times higher in HBsAg carriers and patients with antibodies to HBV than in patients with no previous HBV infection, suggesting enhanced liver cell necrosis (4). The reason of the higher ALT in patients who had seroconverted after full recovery from HBV infection might reflect persistence of HBV in the hepatocytes of some of these patients.

It has been suggested that liver damage caused by HBV is associated with cell-mediated cytotoxicity to HBV infected cells. This mechanism has also been implicated in the pathogenesis of HAV infection. Hepatitis A might therefore enhance the cytotoxicity of HBV. Other case series (5-7) or case reports (8,9), however, suggest that the course and outcome of hepatitis A are not different in patients with underlying hepatitis B. These reports are limited by the small number of patients, the absence of control groups with hepatitis A alone and little information to distinguish HBsAg carriers from patients with chronic hepatitis B.

Hepatitis A superimposed on chronic hepatitis C

The burden of disease of HAV superinfection of patients with chronic hepatitis C has been considerably debated in the past years. A recent study by Vento *et al.* (7) reported on a 7-year follow-up of 432 patients with histologically confirmed chronic hepatitis C : of 17 patients with HAV superinfection 7 developed fulminant hepatitis and 6 died (case fatality rate 35%). Of these patients, none had cirrhosis. In 4 patients high titres of autoantibodies were found. It was therefore suggested that not the underlying damage caused by HCV could explain the massive hepatic necrosis produced as a response to hepatitis A in these susceptible patients but the triggering of an autoimmune response. This autoimmune response could have been partially primed by HCV.

The results of this prospective study contrasts with several retrospective surveys (10-14). Further prospective studies are therefore necessary to clarify this issue.

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Hepatitis A in CLD

Data on the influence of CLD on hepatitis A disease progress suggest a higher fatality rate.
Epidemiological data from CDC show a case fatality rate of 4.6% in patients with pre-existing CLD (primarily nonalcoholic cirrhosis), i.e. 23-fold higher than in patients without liver disease (2).

Four cases of fulminant hepatic failure and death secondary to acute hepatitis A in intravenous drug users with pre-existing alcoholic liver disease were reported by Akriviadis *et al.* (15).

A large survey conducted by Williams *et al.* (16) showed that HAV superinfection in patients with CLD did increase mortality to 27.5% compared with 3.4% of patients without.

Safety and immunogenicity of inactivated hepatitis A vaccine in patients with CLD

Two studies investigated the safety and immunogenicity of hepatitis A vaccine in patients with CLD (17,18). The vaccine appeared to be well tolerated. The geometric mean titres of anti-HAV were lower than those normally seen in healthy adults but titres were still protective.

Conclusions on hepatitis A vaccination in patients with pre-existing CLD

The International Symposium on hepatitis A vaccination in patients with CLD in Phuket (26.04.1999) reviewed the available data and reached following consensus :

1. In non-endemic areas hepatitis A infection can cause severe hepatitis, especially in adults
2. Certain groups of patients with hepatitis B infection, especially older people, those with chronic hepatitis or cirrhosis, can have a more severe outcome when infected with hepatitis A.
3. Based on currently available data, hepatitis A infection may also be more severe in patients with pre-existing chronic hepatitis C.
4. Data suggest that this is also the case in other, non-viral, CLD.
5. In developing countries, with improving sanitation and hygiene, there is an increasing number of adults who are susceptible to HAV.
6. Although hepatitis A is a vaccine-preventable disease and may ultimately be eradicated through universal vaccination, initially targeted groups should further be targeted for vaccination. These groups include those with CLD (viral and non-viral) and those at high risk of developing viral hepatitis.
7. The most appropriate time to vaccinate patients with CLD against hepatitis A is as soon as the diagnosis of CLD is made.

The 1995 World Health Organisation Bulletin stated that inactivated hepatitis A vaccine should be considered in persons with CLD caused by viral hepatitis or other etiologies (19). The Advisory Committee on Immunisation Practices (ACIP) of the CDC also recommends that patients with CLD receive hepatitis A vaccination (20).

2. Hepatitis B and C coinfection

Epidemiology

Hepatitis B and C virus are both transmitted by parenteral routes such as blood transfusion, parenteral drug use and haemodialysis. Transmission through inapparent percutaneous or mucosal routes may also occur. Although less efficient than for HBV, sexual and mother-to-child transmission of HCV is possible (21,22). As a consequence, dual infection by HBV and HCV is observed in some patients with acute or chronic liver disease. The seroprevalence of HBV and HCV in chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) was investigated by several authors. Around 10-20% of HBsAg chronic carriers in Asia and western countries have been reported to be positive for anti-HCV, while 2-10% of anti-HCV positive patients have markers of HBV infection (23,24).

Acute hepatitis

Several authors indicate that coinfection of HBV and HCV, acute HBV infection in a patient with pre-existing chronic hepatitis C or superinfection of HCV in a HBV carrier can lead to severe, even fulminant or subfulminant hepatitis (24-27).

Chronic liver disease

Liver disease in patients with coinfection of HBV and HCV appears to be more severe, clinically as well as histologically, than infection with HBV or HCV alone (28-32). The relative risk to develop cirrhosis was found to be 20 in HBsAg positives only, 49 in the presence of anti-HCV only, and 81.8 in patients positive for the two markers (33). "Past" HBV infection, with presence of only anti-HBc or HBV-DNA has been reported to play a role (32).

The report of Colombari *et al.* (34), however, does not show any effect of double infection on the cirrhotic evolution of liver lesions.

Hepatocellular carcinoma

Most case-control (29, 35-38) and prospective studies (39,40) have shown that patients with dual infection HBV and HCV are at greater risk to develop HCC than those infected with only one of the viruses. Also here "past" infection with HBV could still play a role. Some reports, however, do not show an increased risk for development of HCC in dual infection with HBV and HCV (41-43).

Response to interferon treatment

A few reported small case-series suggest a diminished efficacy of interferon treatment on HBV-HCV coinfection (23,31,44,45). This weak response might be a direct result of multiple viral infection or a consequence of the severity of the liver disease in coinfected patients.

Safety and immunogenicity of hepatitis B vaccine in patients with chronic hepatitis C

HBV vaccination has been reported to be less effective in patients with chronic liver disease (46). Seroconversion rates after three 10 µg recombinant HB vaccine was not different with regard to anti-HCV seropositivity, also the geometric mean anti-HBs values were not different (47). Durand *et al.* (48) report a seroconversion rate of 32/40 (80%) in patients with chronic hepatitis C (decompensated cirrhosis excluded) after three 20 µg doses of HBV recombinant vaccine ; the vaccine was also well tolerated. In a series of haemodialysis patients, HBV vaccination with three doses of 40 µg recombinant HB vaccine resulted in a similar seroconversion rate in anti-HCV negatives and positives ; the number of patients with a titre of $>$ 100 IU/L, however, was significantly higher in the anti-HCV negative patients (49).

Conclusions on hepatitis B vaccination in chronic hepatitis C

Coinfections of HBV and HCV are not infrequent. There are strong indications that acute coinfection of HBV and HCV or acute HBV infection in a HCV carrier can cause serious disease. There are also strong indications that patients with HBV-HCV coinfection develop more severe chronic liver disease and have a higher risk to develop HCC than those infected with only one virus. Moreover, in the case of coinfection, interferon therapy could be less efficaceous. The recombinant HB vaccine is safe and seems to give sufficient seroconversion in patients with chronic hepatitis C, although in more advanced liver disease, efficacy might be less. The National Institutes of Health Consensus Conference on hepatitis C of 1997 strongly favours HB vaccination of patients with chronic HCV (50).

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