Acute Exacerbation with Severe Jaundice in Chronic Hepatitis B Patients

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INTRODUCTION

Acute exacerbation of chronic hepatitis-B (CHB) is usually manifested by an abrupt elevation of serum aminotransferases, without accompanying severe jaundice, and usually proceeds to a spontaneous HBeAg clearance (McIntyre et al., 1991 a). Rarely, serum bilirubin may rise, but hepatic failure is rather rare (Hoofnagle et al., 1981; Sheen et al., 1985; Bortolotti et al., 1990; Meyer and Duffy, 1993). On the other hand, acute exacerbation of clinical symptoms with rise in both aminotransferases and bilirubin may have causes other than CHB; hepatitis C virus (HCV), hepatitis D virus (HDV), hepatotoxic drugs and alcohol are suspected to be as etiologic agents (Chu et al., 1989).

To evaluate or differentiate the causes of severe jaundice in patients with acute exacerbation of CHB, we have investigated comparatively between those patients with severe jaundice, and those without jaundice, who had visited our hospital in Taegu, Korea.

PATIENTS AND METHODS

Patients

Among the patients with HBsAg-positive chronic liver disease, and chronic active hepatitis (CAH), confirmed by liver biopsy, and patients with compensated early cirrhosis, we have divided them into two groups. The first group consists of 16 patients (14 men and 2 women ages 22 to 59 years) having abnormal liver function tests as well as severe clinical jaundice (study group). The second group consists of 13 patients (11 men and 2 women ages 21 to 50 years) with similar conditions but without severe clinical jaundice (control group). Two patients (both men) had been admitted to the hospital twice because of jaundice. Prior to the study began, all patients had had stable liver function tests without clinical jaundice, ascites, hematemesis
or hepatic encephalopathy. None of the patients in both study groups was chronic alcoholic, homosexual, or intravenous drug user, and none had received blood transfusion or traveled outside of South Korea.

**Laboratory Methods**

All the patients were tested for HBsAg, anti-HBs, HBeAg, anti-HBe, IgM anti-HBc, HBV DNA, anti-HAV IgM and anti-HCV on admission day. For these tests, commercially available solid-phase radioimmunoassay kits (Austria-II, Ausab, HBeAg, Corab, IgM anti-HBc, IgM anti-HAV: Abbott Laboratories, Chicago, IL), an enzyme immunoassay kit (Abbott HCV second-generation enzyme immunoassay) and a dot-blot hybridization assay using P32 for the detection and semiquantitation of HBV DNA were utilized. The Hitachi 747 autoanalyzer was used for all of the biochemical tests.

All the patients had a full range of clinical laboratory tests to evaluate the severity, sequelae and complications of their chronic liver disease. In addition, Tc99m liver scanning, a DICIDA biliary scan, ultrasonography, gastrofiberscopy and intravenous bolus abdominal CT were performed whenever necessary. Percutaneous liver biopsy was done in Case No.1 in the study group. After the discharge from the hospital, all the patients were followed as outpatients for continuous evaluation of the liver functions and for HBV markers a few times a year.

**RESULTS**

Among 16 patients with one or more episodes of sudden onset of severe jaundice and acutely elevated serum transaminases levels, 11 (69%) had recent (within 0.3-3 months) histories of taking biphenyl-dimethyl-dicarboxylate (PMC)(Xie et al., 1974; Lee et al., 1991) at the time of discovery of jaundice (Table 1). Other therapeutic agents taken at their own will by the patients were herval medicine, alcohol, a polysaccharide hepatotonic (Livax®) and NSAID (Tarivid®). Eleven patients in this group had cirrhosis, and 6 of these died of liver failure. The remainder have shown improvement to their previous stable conditions over an average of 3.9 months. The mortality rate therefore was 38% for the study group; 50% among the patients with CAH only, and 27% in those with cirrhosis.

In control group, only 1(7.7%) was diagnosed to have developed into liver cirrhosis clinically, and all the others showed improvement to the clinical levels as those prior to the exacerbation after an average time of 2.8 months(Table 2). Only one patient among them had history of taking a drug, PMC over 12 months. Two other patients, number 6 and 13, were treated with interferon alpha, when an abrupt elevation of transaminases was noted.

All of the 12 patients who took PMC had shown more significantly reversed AST/ALT ratios, compared with the patient who didn't
take PMC (Table 3, 4).

Cases Nos. 1 and 2 in the study group were readmitted twice for flare-ups of clinical symptoms accompanied by severe jaundice. Case No. 1, a 27-year-old man, was readmitted because of a flare-up of CAH after prescription of PMC. The correlation between changing levels of AST, ALT and bilirubin and PMC use of this patient is shown in Figure 1A. Four months after the first discharge, when he showed seroconversion from HBeAg positive to anti-HBe positive, HBeAg and HBV DNA reappeared in the serum. He had also shown fluctuating liver function abnormalities (Fig. 1B) without further drug exposure. He died of hepatic failure on the 45th day of his second admission.

The second case was a 23-year-old man who had been infected by vertical transmission. He was admitted the first time (case No. 10 in control group) because of acutely elevated AST and ALT levels during the 7th year of a known HBsAg-positive carrier state. One year later, he was admitted for the second time (case No. 2 in study group), because of severe jaundice and high AST and ALT levels after taking PMC for 3 months. The values for aminotransferases and bilirubin during the two episodes are shown in Figure 2.

In the control group, only one patient had cirrhosis clinically, and all the rest of the patients regained their pre-exacerbation disease status after an average time of 2.8 months (Table 2). Only one patient had a history of taking PMC, and another had taken herbal medicine. Two patients were receiving treatment with interferon-alpha, when abrupt elevation of aminotransferases was noted.

All 12 patients who were taking PMC showed markedly reversed AST/ALT ratio (McIntyre et al., 1991 b) (Table 3 and 4). In study group, HBeAg and HBV DNA were positive in 7 patients (44%) (Table 5). Seroconversion to anti-HBe positive was noted in one patient, but HBeAg and DNA reappeared 2 months later with disappearance of anti-HBe. In control group, HBeAg was positive in 13 patients (100%) and DNA was positive in 6 patients (46%), respectively. Seroconversion was noted in 11 (85%) after an average time of 1.8 years (Table 6). Seroconversion to anti-HBe positive and DNA-probe negative occurred in 7 of 13 patients, who originally were HBeAg and HBV DNA positive; 2 of these 7 had been treated with interferon. The annual rate of spontaneous seroconversion was 31% (4/13).

Anti-HCV was negative in all patients of both groups, although one patient in the study group had HCV RNA detected by polymerase chain reaction (PCR).

**DISCUSSION**

Spontaneous remission during the active disease phase of CHB infection occurs with rates from 2.7% to 30% of cases per year,
and the annual spontaneous HBeAg clearance rate has been reported as 16.3% (Liaw et al., 1984; Schiff and Schiff, 1993). Many such clearances (62.1%) are preceded by an abrupt elevation of serum ALT levels, and 23% of exacerbation episodes are followed by HBeAg clearance within 3 months (Liaw et al., 1984). Thus, not every exacerbation is followed by HBeAg/anti-HBe seroconversion, and the factors underlying spontaneous seroconversion are not yet clearly identified.

No patients in the study group showed seroconversion from HBeAg positive to anti-HBe positive, and only one patient showed newly developed anti-HBe after e-window phase (Liaw et al., 1984). Case No.1 showed transient seroconversion, but after 2 months, HBeAg reappeared with loss of anti-HBe. The causes of persistent chronic necroinflammatory disease activity in patients with CAH after seroconversion may be due to various concomitant diseases or continuing HBV replication (Hadziyannis et al., 1983; Matsuyama et al., 1985; Schiff and Schiff, 1993). A mutant virus that has a novel translational stop codon in the precore/core gene might have a part in continuous viremia causing relatively low, fluctuating levels of viral DNA in the serum, and more severe and rapidly progressive liver disease even after seroconversion (Chu et al., 1985; Bonino et al., 1986; Carman et al., 1989). In our study group, Seven patients showed a positive DNA-probe reaction, but only two of them revealed positive anti-HBe reaction. On the other hand, one patient in the control group was DNA-probe positive and antiHBe positive. Infection with other hepatotropic viruses does not appear to be a factor, as HCV testing was negative in all but (possibly) one patient. Also, although HDV testing was not carried out, the prevalence rate of this infection among patients in Taegu area, who also have chronic HBV infection, is only 2.5% and 0, among patients of CAH, and those with cirrhosis (Choi et al., 1987).

The differences between the study group and the control group were: (1) a greater severity of underlying chronic hepatopathy in the former; (2) status of HBV infection and HBV markers; (3) more use of PMC or other oral agents by the study group. The factors most often correlated with exacerbation were the history of taking PMC in the study group and seroconversion to anti-HBe positive in the control group.

PMC is a synthetic analog of Schisandrin C, one of the components isolated from Fructus Schisandraceae, which is a traditional Chinese medicine (Xie et al., 1974). Seems to improve the liver function and symptoms and in patients with HBV-related chronic active liver disease. In particular, it shows a dramatic effect on serum ALT, although the mechanism is unclear (Xie et al., 1974; Lee et al., 1991). This effect complicates the interpretation of laboratory results. In uncomplicated viral hepatitis, the AST/ALT ratio is usually below 1, but the ratio changes according to the progress of chronic liver
disease toward chronic hepatitis, cirrhosis and hepatocellular carcinoma-and chronicity can be suspected on this basis (McIntyre et al., 1991b). All patients in our series, who had taken PMC, showed a markedly reversed AST/ALT ratio, which returned to 1 or below in the non-cirrhotic patients after PMC was stopped. We conclude that interpretation of the AST/ALT ratio should be a good indicator for the patients taking PMC.

In addition, PMC might affect bilirubin metabolism, including jaundice. Many Korean patients with chronic viral liver diseases take PMC, which they can easily obtain over the drug store counter, although it is not proven to be specific therapy for hepatitis of any type. Eleven of the patients in our study group took PMC. Of these, 10 had no visible icterus or elevated serum bilirubin before using the drug, but had developed flare-ups after the use. For example, Case No. 1 in the study group was given PMC in the Department of Family Medicine when the serum levels of bilirubin, AST and ALT were 1.3 gm/dL, 279 IU/L and 672 IU/L respectively. After 2.5 months of PMC usage, liver function tests revealed bilirubin at 2.7 mg/dL, and prominent yellow discoloration of the skin and sclera followed clinically. The levels of both serum aminotransferases had declined (see Fig. 1). At the 3rd month of PMC usage, liver function testing revealed a bilirubin level of 28.2 mg/dL and increases of serum AST and ALT. Four months after cessation of PMC with seroconversion, bilirubin, AST, and ALT had all declined. Reappearance of HBeAg after 2 months was followed by a second exacerbation, with reappearance of HBV DNA in the serum and a peak serum bilirubin level of 12.4 mg/dL. In this patient, a liver biopsy on the first admission day after PMC use showed CAH and cholestasis in acute exacerbation, with spotty necrosis, ballooning degeneration of hepatocytes, Kupffer cell hypertrophy and hyperplasia, moderate portal fibrosis, piecemeal necrosis, and acidophil bodies.

The most important factor in severe acute exacerbations of CHB is reported to be reactivation of HBV infection (Kanno et al., 1988), as the patients in the control group had shown in our study. However, acute exacerbation of viral liver disease with severe jaundice and hepatic decompensation can develop in patients with a past anti-HBe seroconversion, and one of the main causes might be the use of PMC, alcohol or other drugs. Any drug may have a toxic effect on the liver, and drugs for liver disease should not be excluded from this rule (Sticker, 1992). Usually, patients with chronic viral liver disease who have monitoring of serum aminotransferases, and who take PMC show only normalization of these enzyme levels. However, as noted above, by unknown mechanisms, PMC can create disturbances in liver function that are reflected in the results of common laboratory tests. The drug also might affect the metabolism of bilirubin in some patients. Therefore, PMC should be
prescribed only for patients in whom it is clearly indicated and should be avoided in patients with ACH, cirrhosis or decompensated liver disease. The warning label should be placed to reflect these effects, and inquiries should be made for an appropriate use of all "traditional" herbal medicines as the popularity of herbal medicine grows. Greater care is needed in selecting drugs for patients in the nonreplicative phase of HBV infection.

The cause of acute exacerbation in CHB may be different in the patients, who develop severe jaundice, and those who do not; i.e., between patients with advanced CHB and those with no cirrhotic change. Further study is recommended to gain a better understanding of the pathogenicity of acute exacerbation of CHB, with severe jaundice, which is sometimes fatal.

REFERENCES


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만성 B형 간질환 환자에서 심한 향달을 동반한 급성 악화

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만성 B형 간염의 경과중 환자들 중 만성 간염의 양상은 대부분 심한 향달의 동반없이 혈청 AST와 ALT의 증가만 보이며 악화되는 것이다. 저자는 심한 향달을 동반한 16명의 만성 B형 간염 악화 환자(연구군)와 심한 향달없이 AST와 ALT만 증가된 13명의 환자(비교군)를 비교관찰하였다.

PMC 세제를 복용했던 환자는 연구군에서 11명(68.8%), 대조군에서 1명(7.7%)으로 나타났으며 PMC를 포함하여 각종 약제 및 알콜 섭취가 저명했던 환자인 연구군에서 15명(93.8%), 대조군에서는 2명(15.4%)이었다.

혈청 HBeAg 양성율은 급성 악화전에는 연구군에서 14명 중 7명(50.0%), 비교군에서는 13명 모두(100%)에서 양성이었으며, 급성 악화 경과후에는 연구군에서는 변함없이 비교군에서는 13명 중 3명(23.1%)에서 양성이었다. 연구군 중 anti-HBe 양성화는 한 사람도 생기지 않았고 6명이 사망하였으며 대조군에서는 8명의 환자에서 anti-HBe 양성화가 생겼고 아무도 간기능 부진으로 사망하지 않았다.

만성 B형 간질환에서 심한 향달을 동반한 급성 악화의 관련있는 요인은 진행된 만성 활동성 간염, 간경변 등 근본적으로 진행된 간기능 저하와 동반된 부적절한 약제나 알콜 복용이 확실히 관계있을 것으로 사료되며 간기능 부진도 그뿐은 되지 않는다. 반면에 간경변으로 진행되기 전 상태에서는 간기능 저하없이 간기능이 관저되 악화될 때는 자연적인 혈청 anti-HBe 양성 전환의 동반에 혼란 것으로 나타났다.

중심 단어: B형 간염, 만성 간염, 향달