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# A case of Primary Biliary Cirrhosis with Beneficial Effect of Secretin in the Treatment of Jaundice — with a Study of Secretin Induced Choleresis in Man —

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**Summary** Primary biliary cirrhosis (PBC) is a chronic liver disease and no definite therapy has been established yet. The patient had jaundice during her clinical course of PBC. As the development of jaundice is an important sign of a poor prognosis, secretin, which is reported to have a choleretic effect, was administered to improve the jaundice. Soon after the treatment, her serum level of bilirubin decreased. Additionally, supplmental study of secretin induced choleresis was taken in another patient who underwent percutaneous transhepatic choledocal drainage. Secretin therapy appeared to be usefull for the resolution of jaundice in PBC patient.

*Key words*: Primary biliary cirrhosis; Secretin; Cholestasis; Bile flow

## Introduction

Primary biliary cirrhosis (PBC) is a disease that is characterized by a chronic inflammatory process involving small and middle-sized bile ducts and progresses to liver cirrhosis. Since immunological abnormalities associated with PBC have been identified, the mechanism of bile duct damage is not elucidated yet.[1,2] Despite the number of agents tried to find a cure for PBC, the specific treatment remains far from satisfactory. One of the key objectives in improving the prognosis seems to be the prevention of a development of jaundice during treatment. A potent agent to increase the bile flow is considered to be effective in suppression of jaundice. Secretin has been known to promote the volume of not only pancreatic juice but also bile flow.[3-5] This paper reports a recent case of a 65-year-old woman with PBC in the Scheuer's stage III, whose serum level of bilirubin and biliary enzymes gradually increased during her clinical course, for the first time. In order to resolve the jaundice, intravenous administration of secretin was given and its efficacy for jaundice was evaluated. In addition to the case, the choleretic effect of secretin was studied in another patient who underwent percutaneous transhepatic choledocal drainage (PTCD) for the common bile duct cancer. The actual bile flow was examined from the external biliary fistula and the mechanism of secretin induced choleresis was evaluated also.

## Case report

The patient was a 65-year-old woman. In February 1990, she felt generalized easy fatigability at some times and visited a general hospital. She had been diagnosed as having chronic liver disease from the data of examinations of blood chemistry in other hospital, when she was 45-years-old. Physical examination revealed hepatomegaly and splenomegaly, and

Table 1. Laboratory finding on admission.

| Serum chemistry | | Hematology | |
|---|---|---|---|
| Albumin | 3.2 g/dl | RBC | $344\times10^4$ /mm$^3$ |
| $\gamma$-globulin | 1.4 g/dl | Hemoglobin | 11.0 g/dl |
| Total bilirubin | 0.7 mg/dl | Hematocrit | 32.4 % |
| Direct bilirubin | 0.4 mg/dl | WBC | 1900 /mm$^3$ |
| Alkaline phosphatase (16-48) | 49 IU | Platelet | $8.7\times10^4$ /mm$^3$ |
| AST (1-20) | 43 IU | Immunological chemistry | |
| ALT (1-17) | 42 IU | Immunoglobulin (Ig) | |
| $\gamma$-GTP (1-38) | 187 IU | Ig G (1365±218) | 1630 mg/dl |
| Cholesterol (130-220) | 251 mg/dl | Ig A (247.0±77.5) | 583 mg/dl |
| Total bile acid (<10.0) | 331 $\mu$mol/l | Ig M (87.0±23.0) | 744 mg/dl |
| | | AMA | ×320 (+) |
| Secretin (60-120) | 67 pg/ml | ANA | (−) |
| | | SMA | (−) |
| | | LE test | 0.1 %(+) |
| $HB_sAg$ | (−) | DNA test | (−) |
| $HB_sAb$ | (−) | RA test | (−) |
| anti-HCV | (−) | | |

studies of blood chemistry indicated a hepatic dysfunction and mild pancytopenia. Furthermore, esophageal varices were found on fiberscopic endoscopy. She was referred to the Yamaguchi University Hospital for further examination and treatment of her portal hypertension.

On August 1990, she was admitted to our hospital with no subjective complaints. In the physical examination on admission, icterus and itching were not seen. Liver and spleen were palpable at 2.5 cm below the right costal margin and at 2 cm below the left, respectively. Her consciousness was clear and no other neurological findings were detected. As shown in Table 1, studies of blood chemistry disclosed a slight anemia and decreases of white blood cell and platelet count. Liver function tests showed that serum bilirubin, alkaline phosphatase (ALP) and copper were in normal, but transaminase level was slightly increased, and $\gamma$-GTP and total bile acids were elevated. Serum antimitochondrial antibody (AMA) was positive and immunoglobulin class M (Ig M) level was elevated, but virus markers of hepatitis B and C were negative.

Abdominal ultrasonography revealed marked splenomegaly and hepatomegaly, and no dilatation of common bile duct. There were no stones in the gallbladder. In laparoscopic observations, both lobes of the liver were enlarged and their surface was wavy with shallow groovy depressions. Liver biopsy under laparoscope showed that the portal area was enlarged and that the connective tissue was extended (Fig. 1). Bile canaliculus in the portal area were reduced in number and some bile epithelial cells were degenerated and necrotic. Mononuclear cell infiltration was also seen. In the endoscopic study for upper gastrointestinal tract, three tortuous esophageal varices were seen with erythemas. Gastric and duodenal bulbus mucosas were free from lesions such as ulcer.

Based on the data of these studies, the patient was diagnosed as having PBC ac-

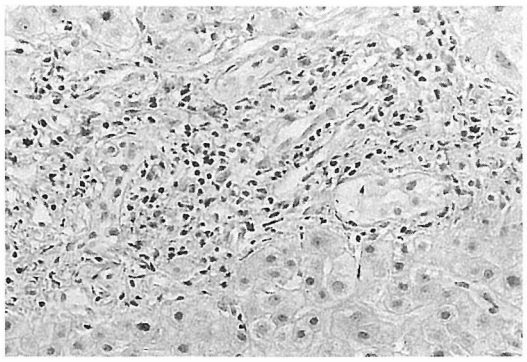

Fig. 1. Light microscopic findings of the liver biopsy specimen under laparoscope. The portal area was enlarged and bile duct epithelial cells were degenerated with infiltration of mononuclear cells. HE stain ×200.

companied with marked portal hypertension. As her splenomegaly, esophageal varices and pancytopenia were remarkable, an indication for surgical treatment by esophageal transection and splenectomy was considered. On October 1, 1990, she was transferred to the department of surgery, and the operation (esophageal transection and splenectomy) was performed. After the surgery, peripheral blood cell counts of RBC, WBC and platelet were increased to 370 × $10^4$/$mm^3$, 15500/$mm^3$ and 19.9 × $10^4$/$mm^3$, respectively. Liver function tests also improved so that total bilirubin (T. Bil) was 0.6 mg/dl, AST (GOT) 33 IU, ALT (GPT) 19 IU, γ-GTP 79 IU and cholesterol 194 mg/dl.

About three weeks after the surgery, serum ALP and γ-GTP was increased to 112 IU and 144 IU, respectively. On November 8, 1990, the patient was returned to our department for medical treatment. Administrations of ursodeoxycholic acid (UDCA) 600 mg/day and Colchicine 1 mg/day were started. However, the serum T. Bil level gradually increased to 1.9 mg/dl. When the serum T. Bil was rapidly elevated to 3.0 mg/dl (direct bilirubin (D. Bil) 2.3 mg/dl), secretin administration was considered. Secretin was given by drip venous infusion in a dose of 100 unit/day of Secrepan®, which is extracted from porcine intestine (Eisai Co. Ltd., Tokyo, Japan). Soon after the treatment, elevation of the serum T. Bil was suppressed and it began to decrease. Secretin was administered continuously for 3 weeks. On January 25, 1991, the serum T. Bil level was 1.0 mg/dl, and other liver function tests were in normal levels. RBC, WBC and platelet counts were 374×$10^4$/$mm^3$, 3200/$mm^3$ and 30.9×$10^4$/$mm^3$, respectively (Fig. 2). Secretin was thought to be effective in improvement of the jaundice which was observed for the first time during her clinical course of PBC.

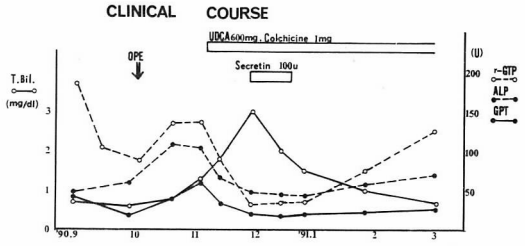


Fig. 2. Clinical course and treatments in the case of a 65-year-old woman with PBC.

Histological findings of the wedge-resected liver specimen on laparotomy (Fig. 3) showed increased connective tissue in the portal area, to form the bridge between each portal region. In some bile canaliculus, the basement membraine was destroyed and bile duct epithelial cells were degenerated with an infiltration of many mononuclear cells. In the area near the parenchyma, regenerated bile canaliculi were observed. They were compatible with the finding of non-supprative destructive cholangitis.

In February, 1991, the patient was discharged from our hospital and was attending the outpatient clinic. On December 16, 1992, her conditions did not change and her serum T. Bil level was 1.0 mg/dl, AST 62 IU, ALT 36 IU and γ-GTP 66 IU. Even in May 1993, she continued to have the treatment for PBC with no findings such as jaundice, and serum

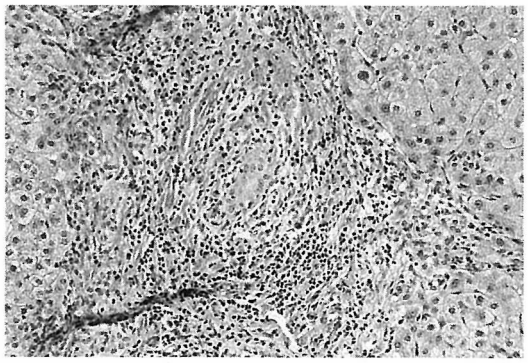

Fig. 3. Light microscopic findings of the wedge-resected liver specimen on laparotomy. Connective tissues in the portal area were increased to the bridge formation between each portal area. Bile canaliculus were reduced in number and some bile epithelial cells were degenerated and necrotic. Mononuclear cells were infiltrated there. HE stain ×100.

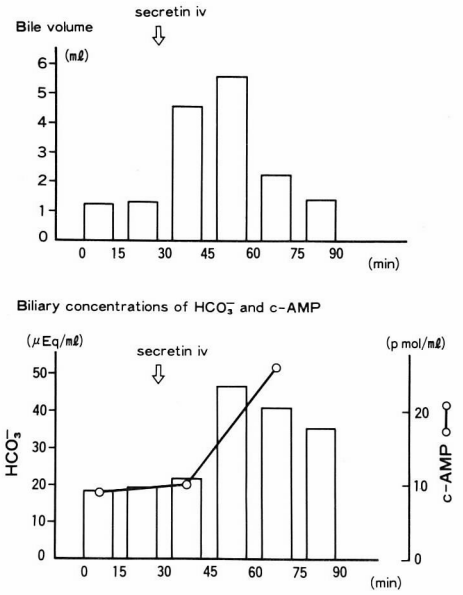


Fig. 4. Effects of secretin on the bile flow and biliary concentrations of bicarbonate and c-AMP in the case of a 70-year-old woman who recieved PTCD.

level of T. Bil was 0.9 mg/dl, AST 56 mg/dl, ALT 33 IU and γ-GTP 58 IU.

The effect of secretin on bile flow in the patient with pericutaneous transhepatic choledocal drainage (PTCD).

A 70-year-old woman visited our hospital with jaundice. After examinations of ultrasonography and ERCP, she was diagnosed as an obstructive jaundice due to the common bile duct cancer. As the serum bilirubin level rose to 17.6 mg/dl, PTCD was indicated. Four weeks after PTCD, the effect of secretin on bile flow was studied. The bile was collected though the PTCD tube at 15-minute intervals for 90 min. Secretin (Secrepan®) was injected intravenously in a dose of 1 u/kg body weight at 30 min after starting the bile collection. As shown in Fig. 4, the bile volume after secretin administration increased about 3.5-fold as compared with basal flow. The biliary concentration of bicarbonate elevated to 47.0 μEq/ml (about 2.5-fold increase) and concurrently examined c-AMP level clearly increased to 25.8 p mol/ml (about 2.5-fold elevation) after secretin. As the dead space of the drainage tube was 2 to 3 ml, the peak value of bile volume differed from the peak level of the biliary concentrations of bicarbonate and c-AMP. As a result, secretin induced choleresis was observed with elevations of biliary bicarbonate and c-AMP concentration.

## Discussion

Recently, many studies on the natural course and prognosis of PBC patient have been reported.[2,6-8] It is generally acknowledged that the survival period of PBC patient has been prolonged. Advancement of the diagnositic procedure and induction of more effective treatments are considered to account for the improvement of the clinical course of PBC. Among treatments, azathioprine, cyclosporine A and UDCA have been evaluated for their certain efficacy.[9-14] Above all, liver transplantation seems to be the only effective treatment and cure for PBC patients,[15-17] but has not widely be practiced yet in Japan. However, treatments by drugs that inhibit the progression of liver disease are also necessary.

Various evaluations have been conducted concerning the prognosis of PBC. The Yale

University group, which carried out a statistic study on 280 patients with PBC,[19] found the elevated serum bilirubin, old age and complication of liver cirrhosis as independent risk factors associated with poor prognosis. An European group has also investigated the prognosis using 248 PBC patients.[9,20] Serum bilirubin, age, complication of liver cirrhosis, serum albumin and cholestasis were independently predictive for the mortality. The Mayo Clinic group also reviewed clinical and biochemical features as a factor related to the prognosis of PBC from 312 PBC patients.[21] In their report, serum bilirubin was the most important of all risk factors; which also included age, serum albumin, prothrombin time, edema and use of diuretics. The Royal Free Hospital group which analyzed data obtained at the first visit of the patient[22,23] showed that serum bilirubin had the greatest impact in affecting the prognosis of PBC, followed by age, hepatomegaly, serum albumin, ascites, complication of lung disease and serum alkaline phosphatase.

The analyses of the prognosis in PBC patients from these reliable institutions have demonstrated that serum level of bilirubin is the single most important factor affecting it. In another report, once serum bilirubin level was elevated to 34 $\mu$mol/l over 6 months period, only half the PBC patients lived to 49 months.[19] Our PBC patient was histologically in Scheuer's Stage III and her age (65 years) was far beyond the mean age of the Mayo group (49.8 years). She had also hepatomegaly, splenomegaly and esophageal varices, accompanied with low serum albumin. In relation to the risk factors of the study groups mentioned above, her risk factors were four to five. Moreover, her serum bilirubin was elevated so that her prognosis seemed to be ominous.

After surgical treatment, levels of serum bilirubin rose, following the elevation of serum biliary enzymes. In order to improve the cholestatic condition, treatment was started using UDCA with a view to an increase of the bile acid-dependent bile flow from the hepatocyte. However, as the serum bilirubin level was further elevated, secretin administration was taken additionally. Soon after the secretin treatment, the serum level of bilirubin decreased.

It can not be determined whether the occurrence of jaundice in this case was due to an aggravation of liver disease of PBC or an incidental intervention of surgery. But, the surgical affect can hardly be considered because there was no profound bleeding or fall in blood pressure during the operation and the elevation in serum bilirubin began about one month after surgery.

Various animal experiments have demonstrated that secretin has a choleretic effect, and this reaction was also confirmed in man from our case with PTCD in this paper. In previous studies of some cases,[5] secretin was shown to produce about 3 to 4-fold increase in bile flow as compared with the basal flow. Although the mechanism of cholestasis in PBC is due to the destruction of bile duct epithelium, in this patient wash out effect through the biliary tree by secretin was effective in resolution of jaundice. Other liver function tests were also improved and no side effects were detected. Secretin therapy for PBC with jaundice is entirely a new application and appears to be useful as a medical treatment before induction of the curative therapy such as liver transplantation.

As the receptor of secretin in the liver is recognized in bile duct epithelial cells rather than in hepatocytes,[24] the promotion of bile flow with excretion of bicarbonate ions by secretin is thought to reside from bile duct epithelial cells. The system of secretin induced choleresis differs from that of UDCA which stimulates bile flow from the hepatocyte. The fact that the biliary concentration of cyclic AMP (c-AMP) was elevated in man and baboons[26] by secretin suggests the secretin reaction on the bile duct epitheilum is mediated by c-AMP.

The cellular content of c-AMP was increased after secretin administration and it is conceivable that it enhances the metabolic activity in the bile duct epithelial cells. Since the pathogenesis of PBC comprises the degenerative destruction of small and medium-sized bile duct epithelial cells, secretin is expected to improve the injured bile duct cells. When the bile duct epithelial cell function is impaired, the water re-secretion into bile may diminish to deteriolate the bile flow.

This postulate may be supported by the formation of bile thrombi in the liver biopsy specimens. The effects of secretin for cholestasis may be explained by the process in which the biliary tree is washed out by the increased bile volume from the bile duct epithelium, and the activation of bile duct epithelial cells through c-AMP maintains this function to inhibit any further development of jaundice.

The efficacy of secretin in PBC should be confirmed by the studies in large populations. Since secretin is presumed to improve the dysfunction of bile duct epithelial cells and to enhance the bile volume, secretin may be recommended in the therapy for these bile duct diseases.

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