HLA-A33/B44/DR6 Is Highly Related to Intrahepatic Cholestasis Induced by Tiopronin

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In order to elucidate the immunogenetic predisposition of tiopronin (mercaptopropionyl-glycine)-induced intrahepatic cholestasis, human leukocyte antigen (HLA) was analyzed in patients with tiopronin-induced liver injury. HLA-A, -B, -C, and -DR loci of 14 patients (10 males and 4 females) with tiopronin-induced liver injury were compared with those of control subjects. The mean duration of tiopronin administration was 26 days and that of jaundice was 4.5 months. The elevation of biliary enzymes lasted from 2 months to up to 10 years. Most of the cases manifested intrahepatic cholestasis on liver biopsy. Lymphocyte transformation test with tiopronin was positive in 6 of 8 (75%) tested cases. Thirteen patients (92.9%) had HLA-A33, 10 (71.4%) had B44, and 9 (64.3%) patients had DR6. These are statistically higher in the patients with tiopronin-induced cholestasis than in the general population. Ten of those with tiopronin-induced liver dysfunction (71.4%) had A33/B44 and 8 (57.1%) had A33/B44/DR6 in their haplotype. In conclusion, long-lasting tiopronin-induced intrahepatic-cholestasis is highly linked to specific HLA-A33, -B44 and -DR6.

KEY WORDS: drug; jaundice; cholestasis; major histocompatibility antigen; mercaptopropionyl-glycine.

Drug-induced liver injury occurs in an apparently unpredictable fashion in patients receiving therapeutic doses of drugs (1). Long-lasting jaundice induced by drugs is intractable and sometimes fatal (2). The mechanisms of hepatotoxicity and the reasons for the susceptibility of certain patients remain largely unknown. There is some evidence that immunological reactions, such as fever, rash, and eosinophilia, are involved with drug-related hepatic damage. Furthermore, the disease recurs more quickly after a drug rechallenge than after the first administration. The drugs themselves or their metabolites may cause toxic hepatitis or immunological hepatitis (1, 3, 4).

2-Mercaptopropionyl-glycine (commercially known as tiopronin) is a chemical compound having a thiol bond and is known for its detoxification effects on heavy metals such as mercury, iron, and copper; protection against radiation; and stimulation of the reticuloendothelial system (reviewed in reference 5). Tiopronin is now clinically used for liver disease; dermatitis, including progressive systemic sclerosis (PSS); and cataracts in Japan (5); and for rheumatoid arthritis in Europe (6). Side effects such as hypersensitivity manifested by itching, rash, and fever; pemphigoid dermatitis; liver dysfunction; and granulocytopenia have been reported (5). In addition, an increasing incidence of severe intrahepatic cholestasis induced by tiopronin, mostly in Japan, has been reported (7–9). These patients required hospitalization and frequently required plasmapheresis for more than a half year (7–9).

Drug-induced liver injury has been considered to be an immunological phenomenon according to data
of drug-related antigen-specific T-cell lines in drug-induced allergic hepatitis (10). Some cases of intrahepatic cholestasis were reported to involve the response of lymphocytes to the expression of HLA class II on the bile duct (11). Berson et al. revealed a possible role of HLA in drug-induced liver injury (12), but tiopronin-induced liver injury was not discussed in this report. Tiopronin intolerance in the treatment of rheumatoid arthritis was linked to HLA-DRB in France (13), but no data on tiopronin intolerance were reported in Japan except that which was manifested as liver injury. The toxicity of gold salts or D-penicillamine, which has a structure similar to that of tiopronin in that it has a thiol compound, was reported to be associated with HLA-B8-DR3 (14–16). Because of the pharmacological similarity of the chelating function and the structure of these two drugs, HLA-linked side effects of these drugs can be postulated for predisposed individuals.

Here we investigated the linkage of HLA in 14 cases with tiopronin-induced liver injury and found a genetic predisposition to this reaction.

**MATERIALS AND METHODS**

The clinical data for each patient with tiopronin-induced liver injury are shown in Table 1. Between 1985 and 1997, nine men and five women (mean age 46.3 years) were diagnosed as having tiopronin-induced liver injury in Gunma University Hospital and related hospitals in Gunma Prefecture, Japan, following criteria described elsewhere (17, 18). All the patients had been given 300 mg of tiopronin for 10–90 days (mean 26 days) for various diseases, as follows; seven patients with fatty liver, four cases with dermatitis, one with alcoholic liver injury, and two with cataract. Those who were given tiopronin for fatty liver showed slight elevation of serum aminotransferase and γ-glutamyl aminotransferase, and had features of fatty liver on ultrasonography, such as bright liver, positive liver–kidney contrast, and so on. They had no viral hepatitis A, B, and C markers or signs of autoimmune liver disease such as anti-mitochondrial antibody and anti-nuclear antibody. Furthermore, they had no jaundice or cholestatic liver damage noted during liver function tests before receiving tiopronin. No patients enrolled as having tiopronin-induced liver injury had a past history of jaundice or severe liver damage before taking tiopronin. Criteria of drug-induced liver injury were cited from Japan (17) and International Consensus Meeting (18). The Japanese criteria were: (1)}