INTERNAL MEDICINE

□ CASE REPORT □

Drug-induced Liver Injury Associated with Mosapride Citrate: A Report of Two Cases

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Abstract

We herein report two cases of drug-induced liver injury (DILI) due to mosapride. Case 1: A 78-year-old man was admitted with elevated transaminase levels. The cessation of mosapride led to the improvement of elevated liver enzyme levels. Case 2: A 54-year-old man was admitted with jaundice. Mosapride was discontinued immediately, and methylprednisolone was administered for acute liver failure. The patient's data showed improvement, and he was discharged on Day 32. In both cases, mosapride gave a positive response to a drug-induced lymphocyte stimulation test (DLST), and the patient's score based on the criteria for DILI was "highly probable".

Key words: mosapride citrate, drug-induced liver injury, drug-induced lymphocyte stimulation test

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Introduction

Mosapride citrate (mosapride) is a serotonin 5-hydroxytryptamine 4 (5HT4) receptor agonist that is known to promote gastric emptying and large-intestine motility (1). It is available in Japan, as well as in some other Asian countries, but not in the USA or European countries (2). In general, mosapride is considered to be safe and is well-tolerated by patients; however, the potential for drug-induced liver injury (DILI) should be considered. DILI can be subdivided into 'idiosyncratic' and 'intrinsic' categories (3). Idiosyncratic DILI, which is associated with a prolonged latency, occurs in a small number of susceptible individuals. Intrinsic DILI results from direct drug-induced hepatotoxicity over the course of a few days. We herein report two cases of idiosyncratic DILI due to mosapride.

Case Reports

Case 1

A 78-year-old man was admitted to our hospital with elevated transaminase levels. He had been taking mosapride (15 mg per day) and trimebutine maleate (trimebutine) (300 mg per day) for functional dyspepsia (FD) for 4 months prior to his admission. He reported that he had no history of alcohol abuse, recent travel, blood transfusion, eating raw meat, or sexual contact. On examination, he had neither jaundice nor edema, but mild epigastralgia was present. His blood test results (Table 1) were as follows: aspartate aminotransferase (AST), 800 IU/L; alanine aminotransferase (ALT), 983 IU/L; alkaline phosphatase (ALP), 127 IU/L; γ-glutamyltranspeptidase (γGTP), 307 IU/L; prothrombin time (PT) 82.1%; and eosinophils, 0.7%. The patient's serum immunoglobulin G (IgG) level was 1,067 mg/dL. The patient was negative for IgM hepatitis A antibody (IgM anti-HA),

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Table 1. Laboratory Findings (Case 1).

WBC (/μL)	6,000	AST (IU/L)	800	HBs Ag	Negative
Neutrophils (%)	63.1	ALT (IU/L)	983	IgM anti-HBc (S/CO)	< 0.05
Lymphocytes (%)	30.2	LDH (IU/L)	537	anti-HCV	Negative
Eosinophils (%)	0.7	ALP (IU/L)	127	IgM anti-HA (S/CO)	< 0.40
Basophils (%)	0.2	γGTP (IU/L)	307	IgA anti-HEV	Negative
RBC (10^4/μL)	477	CRP (mg/dL)	0.55	anti-CMV IgM	Negative
Hemoglobin (g/dL)	14.7	IgG (mg/dL)	1,067	anti-CMV IgG	18.8
Platelets (10^3/μL)	119	IgM (mg/dL)	66	anti-EBV VCA IgM	Negative
PT (%)	82.1	IgA (mg/dL)	160	anti-EBV VCA IgG	0.9
Albumin (g/dL)	4.4	ANA	< ×40	anti-EBNA IgG	3.9
Total bilirubin (mg/dL)	1.08	AMA-M2	< 1.5		

WBC: white blood cell, RBC: red blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γGTP: γ-glutamyltranspeptidase, CRP: C-reactive protein, Ig: immunoglobulin, ANA: antinuclear antibodies, AMA: antimitochondrial antibodies, HBsAg: hepatitis B surface antigen, anti-HBc: hepatitis B core antibody, anti-HCV: hepatitis C virus antibody, anti-HA: hepatitis A antibody, anti-HEV: hepatitis E virus antibody, anti-CMV: cytomegalovirus antibody, anti-EBV VCA: anti-Epstein-Barr virus viral capsid antigen antibody, EBNA: Epstein-Barr virus nuclear antigen

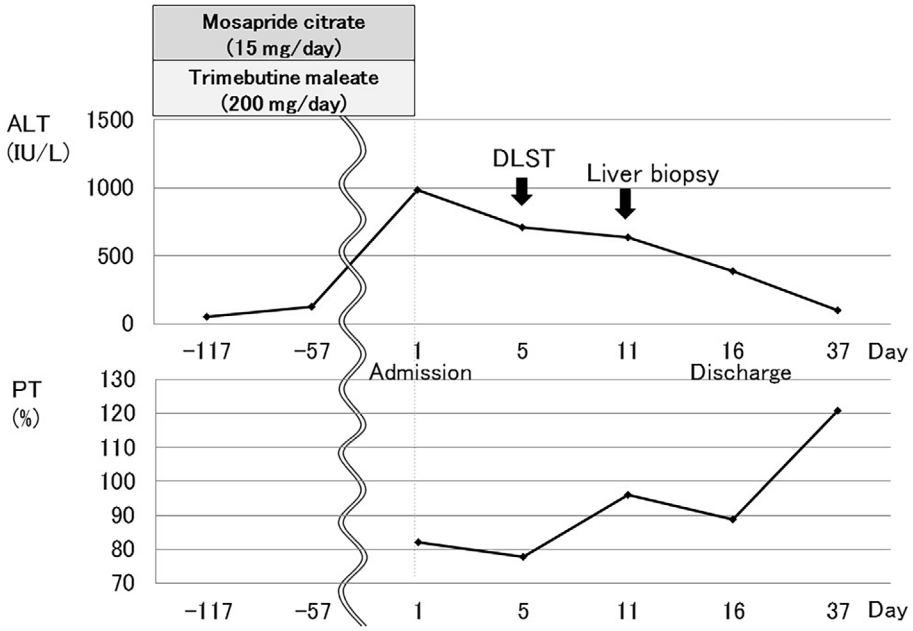

Figure 1. The clinical course of Case 1.

hepatitis B surface antigen (HBs Ag), hepatitis C virus antibody (anti-HCV), anti-cytomegalovirus IgM (anti-CMV IgM), and anti-Epstein-Barr virus viral capsid antigen IgM (anti-EBV-VCA IgM). Tests for antinuclear antibodies (ANA), and antimitochondrial antibodies (AMA)-M2 were both negative. An abdominal ultrasound scan and computed tomography (CT) revealed neither biliary obstruction nor space-occupied lesions. A probable diagnosis of DILI was considered, and mosapride and trimebutine were discontinued (Fig. 1).

Liver biopsy at Day 11 showed the presence of collapsed hepatocytes in zone 3 with slight infiltration of the acini by inflammatory cells, including lymphocytes and histiocytes (Fig. 2). A drug-induced lymphocyte stimulation test (DLST) was performed [a stimulation index (SI) of 180% was considered to indicate a positive response]. Mosapride gave a positive response, with an SI of 219%; trimebutine also gave a positive response, with an SI of 263%. The patient's score, based on the criteria for DILI from the Digestive Disease Week Japan (DDW-J) 2004, was 9 (hepatocellular type), which suggested that DILI was "highly probable". On the basis of these results, a diagnosis of DILI due to mosapride and trimebutine maleate was confirmed. The cessation of these drugs led to the immediate improvement of elevated liver enzyme levels, and he was discharged 17 days after admission. He is currently being followed up in our outpatient clinic, and his liver enzyme levels have remained within the normal ranges.

Case 2

A 54-year-old man visited our hospital because of jaundice and elevated transaminase levels. He had been taking mosapride (15 mg per day) for chronic gastritis for 6 months prior to his admission. The patient had no history of

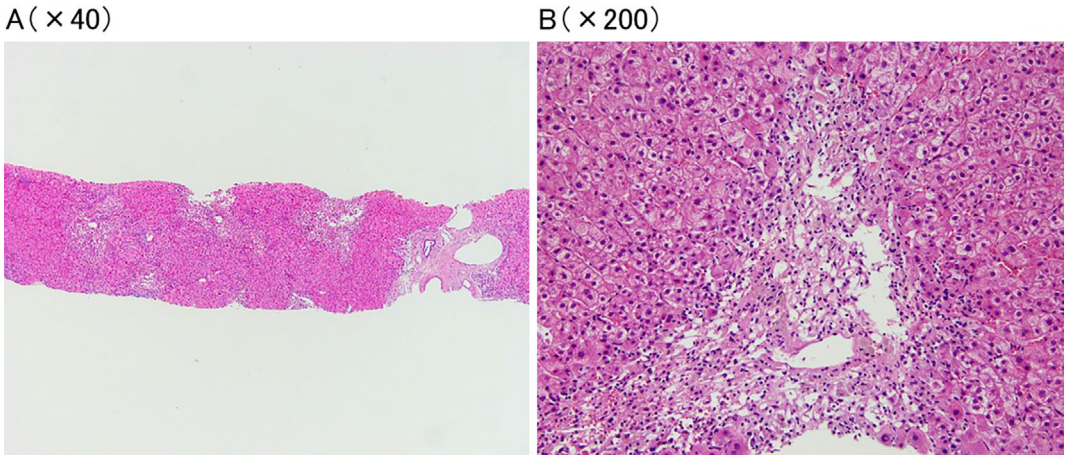

Figure 2. **Liver biopsy at Day 11 showed collapsed hepatocytes in zone 3 with slight infiltration of the acini by inflammatory cells, including lymphocytes and histiocytes.**

Table 2. **Laboratory Findings (Case 2).**

WBC (/μL)	7,200	AST (IU/L)	1,407	HBs Ag	negative
Neutrophils (%)	73.8	ALT (IU/L)	1,290	anti-HCV	negative
Lymphocytes (%)	15.2	LDH (IU/L)	415	IgM anti-HA (S/CO)	negative
Eosinophils (%)	0.1	ALP (IU/L)	499	anti-EBV VCA IgM	negative
Basophils (%)	0.1	γGTP (IU/L)	420	anti-EBV VCA IgG	6.5
RBC (10^4/μL)	515	CRP (mg/dL)	< 0.30		
Hemoglobin (g/dL)	14.7	IgG (mg/dL)	1,500		
Platelets (10^3/μL)	111	IgM (mg/dL)	120		
PT (%)	61.9	IgA (mg/dL)	326		
Albumin (g/dL)	4.7	ANA	×80		
Total bilirubin (mg/dL)	11.9	ASMA	×40		
Direct bilirubin (mg/dL)	7.3	AMA	negative		

WBC: white blood cell, RBC: red blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γGTP: γ-glutamyltranspeptidase, CRP: C-reactive protein, Ig: immunoglobulin, ANA: antinuclear antibodies, ASMA: anti-smooth muscle antibodies, AMA: antimitochondrial antibodies, HBsAg: hepatitis B surface antigen, anti-HCV: hepatitis C virus antibody, anti-HA: hepatitis A antibody, anti-EBV VCA: anti-Epstein-Barr virus viral capsid antigen antibodies

excessive alcohol intake, recent travel, blood transfusion, eating raw meat, or sexual contact. A physical examination revealed that he was icteric with mild to moderate pruritus. His blood test results (Table 2) were as follows: T-Bil, 11.9 mg/dL; AST, 1,407 IU/L; ALT, 1,290 IU/L; ALP, 499 IU/L; γGTP, 420 IU/L; PT 61.9%; and eosinophils, 0.1%. His IgG level was 1,500 mg/dL. The patient was negative for IgM anti-HA, HBsAg, anti-HCV, anti-EBV-VCA IgM. The ANA was ×80 and anti-smooth muscle antibodies (ASMA) was ×40. The findings for AMA were negative. An abdominal ultrasound scan and CT revealed no abnormalities. Since DILI was suggested based on the patient's clinical course and the laboratory data, mosapride was discontinued soon after admission.

On Day 5, his PT was 45.5% (PT-INR 1.57), and methylprednisolone (500 mg/day) was administered for 3 days based on the diagnosis of acute liver failure (ALF) without hepatic coma (Fig. 3). The patient's clinical findings and biological data showed gradual improvement, and laparoscopy on Day 11 showed reddish markings on the surface of the liver (Fig. 4). A histological examination of a liver specimen taken at laparoscopy demonstrated distinct interface hepatitis, bridging necrosis with regenerative micronodules, numerous foci of lobular inflammation and collapsed hepatocytes (Fig. 5). Mosapride gave a positive response in a DLST with an SI of 794% (positive SI: >180%). The patient's score, based on the criteria for DILI from the DDW-J 2004, was 8 (hepatocellular type), which suggested that DILI was "highly probable". The diagnosis of DILI due to mosapride was confirmed based on these results. The patient was discharged 32 days after admission and is currently in a favorable condition with normal liver enzyme levels.

Discussion

Mosapride was made available in 1998. At the time of writing, mosapride is said to be administered to about 9 million patients per year in Japan (4). Although mosapride is known to be a causative agent of DILI, there are very few original case reports on this topic. In 2004, the Ministry of Health, Labour and Welfare (MHLW) revised its cautions on the use of mosapride. In this revision, close observation was recommended during administration due to the possibility of liver dysfunction. In 2012, the MHLW revised its cautions for a second time. Based on this instruction, the package in-

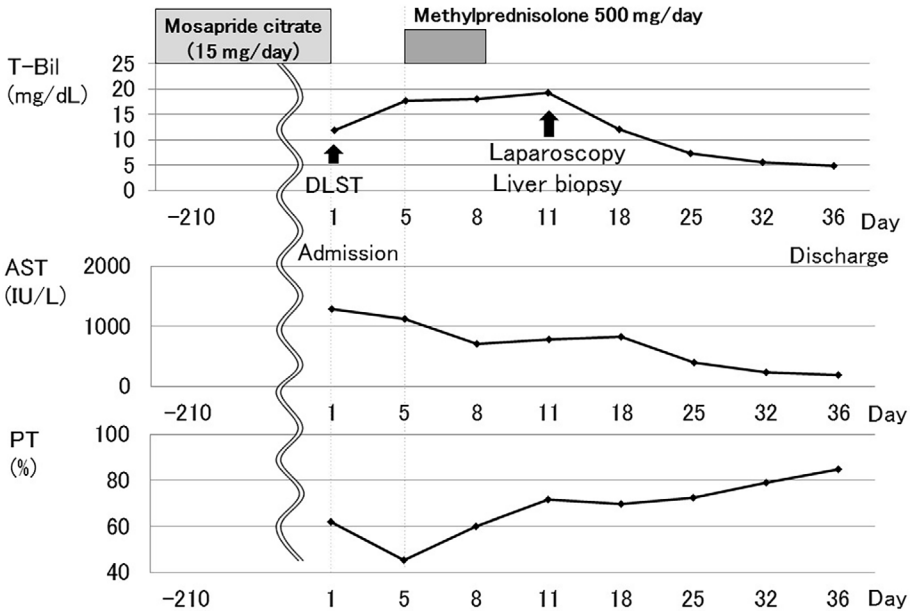

Figure 3. **The clinical course of the Case 2.**

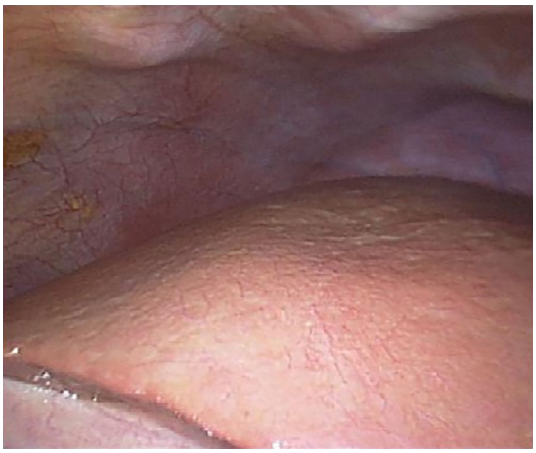

Figure 4. **Laparoscopy at Day 11 showed reddish markings on the surface of the liver.**

sert was revised to indicate that after the two-week administration of mosapride, a patient's gastrointestinal symptoms should be assessed for improvement and the necessity of continuing administration should be evaluated.

In the two case reports presented here, DILI due to mosapride was the most likely etiology of the patient's acute liver injury, and the results of extensive testing performed to identify other causes were negative. Two algorithms have been published that are specifically designed to assess the cause of DILI in suspected cases: the Roussel Uclaf Causality Assessment Model (RUCAM) and the Maria & Victorino (M&V) Scale (5). Although they are not widely used in the clinical setting, they do offer useful frameworks for investigating cases of suspected DILI. In Japan, the criteria for DILI from the DDW-J 2004 is well known and widely used (6). The DDW-J 2004 scores of Cases 1 and 2 indicated that DILI was "highly probable" in both, while the patients' RUCAM scores (8 and 7) indicated that DILI was "probable". Although the M&V scores of both cases (9 and 6) indicated that DILI was "unlikely", the performance of this scale has been said to be poor in reactions that involve long latency periods, and the score is heavily weighted based upon whether a rechallenge with the offending medication results in repeated DILI. Rechallenge with mosapride was not attempted in the present cases due to concerns for the patients' safety. The histological findings are not included in any of the three existing DILI scoring systems.

Liver biopsy was performed in order to diagnose the liver injury in both cases. In Case 1, the histological examination revealed collapsed hepatocytes with inflammatory cell infiltration in zone 3. These findings were compatible with a pattern of drug-induced hepatocellular injury. In Case 2, the histological examination revealed distinct interface hepatitis, bridging necrosis with regenerative micronodules, numerous foci of lobular inflammation, and collapsed hepatocytes. These findings also indicated severe drug-induced hepatocellular injury. It is well known that some commonly used agents, such as acetaminophen, amiodarone, and methotrexate, are associated with patterns of liver injury (7). However, the histological pattern of DILI due to mosapride remains unclear. The accumulation of further cases will hopefully elucidate the relationship between mosapride and liver injury.

To date, there is only one previously published case of DILI associated with the administration of mosapride in the Japanese literature (8). In 2004, Suyama et al. described the case of a 68-year-old man who developed jaundice and liver dysfunction after the initiation of mosapride treatment. The patient developed severe hepatitis four months after the initiation of mosapride, which resolved after discontinuing the medication. Suyama et al. reported the data of seven cases of DILI due to mosapride, which were introduced on the basis of information from the MHLW; however, the detailed

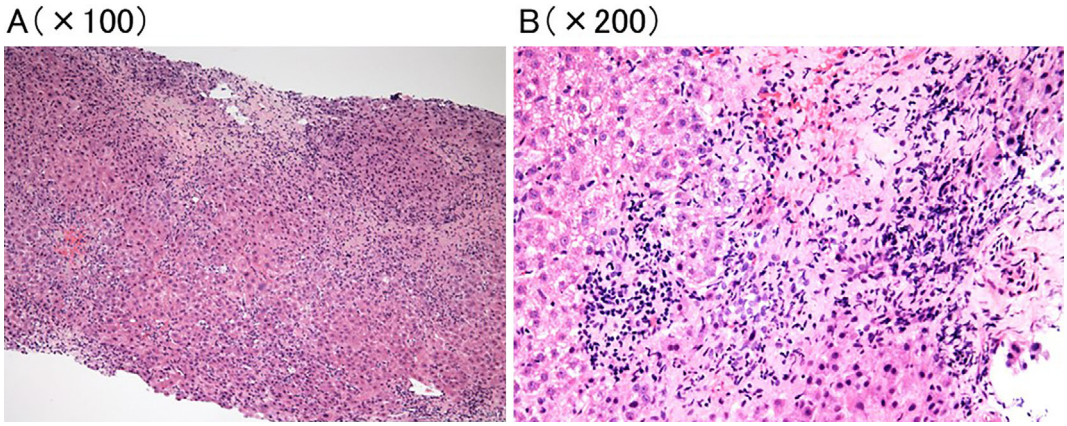

Figure 5. **Liver biopsy at Day 11 showed distinct interface hepatitis, bridging necrosis with regenerative micronodules, numerous foci of lobular inflammation, and collapsed hepatocytes.**

clinical courses of the patients were not shown. They concluded that mosapride can induce acute cellular injury or mixed liver injury, and that a DLST is useful in the diagnosis of DILI. Our cases were similar to the previously published case in that both patients had acute cellular injury-type DILI and that the latency period to the onset of DILI was relatively long. These common findings may be meaningful in resolving the characteristics of DILI due to mosapride.

Several limitations associated with the present study warrant mention. First, the patient in Case 1 was taking another medication, trimebutine. We believe that it was much less likely that trimebutine explained the patient's clinical picture, because this drug has not been associated with significant hepatotoxity in previous reports. However, the results of the DLST show that trimebutine might have had some effect on the liver dysfunction in Case 1. Second, the exact mechanism underlying the emergence of DILI due to mosapride was not elucidated. Idiosyncratic DILI development is thought to involve multiple events, such as reactive metabolite formations, oxidative stress, and signaling pathway inductions, with the mitochondria taking center stage (9). In mosapride, the main metabolite M1 (des-p-fuluorobenzyl mosapride) is catalyzed by cytochrome P450 3A4 (CYP3A4) (10). It is possible that M1 has an influence on liver injury; however, further studies are required to clarify the relationship between mosapride and DILI.

In summary, our patients experienced DILI due to mosapride. Mosapride is very popular and is frequently prescribed in Asian countries; however, the potential for DILI should be kept in mind. To our knowledge, this is the first English language case report of DILI due to mosapride. In Japan and other Asian countries, we urge clinicians to be alert when performing follow-up liver function tests and to monitor patients' gastrointesitinal symptoms carefully when mosapride is administered.

The authors state that they have no Conflict of Interest (COI).

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