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Original Article

Experimental verification of factors influencing calcium salt formation based on a survey of the development of ceftriaxone-induced gallstone-related disorder

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ABSTRACT

Ceftriaxone (CTRX) forms salts with calcium (Ca) in the gall bladder and bile duct, and induces the formation of gallstones. In this study, factors of CTRX-induced gallstone formation were extracted from the results of a retrospective survey using the Japanese Adverse Drug Event Report (JADER), and the causal relationship between the factors and gallstone formation was investigated. From JADER, 136 patients who developed 'gallstone-related disorder' with CTRX as a suspected drug were extracted. The incidence of gallstone-induced adverse effects was high in patients treated with CTRX at a dose exceeding the normal daily dose and in children younger than 10 years old, suggesting that CTRX at a high level is a factor for gallstone formation. Thus, after mixing CTRX and Ca^{2+} at different concentrations under different pH condition, the number of particles in the solutions was measured using a Coulter counter. As a result, the number of minute particles significantly increased at all pH values when Ca^{2+} and CTRX were mixed at a concentration of 10 mEq/L or higher and 1.5 g/L or higher, respectively. At pH 6.5 or 7.0, visible crystals were detected when 25 mEq/L of Ca^{2+} and 2.0 g/L of CTRX were mixed. Based on these findings, attention should be sufficiently paid to the development of 'gallstone-related disorder' in pediatric patients and in patients treated with CTRX at a dose exceeding the normal dose. Furthermore, gallstone formation and growth may be promoted when CTRX and Ca^{2+} coexist at high concentrations under low pH conditions.

1. Introduction

A 3rd-generation cephem antibiotic, ceftriaxone (CTRX), has a broad antibacterial spectrum for gram-positive and −negative bacteria, and exerts strong antimicrobial activity against Streptococcus pneumoniae, Haemophilus influenzae, and *Escherichia coli*. Tissue penetration of CTRX is favorable. In addition, approximately 40−60% is excreted in urine and approximately 11−65% is excreted in bile as an unchanged compound [1]. Furthermore, as its half-life is 8 hours, being long, once-a-day administration is effective to treat many infections in clinical practice such as respiratory, biliary tract, and urinary tract infections and purulent meningitis. On the other hand, precipitation of calcium (Ca) salt in CTRX excretion regions, i.e., the bile duct and kidney, as gallstones and urinary tract stones, respectively, mainly in children has been reported in Japan and other countries [2−5]. In response to this, the US Food and Administration revised CTRX prescription information in 2007, and issued a warning for the simultaneous administration of CTRX and Ca-containing preparations. In Japan, the following important precautionary statement is included in the package insert: 'Do not simultaneously administer this drug with injections or infusions containing calcium'.

Factors involved in Ca-CTRX salt formation by mixing CTRX and Ca-containing preparations have been reported. Kobo reported that when CTRX is dissolved in Ca-containing electrolyte solution and administered by drip infusion using an infusion pump, the CTRX concentration, type of pump, flow rate, and type of infusion are factors affecting Ca-CTRX salt formation [6]. Nakai et al. investigated

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the number of minute particles formed when CTRX saline solution for injection was combined with calcium chloride injection using a light-shielded automatic fine particle counter, and found that, in addition to the Ca concentration, the temperature and shaking influence Ca-CTRX salt formation [7,8]. However, these studies focused on changes in the composition of CTRX and Ca-containing preparations, and it remains unclear whether these are factors of gallstone and kidney/urinary tract stone formation in the body.

In this study, the following investigation was performed to clarify factors influencing Ca-CTRX salt (gallstone) formation in the biliary tract and gall bladder. Firstly, to clarify the causal relationship between CTRX and the adverse effects of gallstones, the dose of CTRX and the adverse effects of gallstones suspected to be induced by CTRX were investigated using a database of spontaneous reports of adverse events open to the public by the Pharmaceuticals and Medical Devices Agency, Japanese Adverse Drug Event Report (JADER). In JADER, more than 300,000 spontaneous adverse event reports of prescription and over-the-counter drugs and drugs requiring guidance in Japan were collected. Information on adverse effects that cannot be acquired from packaged inserts and interview forms, such as sex differences, and frequent ages and doses, can be acquired and were utilized in retrospective studies [9]. Then, we investigated whether the factors influencing gallstone formation based on the survey results influence Ca-CTRX salt formation under physiological conditions *in vitro*.

2. Materials and methods

2.1. Analysis of adverse effects using JADER

JADER data was downloaded from the Pharmaceuticals and Medical Devices Agency homepage (https://www.pmda.go.jp/index.html). 'Gallstone-related disorder (SMQ: 20000127)' developed in 136 of 2,070 cases of adverse events with CTRX as a suspected drug between April 2004 and December 2016, and these patients were selected as the subjects. Preferred terms included in the SMQ were limited to "Narrow" used to detect reports with a high possibility of adverse events. The daily dose was calculated by multiplying the single dose by the dosing frequency.

2.2. Influences of CTRX concentration, Ca^{2+} concentration, and pH on Ca-CTRX salt formation

To investigate the influences of the CTRX concentration, Ca^{2+} concentration, and pH on Ca-CTRX salt formation under physiological conditions, the following conditions were used: As the CTRX concentration in bile 24 hours after intravenous injection of 2 g of CTRX was 449 μg/mL [10] and it increased to 20-times or higher when the dose was increased to 4 g per day for severe infection [1], the CTRX concentration was set at 0.1, 0.5, 1.0, 1.5, or 2.0 g/L. The Ca^{2+} concentration was set at 5, 10, or 25 mEq/L because the bile Ca^{2+} concentration in the gall bladder increases to 25 mEq/L [11,12]. The pH was set at 6.5, 7.0, or 8.0 because the bile pH in the gall bladder is 6.5 and that in the liver is 8 [12]. As a decrease in Ca-CTRX salt formation in the presence of cations, such as Na^+, has been reported [13], Tris-HCl buffer containing no Na^+ was selected for the solvent. Base on the interview form, residual CTRX rate is approximately 100% for 24 h in solution.

Calcium chloride dihydrate (Nacalai Tesque Co.) and CTRX (rocephin intravenous injection 0.5 g, Chugai Pharmaceutical Co., Ltd.) were dissolved in 50 mM Tris-HCl buffer (pH 6.5, 7.0, or 8.0), adjusting the final concentrations of Ca^{2+} and CTRX to 0, 5, 10, or 25 mEq/L and 0, 0.1, 0.5, 1.0, 1.5, or 2.0 g/L, respectively. The prepared solutions were left in a 37 °C water bath. After 24 hours, the

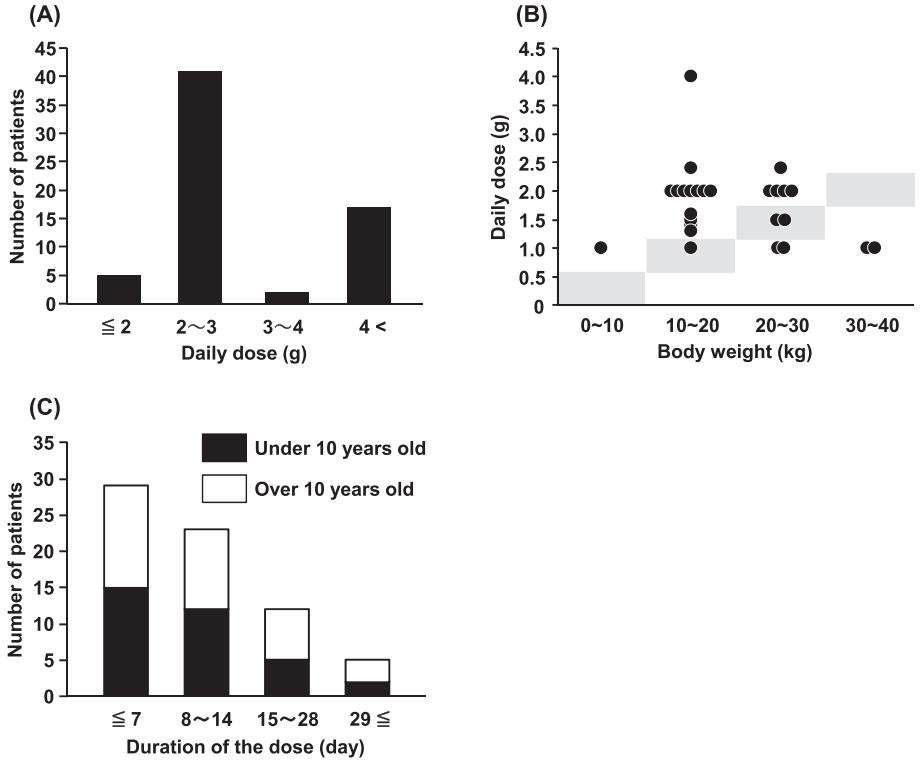

Fig. 1. (A) Number of 10-year-old or older patients with 'gallstone-related disorder' with CTRX as a suspected drug in JADER according to the daily dose of CTRX at the onset time (n = 65). (B) Daily dose grouped by the body weight at the onset time of 'gallstone-related disorder' in patients younger than 10 years old with CTRX as a suspected drug in JADER (n = 26). The gray zone represents the maximum recommended dose (60 mg/kg). (C) Number of patients with 'gallstone-related disorder' with CTRX as a suspected drug grouped by the onset time (n = 69).

number of particles in the solutions was measured using a Coulter counter (BECKMAN COULTER Z, Beckman Coulter, Inc.). After measurement, the solutions were filtered through a filter paper to remove particles, and the CRTX concentration in the filtrates was measured. The CTRX concentration was quantitated by measuring the absorbance at 241 nm using a spectrophotometer (UV-1700, SHIMADZU CORPORATION).

2.3. Statistical analysis

The number of minute particles and results of residual CTRX rate measurement were presented as the mean ± standard deviation (n = 9). Multiple comparison was performed regarding the 0 g/L CTRX group as a control, and $p < 0.05$ and $p < 0.01$ as significant. All statistical analyses were conducted using SPSS version 22 for Windows (IBM Japan Co., Ltd., Tokyo, Japan).

3. Results

3.1. Analysis of adverse effects using JADER

During the survey period, 2,070 cases of adverse events with CTRX as a suspected drug were reported and the number of patients with 'gallstone-related disorder' was 136. This 'gallstone-related disorder' included bile duct and common bile duct stones, cholelithiasis, dropped gallstone, obstructive gallstone, cholelithotomy, gallstone ileus, and intrahepatic cholelithotomy. Of the extracted 136 patients, 57 (42%) and 76 (56%) were male and female, respectively, and the sex was unclear in 3 (2%). No marked sex difference was noted in the incidence of 'gallstone-related disorder'. By generation, 53 patients were younger than 10 years old (39%), 19 (14%), 7 (5%), 3 (2%), 3 (2%), 5 (4%), 8 (6%), 17 (13%), 8 (6%), and 7 (5%) were in their 10s, 20s, 30s, 40s, 50s, 60s, 70s, 80s, and 90s, respectively, and the age was unclear in 6 (4%), demonstrating that the incidence was higher in the young generations.

The upper limit of the normal daily dose of CTRX is 2 g for adults and 60 mg/kg for children. The daily dose was calculated by multiplying the dose by the number of separated doses in cases where the dose was described, and summed in the groups younger than 10 years old and at 10 years old or higher to investigate the causal relationship between the dose and development of 'gallstone-related disorder'. The daily dose was high (2 g, the upper limit of the normal dose for adults, or higher) in 92% of the 10-year-old or older patients who developed 'gallstone-related disorder' (Fig. 1A). The dose and body weight were described for 26 patients younger than 10 years old. When the relationship between the body weight (median) and daily dose was investigated in these patients, the daily dose was the upper limit of the normal dose for children (60 mg/kg) or higher in 73% (Fig. 1B). In addition, the number of days of administration to the development of 'gallstone-

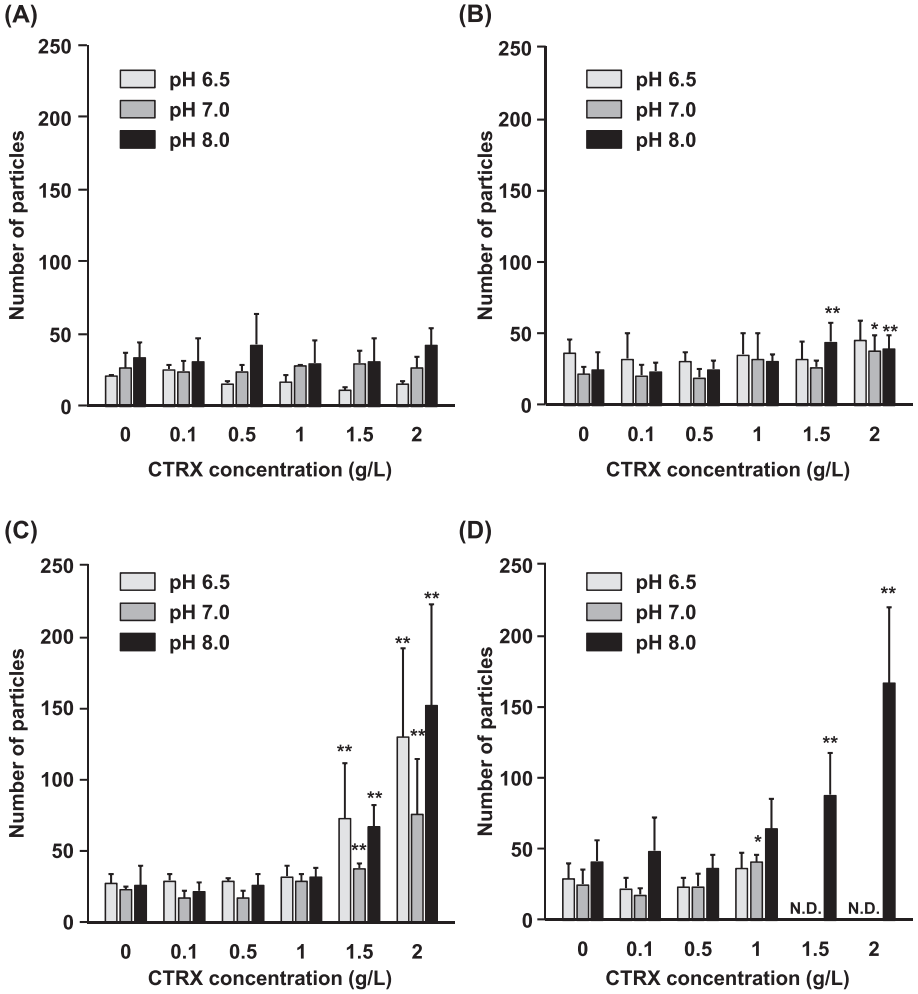

Fig. 2. Number of minute particles measured after incubation for 24 hours under each condition using a Coulter counter. Ca^{2+} concentration: 0 mEq/L (A), 5 mEq/L (B), 10 mEq/L (C), 25 mEq/L (D); N.D., not measurable because of precipitation of 50-μm or larger particles. *p < 0.05, **p < 0.01 vs. CTRX 0 g/L mean ± standard deviation (n = 9).

related disorder' was summed for 69 patients with descriptions of the date of initiation and completion of administration. As shown in Fig. 1C, gallstones appeared within 14 days after initiation of administration in 75% of patients combining the groups younger than 10 years old and at 10 years old or older (median, day 9 [range, 0–93 days]), suggesting that CTRX administration at a dose exceeding the normal dose is associated with development of the adverse event, 'gallstone-related disorder', and the presence of CTRX at a high concentration is a factor for Ca-CTRX salt (gallstone) formation.

3.2. Influences of CTRX concentration, Ca concentration, and pH on Ca-CTRX salt formation

In addition to the CTRX concentration, Ca^{2+} and pH are considered factors influencing Ca-CTRX salt formation on the biological side (the gall bladder and bile duct). Thus, the influences of changes in these factors on Ca-CTRX salt formation were investigated.

3.2.1. Number of minute particles

CTRX and Ca^{2+} were mixed at different concentrations under each pH condition and the number of minute particles was measured after 24 hours using a Coulter counter. In the absence of Ca^{2+}, no change was noted in the number of particles at any pH or CTRX concentration (Fig. 2A). However, the number of particles increased as the Ca^{2+} and CTRX concentrations both increased, and it significantly increased at all pH values in the solutions containing 1.5 g/L or higher CTRX mixed with 10 mEq/L or higher Ca^{2+} (Fig. 2B–D). In addition, at pH 6.5 or 7.0, when 25 mEq/L of Ca^{2+} was mixed with 1.5 g/L or higher CTRX, visible particles larger than the pore size of the Coulter counter, 50 μm, were present (Fig. 3) and the number of particles was unable to be measured.

3.2.2. Residual CTRX rate

As the Ca-CTRX salt particle size was not homogeneous, it was not possible to judge whether the CTRX concentration, Ca^{2+} concentration, or pH promoted Ca-CTRX salt formation based on comparison of the number of particles alone. Thus, we quantitatively analyzed Ca-CTRX salt formation by calculating the residual CTRX rate after removing minute particles from the solution. The residual rate variation was similar to changes in the number of minute particles up to a Ca^{2+} concentration of 5 mEq/L (Fig. 4A,B). When the Ca^{2+} concentration was 10 mEq/L, the number of minute particles was greater at pH 8 than that at pH 6.5 or 7 (Fig. 2C), but the residual rate was lower at pH 6.5 and 7 (Fig. 4C). This tendency was marked at 25 mEq/L Ca^{2+} (Fig. 4D), suggesting that Ca-CTRX salts easily form at a low pH.

4. Discussion

The risk of CTRX administration-induced gallstones was reported to be increased by high-dose administration, intravenous bolus injection, dehydration, past medical history of kidney disease, hypoalbuminemia, and concomitant use of calcium-containing preparations [14]. Moreover, in addition to the induction of

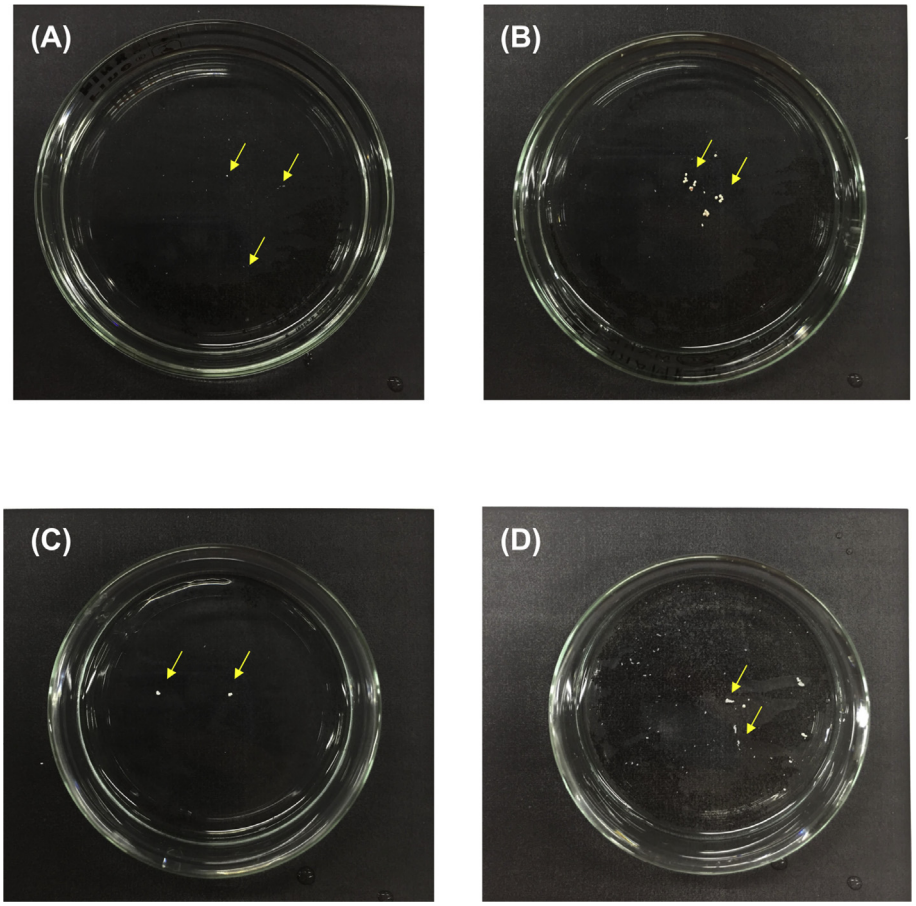

Fig. 3. Particles (arrow) precipitated after incubation for 24 hours under each condition. (A) CTRX 1.5 g/L, Ca^{2+} 25 mEq/L, pH6.5, (B) CTRX 2 g/L, Ca^{2+} 25 mEq/L, pH6.5, (C) CTRX 1.5 g/L, Ca^{2+} 25 mEq/L, pH7, (D) CTRX 2 g/L, Ca^{2+} 25 mEq/L, pH7.

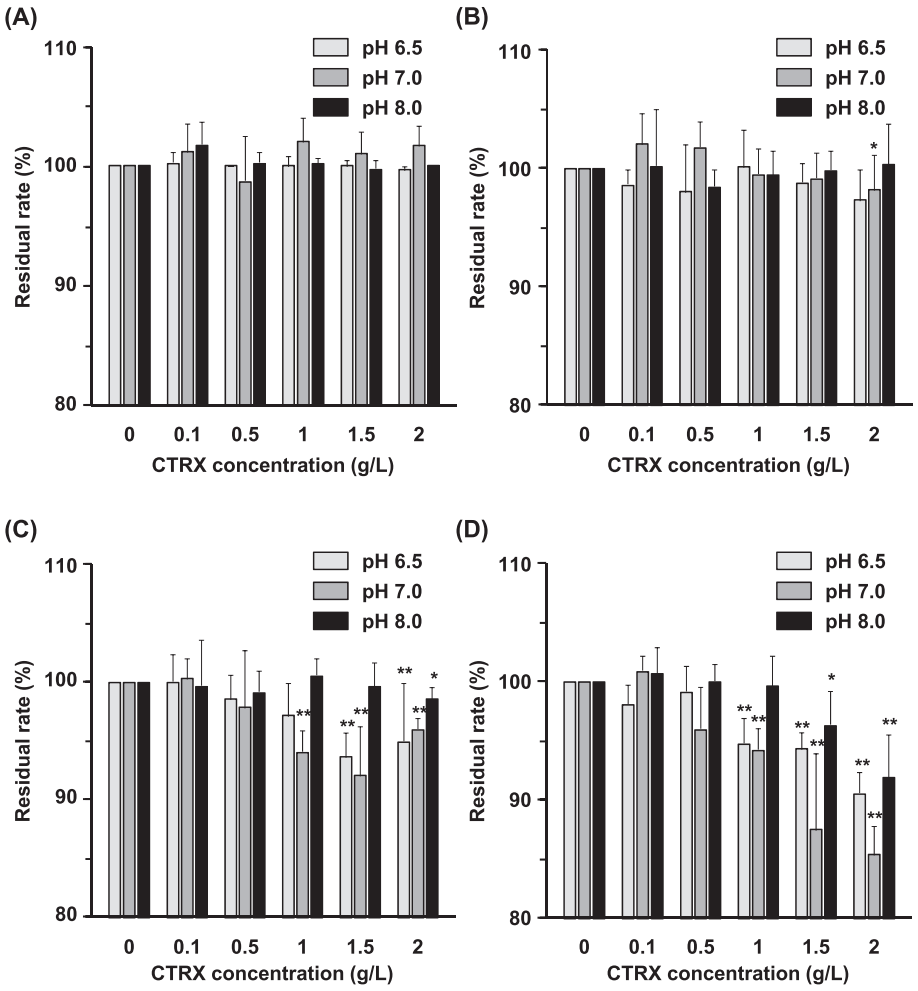

Fig. 4. Residual CTRX rate after incubation for 24 hours under each condition. Ca^{2+} concentration: 0 mEq/L (A), 5 mEq/L (B), 10 mEq/L (C), 25 mEq/L (D) *p < 0.05, **p < 0.01 vs. CTRX 0 g/L mean ± standard deviation (n = 9).

complications by gallstones: cholecystitis, cholangitis, and pancreatitis, fatal cases in neonates have been reported [15–17]. Therefore, attention should be sufficiently paid to the development of gallstones when CTRX is used. To our knowledge, no previous study has investigated sex differences, age, or onset time of gallstones with CTRX as a suspected drug in Japan. Clarification of these developmental tendencies may facilitate the prevention of the development and aggravation of gallstones. Moreover, risk factors of gallstone development can be presumed by closely analyzing the survey results, which is important for the safe use of CTRX in clinical practice in Japan.

In the 136 patients who developed 'gallstone-related disorder' with CTRX as a suspected drug extracted from JADER, there was no sex difference in gallstone development. On the other hand, by generation, the incidence was high in children younger than 10 years old, and patients younger than 10 years old and in their teens comprised more than half of all patients, consistent with patients being children in many case reports of CTRX-related cholelithiasis. The possible reasons for why gallstone-related disorder readily occurs in children as compared with adults are as follows: (i) The biliary tract is thinner and longer than that in adults; therefore, excretion of biliary sludge and gallstones is poor, (ii) the concentration of cholecystokinin, which promotes excretion of the gall bladder content by stimulating bladder contraction and oddi sphincter relaxation, is low, and (iii) biliary sludge and gallstones are easily formed due to dehydration [18]. Thus, attention should be sufficiently paid to the development of gallstones when CTRX is used in children.

Focusing on the daily dose of CTRX in the patients who developed 'gallstone-related disorder', the dose exceeded the normal dose (20–60 mg/kg) in 73% of the pediatric patients (younger than 10 years old) (Fig. 1B). Biner et al. administered CTRX to pediatric patients at 50, 75, or 100 mg/kg per day, and observed the development of bile duct stones in 11.4, 14.3, and 33% in the 50, 75, and 100 mg/kg treatment groups, respectively, which supports our findings [19]. In addition, Ozturk et al. confirmed the presence of biliary sludge or gallstones in the bile duct in 19 of 33 pediatric patients treated with CTRX at a daily dose of 100 mg/kg [20]. Furthermore, 8 cases of meningitis with biliary sludge or gallstones in pediatric patients receiving 100 mg/kg/day of CTRX have been reported [21]. In this study, CTRX was administered at a dose higher than the normal dose (2 g/day) to 93% of the 10-year-old or older patients (Fig. 1A). Although case reports of CTRX-induced gallstones in adults were limited, the dose was also higher than the normal dose in these reports [22], suggesting the necessity of paying attention to the development of gallstones in adults when the drug is administered at a high dose. Of note, the patients in whom gallstones developed at a normal dose (≤2 g/day) were old (80s: 2, 90s: 3). In general, old patients have lows body weights. As the body weight information of the patients was not available, whether

the dose per body weight was high in these patients cannot be confirmed. It may be necessary to keep in mind that gallstones can develop in thin or elderly patients even though the CTRX dose is within the normal range.

Since CTRX administration at a dose exceeding the normal dose is associated with gallstone formation, it is expected that 'gallstone-related disorder' develop as the number of days of administration become longer. However, gallstones appeared within 14 days after initiation of administration in the most patients irrespective of age (Fig. 1C). In a previous report, Meng et al. also reported that biliary precipitation abnormalities detected via ultrasonograph at an early phase after CTRX treatment [18]. Therefore, sufficient attention to signs of 'gallstone-related disorder' would be needed from the early phase when CTRX is administered.

The survey using JADER suggested that CTRX administration at a dose exceeding the normal dose is associated with the adverse event, 'gallstone-related disorder'. Approximately 45% of the administered CTRX is excreted into bile through multidrug resistance-associated protein (MRP2) and breast cancer resistance protein (BCRP) [23,24]. CTRX is concentrated in the gall bladder and bile duct during the excretion process, and the presence of CTRX at this high concentration may be a cause of gallstone formation. In addition, the bile pH in the gall bladder is 6.5 and that in the liver is 8 [12], and the blood Ca^{2+} concentration is 5 mEq/L, whereas that in bile in the gall bladder is 25 mEq/L, being high [11,12]. Furthermore, Ca binds to bile acid in the gall bladder, but MRP2-mediated secretion of bile acid into the gall bladder is competitively inhibited by CTRX, which may further increase the free Ca^{2+} concentration in the gall bladder. Thus, the Ca^{2+} concentration and pH may be factors of gallstone formation. Thus, we investigated Ca-CTRX salt (gallstone) formation *in vitro* on the assumption of physiological conditions of the CTRX concentration, Ca^{2+} concentration, and pH in the gall bladder and bile duct. The number of insoluble particles increased as the Ca^{2+} and CTRX concentrations increased, regardless of the pH (Fig. 2). CTRX existing as bivalent anions in the solution bound to Ca^{2+} at a 1:1 ratio and formed insoluble complexes [25], which may have promoted Ca-CTRX salt formation as the Ca^{2+} and CTRX concentrations increased, resulting in the deposition of insoluble particles.

Under the low pH (pH 6.5 or 7.0) conditions, the residual CTRX rate markedly decreased after mixing Ca^{2+} (10 mEq/L or higher) and CTRX (1.5 g/L or higher) at high concentrations, and visible particles precipitated (Figs. 3 and 4). Tange et al. compared changes in the compositions of the original CTRX and 7 generic drugs by mixing with a Ca-containing preparation, and observed the appearance of the most insoluble minute particles with a generic drug at a low pH after dissolution [26]. Considering these findings, Ca-CTRX salt formation and growth may be promoted under low pH conditions. However, the influence of pH on Ca-CTRX salt formation and growth has not been clarified, and it may be necessary to closely investigate the role of pH in Ca-CTRX salt formation because the bile pH in the gall bladder is 6.5.

In conclusion, Ca-CTRX salt is likely to be formed when CTRX and Ca^{2+} are present at high concentrations, and reduction of the pH promotes salt formation and growth. It may be necessary to pay close attention to the development of 'gallstone-related disorder' induced by Ca-CTRX salt formation in patients receiving CTRX at a dose exceeding the normal dose, pediatric patients, old patients, and patients with a pathology reducing the bile pH such as acute biliary pancreatitis [27].

Conflicts of interest

None.

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