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Report

Adverse Event Profiles of Coagulopathy-Related Events Caused by Intravenous Cephalosporins Using the Japanese Adverse Drug Event Report (JADER) Database

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Introduction: Cephalosporins are widely used antimicrobials; however, their potential to induce coagulopathy-related events, particularly hypoprothrombinemia, raises safety concerns. Methods: This study aimed to comprehensively evaluate the risk of coagulopathy-related events associated with the use of intravenous cephalosporins using the Japanese Adverse Drug Event Report (JADER) database. We analyzed 783,788 cases from the JADER database to identify coagulopathy-related events associated with the use of eleven intravenous cephalosporins between 2004 and 2024. Reporting odds ratios (ROR) with 95% confidence intervals were calculated to detect potential signals. Subsequently, odds ratios were calculated to assess the influence of age and sex on the occurrence of coagulopathy-related events. Results: Cefmetazole (CMZ), cefoperazone/sulbactam (CPZ/SBT), flomoxef (FMOX), and ceftriaxone (CTRX) showed statistically significant signals for coagulopathy-related events (ROR: 10.87, 5.20, 2.67, and 1.38, respectively). Age emerged as a significant factor, with individuals aged >70 years exhibiting higher odds of experiencing coagulopathy-related events associated with CMZ, CPZ/SBT, FMOX, and CTRX use. However, no significant association was observed with sex. Our findings suggest that certain intravenous cephalosporins (CMZ, CPZ/SBT, FMOX, and CTRX) are associated with an increase of coagulopathy-related events, particularly in patients aged >70 years. Conclusions: These findings highlight the need for vigilance and careful consideration of patient-specific factors when prescribing these antibiotics.

Key words coagulopathy-related events, cephalosporins, adverse event profiles, reporting odds ratios, database

INTRODUCTION

Generally, antimicrobial agents are known to induce changes in the intestinal microflora, thereby causing hypoprothrombinemia. This condition is characterized by a decrease in intestinal bacteria, the source of vitamin K2, a cofactor necessary for the synthesis of factors II, VII, IX, and X involved in blood coagulation, thereby causing coagulopathy-related events.[1)] A high-quality systematic review has already investigated the association between cephalosporins and hypoprothrombinemia.[2)] However, reports on coagulation disorders other than hypoprothrombinemia are limited to small observational studies, and no comprehensive research has yet investigated the association between cephalosporin antimicrobial agents and coagulopathy-related events in general.[3-5)] Furthermore, no studies have reported disproportionality analysis utilized real-world data from spontaneous adverse event reporting databases to investigate this association.

In recent years, many countries have opened spontaneous adverse event reporting databases for the early detection of adverse events caused by drugs and to understand trends related to the occurrence of adverse events.[6)] The Japanese Adverse Drug Event Report (JADER) is a spontaneous reporting system developed by the Pharmaceuticals and Medical Devices Agency (PMDA). Although various biases inherent in spontaneous reporting may affect study results using the JADER database,[7)] it is a valuable tool that can be used to assess rare and serious adverse events associated with drugs. This study comprehensively investigated the association between cephalosporins and coagulopathy-related events using the JADER database.

MATERIALS AND METHODS

The JADER database, which contains records from April 2004 to March 2024, was obtained from the PMDA website (http://www.pmda.go.jp/). The JADER dataset consists of four tables: (a) DEMO table, including patient information such as sex and age; (b) DRUG table, including patient drug information; (c) REAC table, including patient adverse events and

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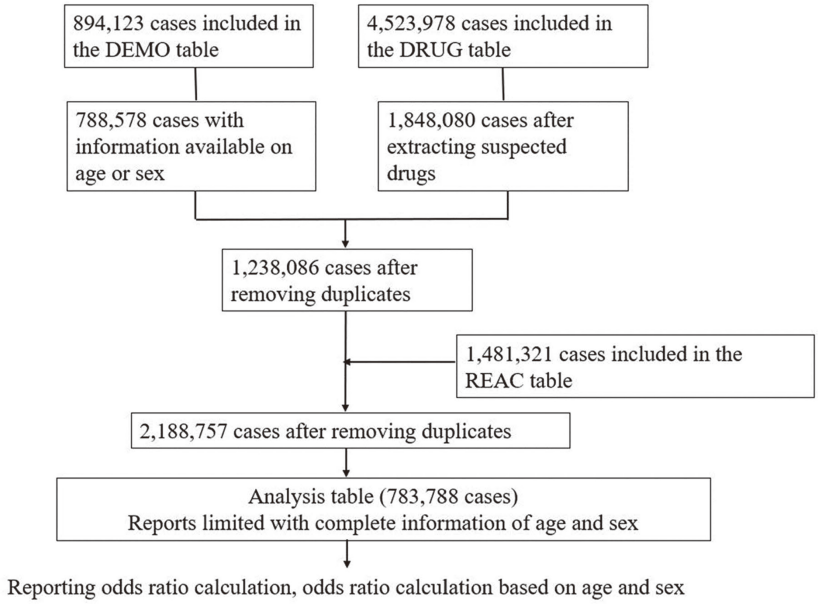

Fig. 1. Flowchart for Dataset Construction from the Japanese Adverse Drug Event Report (JADER) Database

outcomes; and (d) HIST table, including medical history and primary illness. Three tables (a, b, and c) were used for the analysis in this study. When we accessed these tables with an ID number, duplicate data were removed, and the results were combined into a single table. The combined table was defined as "All reports" (783,788 cases), and it was used for constructing a time-to-onset analysis table. Fig. 1 presents a flowchart of the construction of the dataset from the JADER database. We excluded cases in which data on sex and age were missing or unclear from the "All reports." The age classifications used in this analysis were as follows: <10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–99, and ≥100 years.

The definition of adverse events in the present study was compliant with the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J) version 27.0 (https://www.jmo.gr.jp/jmo/servlet/mdrLoginTop).

We evaluated the standardised MedDRA queries (SMQ) "hemorrhage laboratory terms" (SMQ code: 20000040)according to the MedDRA/J.

The SMQ 20000040 survey comprises 119 preferred terms (PT) (Table 1). Eleven intravenous cephalosporins, comprising one first-generation agent: cefazolin (CEZ), one second-generation agent: cefotiam (CTM), four third-generation agents: ceftriaxone (CTRX), cefotaxime (CTX), ceftazidime (CAZ), and cefoperazone/sulbactam (CPZ/SBT), two fourth-generation agents: cefepime (CFPM) and cefozopran (CZOP), one fifth-generation agent: ceftolozane/tazobactam (CTLZ/TAZ), one oxacephem: flomoxef (FMOX), and one cephamycin: cefmetazole (CMZ), approved in Japan as of April 2024 were included in this study. Latamoxef, classified as an oxacephem, and cefmenoxime, classified as a third-generation cephalosporin, were excluded from the study because no adverse events were reported in the JADER database. The details are presented in Table 2. The (a) DEMO table includes 894,123 cases; (b) DRUG table includes 4,523,978 cases; and (c) REAC table includes 1,481,321 cases. After excluding duplicates and cases with missing age and sex data, 783,788 cases were analyzed.

Table 2 was created by combining the DEMO table, which removed data with missing age and sex, the data of drugs suspected to cause adverse events in the DRUG table, and the REAC table, which contains the number of data combinations. In addition, Table 3 was created for intravenous cephalosporins for which adverse event signals were detected.

The reporting odds ratio (ROR) and 95% confidence intervals (CI) were calculated based on a previous study (Fig. 2).[8] A signal was considered positive when the lower limit of the 95% CI was >1. The ROR and 95% CI were calculated for each target cephalosporin using a 2 × 2 cross table for the occurrence of coagulopathy-related and other adverse events. In addition, age and sex distributions were examined in the occurrence of blood coagulopathy administrated intravenous cephalosporins cases.

Next, to directly compare the association between the occurrence of intravenous cephalosporins and coagulopathy-related events, age, and sex, univariate analysis was performed with the presence or absence of coagulopathy-related events for each drug as the objective variable and age (<70 and ≥70 years) or sex as the explanatory variable, and odds ratio (OR) were calculated. Due to the characteristics of the JADER, which categorizes age in 10-year intervals, and the definition of elderly individuals in Japan being 65 years and older, Cutoff age was conducted age of 70 in this study. Determine adverse event signals and associations, the lower limit of 95% CI was defined as >1 for the ROR study, and 95% CI not including 1 for the odds ratio study was defined as having a signal and association, respectively. JMP Pro 17.2.0 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

RESULTS

Table 2 shows the number of cases and reporting ROR of intravenous cephalosporins. Signals of coagulopathy-related events were observed for CMZ (ROR 10.87, 95% CI 8.41–14.04), CPZ/SBT (ROR 5.20, 95% CI 3.93–6.87), FMOX

Table 1. The SMQ 20000040 Survey Comprises 119 PT

Acquired Von Willebrand's disease	Blood thromboplastin decreased	Dilutional coagulopathy	Plasmin decreased
Acquired dysfibrinogenaemia	Capillary fragility abnormal	Ethanol gelation test positive	Plasmin inhibitor increased
Acquired factor IX deficiency	Capillary fragility increased	Factor IX inhibition	Plasminogen activator inhibitor
Acquired factor V deficiency	Capillary permeability increased	Factor VII activity decreased	Plasminogen activator inhibitor decreased
Acquired factor VIII deficiency	Circulating anticoagulant	Factor VIII activity abnormal	Plasminogen decreased
Acquired factor XI deficiency	Clot retraction abnormal	Factor VIII activity decreased	Plasminogen increased
Acquired haemophilia	Clot retraction time prolonged	Factor VIII inhibition	Platelet factor 4 decreased
Activated partial thromboplastin time abnormal	Coagulation disorder neonatal	Factor XII activity decreased	Protein C increased
Activated partial thromboplastin time prolonged	Coagulation factor IX level abnormal	Fibrin D dimer decreased	Protein S abnormal
Activated partial thromboplastin time ratio abnormal	Coagulation factor IX level decreased	Fibrin D dimer increased	Protein S increased
Activated partial thromboplastin time ratio fluctuation	Coagulation factor V level abnormal	Fibrin abnormal	Prothrombin fragment 1.2 increased
Activated partial thromboplastin time ratio increased	Coagulation factor V level decreased	Fibrin decreased	Prothrombin level abnormal
Anti factor IX antibody positive	Coagulation factor VII level abnormal	Fibrin degradation products	Prothrombin level decreased
Anti factor V antibody positive	Coagulation factor VII level decreased	Fibrin degradation products increased	Prothrombin time abnormal
Anti factor VII antibody positive	Coagulation factor VIII level abnormal	Fibrinogen degradation products increased	Prothrombin time prolonged
Anti factor VIII antibody positive	Coagulation factor VIII level decreased	Fibrinolysis abnormal	Prothrombin time ratio abnormal
Anti factor X activity abnormal	Coagulation factor X level abnormal	Fibrinolysis increased	Prothrombin time ratio increased
Anti factor X activity increased	Coagulation factor X level decreased	Haematocrit abnormal	Red blood cell count decreased
Anti factor X antibody positive	Coagulation factor XI level abnormal	Haematocrit decreased	Reticulocyte count increased
Anti factor XI antibody positive	Coagulation factor XI level decreased	Haemoglobin abnormal	Reticulocyte percentage abnormal
Anti factor XII antibody positive	Coagulation factor XII level abnormal	Haemoglobin decreased	Reticulocyte percentage increased
Antithrombin III abnormal	Coagulation factor XII level decreased	Haemosiderin urine positive	Russell's viper venom time abnormal
Antithrombin III increased	Coagulation factor XIII level abnormal	Hypocoagulable state	Septic coagulopathy
Bleeding time abnormal	Coagulation factor XIII level decreased	Hypofibrinogenaemia	Thrombin time abnormal
Bleeding time prolonged	Coagulation factor decreased	Hypoprothrombinaemia	Thrombin time prolonged
Blood fibrinogen abnormal	Coagulation factor deficiency	Hypothrombinaemia	Thrombin-antithrombin III complex abnormal
Blood fibrinogen decreased	Coagulation factor level abnormal	Hypothromboplastinaemia	Thrombin-antithrombin III complex increased
Blood thrombin abnormal	Coagulation time abnormal	ISTH score for disseminated intravascular coagulation	Von Willebrand's factor antibody positive
Blood thrombin decreased	Coagulation time prolonged	International normalised ratio abnormal	Von Willebrand's factor multimers abnormal
Blood thromboplastin abnormal	Coagulopathy	International normalised ratio increased	

Table 2. Number of Cases and ROR of Intravenous Cephalosporins

	Coagulopathy-related events			
	Cases 207	Non-cases 9903	Crude ROR	95% CI
First-generation cephalosporin				
Cefazolin	14	1794	0.80	0.47-1.36
Second-generation cephalosporin				
Cefotiam	5	597	0.86	0.36-2.07
Third-generation cephalosporin				
Ceftazidime	7	424	1.70	0.80-3.58
Ceftriaxone	45	3359	1.38	1.03-1.85
Cefoperazone/Sulbactam	52	1033	5.20	3.93-6.87
Cefotaxime	0	265	N/A	N/A
Fourth-generation cephalosporin				
Cefozopran	5	363	1.41	0.59-3.42
Cefepime	3	1042	0.30	0.10-0.92
Fifth-generation cephalosporin				
Ceftolozane/Tazobactam	1	22	4.55	0.61-33.74
Cephamycin				
Cefmetazole	65	619	10.87	8.41-14.04
Oxacephem				
Flomoxef	10	385	2.67	1.42-5.00

Using all cases (10,110 cases) from the JADER dataset from April 2004 to March 2024. The reporting odds ratio (ROR) and 95% confidence intervals (95% CI) of coagulopathy-related events were calculated for intravenous cephalosporins.N/A: not available.

	Cases of interest	Other cases	Total
Drugs of intetest	A	B	A+B
All other drugs	C	D	C+D
Total	A+C	B+D	A+B+C+D

Formula for calculating the reporting odds ratio(ROR):

$$ROR = \frac{AD}{BC}$$

Formula for calculating the 95% confidence interval(CI):

$$95\ \%CI = \exp\left[\log(ROR) \pm 1.96 \times \sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}\right]$$

Fig. 2. Two-by-Two Contingency Table for Calculating the Reporting Odds Ratio (ROR) and 95% Confidence Intervals (CI) of Coagulopathy-Related Events

Table 3. Profile of Cases of Developing Coagulopathy-Related Events among the Suspected ADE Reports for Intravenous Cephalosporins for Which Signals Were Detected

			Coagulopathy-related events			
			Cases 172	Non-cases 5,475	Odds ratio	95% CI
Ceftriaxone	Age (yr)	≧ 70/<70	30/15	1,433/1,946	2.72	1.51-5.07
	Sex	M/F	27/18	1,769/1,610	1.37	0.79-2.50
Cefoperazone Sulbactam	Age (yr)	≧ 70/<70	40/12	484/571	3.93	2.08-7.58
	Sex	M/F	32/20	622/433	1.11	0.66-1.97
Cefmetazole	Age (yr)	≧ 70/<70	52/13	254/396	6.24	3.39-11.68
	Sex	M/F	35/30	301/349	1.35	0.86-2.26
Flomoxef	Age (yr)	≧ 70/<70	7/3	113/278	5.74	1.57-22.59
	Sex	M/F	8/2	195/196	4.02	0.87-19.17

Using all cases (5,647 cases) from the JADER dataset from April 2004 to March 2024. The odds ratio and 95% confidence intervals (95% CI) of coagulopathy-related events were calculated for intravenous cephalosporins for which signals were detected.

(ROR 2.67, 95% CI 1.42–5.00), and CTRX (ROR 1.38, 95% CI 1.03–1.85). Whereas this was not observed for CEZ (ROR 0.80, 95% CI 0.47–1.36), CTM (ROR 0.86, 95% CI 0.36–2.07), CAZ (ROR 1.70, 95% CI 0.80–3.58), CFPM (ROR 0.30, 95% CI 0.10–0.92), CZOP (ROR 1.41, 95% CI 0.59–3.42), and CTLZ/TAZ (ROR 4.55 95% CI 0.61–33.74).

Table 3 shows the results of the analysis of the intravenous cephalosporins for which signals were detected with respect to sex and age. For all intravenous cephalosporins, no association was observed with sex. Whereas, an association was found with age for intravenous cephalosporins for which a signal was detected, with the OR for coagulopathy-related events for age ≥70 year being CMZ (OR 6.24, 95% CI 3.39–11.68), CPZ/SBT (OR 3.93, 95% CI 2.08–7.58), FMOX (OR 5.74, 95% CI 1.57–22.59) and CTRX (OR 2.72, 95% CI 1.51–5.07).

DISCUSSION

In this study, we conducted an analysis using the JADER database to examine (1) whether the occurrence of coagulopathy-related events, as defined in the SMQ, can be detected as a signal of adverse events of intravenous cephalosporins, which are frequently used in daily clinical practice, and (2) the potential influence of sex and age on the occurrence of coagulopathy-related events. In this study, "hemorrhage laboratory terms" were defined as the occurrence of coagulopathy-related events. Signals of adverse events were detected for CMZ, CPZ/SBT, FMOX, and CTRX.

There are two possible reasons for the strong signals detected for the three drugs (CMZ, CPZ/SBT, and FMOX). The N-methylthiotetrazole (NMTT) group has been reported to inhibit vitamin K epoxide reductase in the liver, which may lead to hypoprothrombinemia and coagulopathy-related events.[9-10] However, this is not the only reason for the development of coagulopathy-related events. Another contributing factor is thought to be the activity of these three intravenous cephalosporins (CMZ, CPZ/SBT, and FMOX) against *Bacteroides spp.*, which are the major vitamin K-producing bacteria in the human intestinal tract, resulting in vitamin K deficiency.[11] The human gastrointestinal tract is home to trillions of bacteria, most of which are commensals and have adapted to the environment of the human colon over time to form the gut microbiota.[12] The gut microbiota produces various nutrients, including short-chain fatty acids and vitamins B and K.[13-14] In particular, biophilic anaerobes such as *Bacteroides spp.* are the major vitamin K-producing bacteria.[15]

CTRX, a third-generation cephalosporin antibiotic, lacks the NMTT group in its chemical structure and does not exhibit an antibacterial spectrum against polar anaerobes. The mechanism by which CTRX induces coagulopathy is not fully elucidated. However, previous reports suggest that CTRX inhibits the carboxylation of prothrombin. This impaired carboxylation leads to reduced calcium binding and decreased prothrombin activity, ultimately contributing to the development of coagu-

lopathy.[16]

Recently, there have been reports on coagulopathy caused by cefazolin,[17-18] however, no signals of cephazolin-induced coagulopathy were detected in this study. On the other hand, 14 cases of cefazolin-induced coagulopathy were included in the data set generated in this study. Although the risk of occurrence cannot be calculated by disproportionality analysis using JADER, it was considered necessary to focus not only on the ROR but also on the number of cases included in the database.

Analysis of adverse event profiles using OR revealed an association between age and the occurrence of coagulopathy-related events for four cephalosporins for which signals were detected. The findings suggest an increased likelihood of coagulopathy-related events in older patients receiving these cephalosporins.

A caveat in interpreting the results of this study is that, while JADER is capable of detecting signals related to adverse events, it only targets the reporting of adverse event occurrence groups and does not include non-occurrence groups, which may lead to statistical problems.[19] Furthermore, because JADER is a spontaneous report, data are often missing in terms of parameters. To obtain the necessary number of cases for analysis using data excluding the missing data, examining data with only basic information such as age and sex is necessary, and detailed patient information is difficult to obtain, such as concomitant use of anticoagulants such as warfarin and nutritional status. The results of this study did not provide true information, making it difficult to determine whether the results of this study represent the occurrence of coagulopathy-related events or factors associated with them. In addition, the primary reporters of JADER are physicians, pharmacists, and pharmaceutical companies, and reporting bias exists because of the influence of market trends such as the topicality and timing of sales.[19] Among them, CTLZ/TAZ, a fifth-generation cephalosporin drug, is a new drug approved in February 2019 in Japan. Therefore, the number of adverse event reports may have been small at the time of this study, and the results of the analysis may not be sufficient after sufficient information is accumulated on JADER. Although the SMQ was used in this study as the definition of occurrence of "coagulopathy-related events," when PT included in the SMQ are used, researchers are free to select PT at their discretion; therefore, the possibility of bias because of the selection of PTs and their effects on signal detection of the target drug cannot be denied.[20] Therefore, the results of this study should be interpreted based on the assumption that there are various biases. To support the results of this study, studies with a high level of evidence are desirable. Furthermore, in combination with the clarification of the reaction mechanism between the results and special functional groups, the occurrence of coagulopathy-related events should be considered.

In conclusion, in the examination of adverse event case profiles using OR, age was associated with the occurrence of coagulopathy-related events for the four intravenous cephalosporins. The possibility of developing coagulopathy-related events should be considered when administering intravenous cephalosporins that are used in daily clinical practice to patients in the study population.

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Conflict of interest The authors declare no conflict of interest.

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