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Assessment of Reye's syndrome profile with data from the US Food and Drug Administration Adverse Event Reporting System and the Japanese Adverse Drug Event Report databases using the disproportionality analysis

Kiyoka Matsumoto[1], Shiori Hasegawa[1,2], Satoshi Nakao[1,3], Kazuyo Shimada[1], Ririka Mukai[1], Mizuki Tanaka[1], Riko Satake[1], Yu Yoshida[1], Fumiya Goto[1], Misaki Inoue[1], Hiroaki Ikesue[2], Kazuhiro Iguchi[4], Tohru Hashida[2] and Mitsuhiro Nakamura[1]

Abstract

Objectives: Reye's syndrome is a rare and potentially fatal illness that is defined as encephalopathy accompanied by liver failure. The aim of this study was to assess Reye's syndrome profiles by analyzing data from the spontaneous reporting system database.

Methods: We analyzed reports of Reye's syndrome using the US Food and Drug Administration Adverse Event Reporting System and the Japanese Adverse Drug Event Report databases. The reporting odds ratio and proportional reporting rate were used to detect the pharmacovigilance signal.

Results: The US Food and Drug Administration Adverse Event Reporting System contains 12,201,620 reports from January 2004 to June 2020, of which 186 are on Reye's syndrome. The Japanese Adverse Drug Event Report contains 646,779 reports from April 2004 to September 2020, of which 30 are on Reye's syndrome. In the US Food and Drug Administration Adverse Event Reporting System database, the reporting odds ratios (95% confidence interval, number of cases) of aspirin, diclofenac, ibuprofen, acetaminophen, and valproate sodium were 404.6 (302.6–541.0, n = 80), 15.1 (6.7–34.1, n = 6), 26.2 (16.1–42.6, n = 18), 10.7 (5.5–20.9, n = 9), and 47.1 (26.2–84.6, n = 12), respectively. In the Japanese Adverse Drug Event Report database, the reporting odds ratios (95% confidence interval, number of cases) of aspirin, diclofenac, ibuprofen, loxoprofen, acetaminophen, and valproate sodium were 14.1 (5.4–36.8, n = 5), 51.7 (22.2–120.5, n = 7), 135.0 (40.8–446.2, n = 3), 17.6 (6.7–46.0, n = 5), 24.0 (9.2–62.6, n = 5), and 13.8 (3.3–57.9, n = 2), respectively. The reported number of female patients aged 30–39 years was the highest in the Japanese Adverse Drug Event Report.

Conclusion: Although the frequency of the occurrence of Reye's syndrome is low, the possible risk of the disease occurring in adult females should be considered.

Keywords

Pharmacoepidemiology/drug safety, Reye's syndrome, FDA Adverse Event Reporting System database, Japanese Adverse Drug Event Report database

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[1]Laboratory of Drug Informatics, Gifu Pharmaceutical University, Gifu, Japan
[2]Department of Pharmacy, Kobe City Medical Center General Hospital, Hyogo, Japan
[3]Department of Pharmacy, Kyusyu University Hospital, Fukuoka, Japan
[4]Laboratory of Community Pharmacy, Gifu Pharmaceutical University, Gifu, Japan

Corresponding author:
Mitsuhiro Nakamura, Laboratory of Drug Informatics, Gifu Pharmaceutical University, 1-25-4, Daigaku-Nishi, Gifu 501-1196, Japan.
Email: mnakamura@gifu-pu.ac.jp

Introduction

Reye's syndrome (RS) is a rare, serious noninflammatory encephalopathy accompanied by liver dysfunction with fat deposition and mitochondrial deformation.[1] RS occurs within a few days of contracting viral diseases such as chickenpox and influenza and is characterized by vomiting and confusion leading to rapid coma with a significant increase in the mortality rate.[1–5] Epidemiological studies in the United States suggest a relationship between RS and the use of aspirin.[2] Other nonsteroidal anti-inflammatory drugs (NSAIDs), such as diclofenac and ibuprofen, and antiepileptic drugs such as valproic acid might trigger RS.[6–10] Although its etiology and pathophysiology are poorly understood, its cause is believed to be multifactorial.[3]

National surveillance of RS by the Centers for Disease Control and Prevention (CDC, USA) began in 1973. A sharp decline in the number of reported cases of RS was observed following the widespread warnings against the use of aspirin in children.[11,12] Similar patterns of incidence were observed in the United Kingdom and France.[1] In 1998[4] and 2001,[5] the Ministry of Health, Labour and Welfare in Japan included the following precaution in the "Pharmaceuticals and Medical Devices Safety Information": salicylic acid should not be administered as a prescription drug to varicella and influenza patients under the age of 15. The Japanese regulatory authority, Pharmaceuticals and Medical Devices Agency (PMDA) released "The Manual for Handling Disorders due to Adverse Drug Reactions: Acute Encephalopathy in Children" for healthcare professionals and patients.[13] The suspected drugs (salicylic acid, diclofenac, valproic acid) related to RS, diagnostic criteria, and treatment methods are described in this manual.

Spontaneous reporting systems (SRSs) such as the FDA Adverse Event Reporting System (FAERS) database maintained by the US Food and Drug Administration (FDA) and the Japanese Adverse Drug Event Report (JADER) database maintained by the PMDA have been used for pharmacovigilance assessments. SRSs have great significance in the analysis of rare adverse events (AEs)[14–19] and serve as valuable tools in post-marketing surveillance as they reflect the realities of clinical practice. Epidemiological research of RS is difficult as the incidence of RS is rare. The aim of this study was to assess the RS profiles by analyzing data from the SRS databases.

Materials and methods

Data configuration

This study is a retrospective observational study. The structure of the SRS database complies with international safety reporting guidelines (International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2B). The FAERS and JADER databases have been publicly accessible since 2004. As the incidence of RS was infrequent, we have downloaded a wide range of datasets from 2004. The FAERS dataset from January 2004 to June 2020 was downloaded from the FDA website (www.fda.gov). The FAERS database consists of seven data tables: patient demographic and administrative information (DEMO), drug/biologic information (DRUG), AEs (REAC), patient outcomes (OUTC), report sources (RPSR), drug therapy start and end dates (THER), and indications for use/diagnosis (INDI). Outcomes in the FAERS database are classified as "death," "life-threatening," "disability," "hospitalization," "hospitalization (initial or prolonged)," and "others." AEs recorded from April 2004 to September 2020 in the JADER database were downloaded from the PMDA website (www.pmda.go.jp). JADER consists of four tables: patient demographic information (demo), drug information (drug), primary disease (hist), AE and outcome (reac). Outcomes are classified as "death," "with sequelae," "not recovered," "convalescent," "recovery," and "others." Data from the FAERS and JADER databases were integrated into a relational database using FileMaker Pro Advanced 17 (FileMaker, Inc., Santa Clara, CA, USA).

Analysis target

The AE definitions of RS used in this study corresponded to those provided by the Medical Dictionary for Regulatory Activities (MedDRA; www.meddra.org). We evaluated the preferred term (PT) of RS (PT code: 10039012) according to MedDRA. The FAERS database permits contributors to register drugs under any name, including a brand name, trade name, generic name, and an abbreviation. The DrugBank Version 4.0 (The Metabolomics Innovation Centre, Edmonton, AB, Canada; www.drugbank.ca) dataset was utilized as a dictionary for the batch conversion and compilation of drug names.[20,21]

Drugs in the FAERS database are classified into four categories: primary suspect drug (PS), secondary suspect drug (SS), concomitant (C), and interacting (I), according to the anticipated degree of involvement in AEs. Only reports with drugs categorized as PS were included in this analysis. In the JADER database, the causality of each drug was assigned a code according to its association with the AE in the "drug" table. Drugs in JADER are classified into "suspected drug," "concomitant drug," or "interacting drug." The analysis was restricted to reports in which drugs were recorded as "suspected drug."

Duplicate reports in SRS are known to affect assessment and analysis. For the analysis using the FAERS, following the FDA's recommendation, we excluded duplicate reports of the same patient from different reporting sources (Figure 1(a)).[22] It is known that duplicate reports of the same patient exist in the JADER database. PMDA introduced the duplication detection method using the similarity score of duplicate reports, as proposed by WHO-Uppsala Monitoring Centre.[23] However, the JADER database does

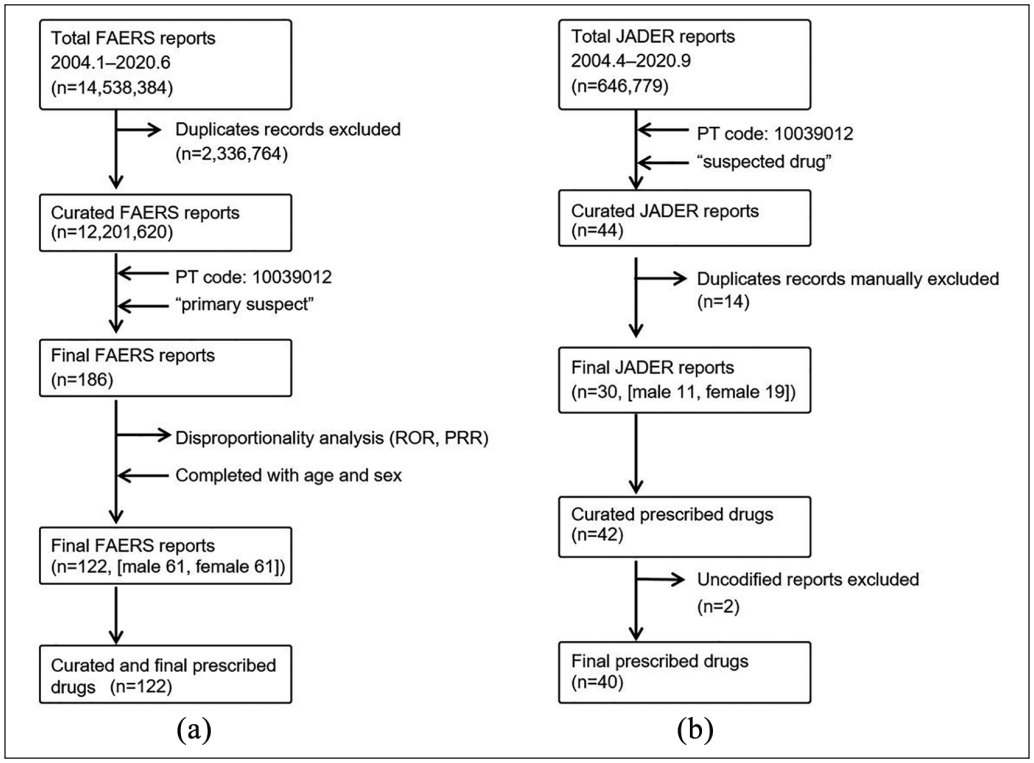

Figure 1. Flowchart of data analysis: (a) FAERS and (b) JADER.

not contain codes for identifying case reports, and therefore we could not exclude duplicate case reports for the same patient based on the proposed method.[23] In contrast, an exclusion method that manually excluded the duplicate cases based on the evaluation of the AE information, AE onset date, outcome, age, and sex in the "reac" table, along with the drug name, the administration start date and end date, and the number of administrations in the "drug" table was reported.[24] We manually excluded cases considered to be duplicates according to the input information of each RS report in the JADER database (Figure 1(b)).

Statistics

Reporting odds ratio (ROR)[25,26] and proportional reporting rate (PRR)[27,28] are used for detecting pharmacovigilance signals. The ROR was calculated using two-by-two contingency tables for the presence or absence of a particular drug and a particular AE in the case reports.[25] Signals were considered statistically significant if the lower limit of the 95% confidence interval (CI) was above 1; at least two cases were required for analysis.[26] The PRR is the proportion of spontaneous reports for the drug of interest that are linked to a specific AE, divided by the corresponding proportion for all other drugs. The threshold for statistical significance was predefined as a PRR of $\geqslant$2.0 with a chi-square test statistic of $\geqslant$4.0 and at least three reports ($n \geqslant 3$) of that PT.[27,28]

Results

The FAERS database contains 14,538,384 reports from January 2004 to June 2020. The number of reports after excluding duplicates according to the FDA recommendations was 12,201,620. The number of AE reports involving RS was 186 (Table 1). The RORs (95% CI, number of cases) of aspirin, diclofenac, ibuprofen, acetaminophen, and valproate sodium were 404.6 (302.6–541.0, n = 80), 15.1 (6.7–34.1, n = 6), 26.2 (16.1–42.6, n = 18), 10.7 (5.5–20.9, n = 9), and 47.1 (26.2–84.6, n = 12), respectively (Table 1). The PRRs of aspirin, diclofenac, ibuprofen, acetaminophen, and valproate sodium were 403.2, 15.1, 26.2, 10.7, and 47.1, respectively (Table 1). After excluding incomplete reports without age or sex information from the 186 cases, the 122 reports included were stratified by age and sex (61 males and 61 females) (Figure 2(a)). The reported number was highest in the stratified age group of 10–19 years for males and 0–9 years for females. The primary illness in the cases reported in the FAERS database were viral pyrexia (13.4%, n = 25/186), infection (8.6%, n = 16/186), influenza (3.8%, n = 7/186), convulsion (2.7%, n = 5/186), Kawasaki disease (2.7%, n = 5/186), epilepsy (2.2%, n = 4/186), and missing data (37.1%, n = 69/186).

The JADER database contains 646,779 reports from April 2004 to September 2020. The total number of reports of RS was 44, of which 30 were selected after excluding duplicate cases. The RORs (95% CI, number of cases) of

Table 1. Reporting odds ratio (ROR) and proportional reporting rate (PRR) of Reye's syndrome.

Database	Category		Total (n)	Case (n)	Noncase (n)	ROR (95% CI)	PRR	Chi-square
FAERS	Total		12,201,620	186	12,201,434			
	NSAIDs	Aspirin	22,797	80	22,717	404.6 (302.6–541.0)	403.2	18062.4
		Diclofenac	26,828	6	26,822	15.1 (6.7–34.1)	15.1	63.5
		Ibuprofen	49,673	18	49,655	26.2 (16.1–42.6)	26.2	371.7
	Antipyretic Analgesic	Acetaminophen	57,790	9	57,781	10.7 (5.5–20.9)	10.7	66.2
	Antiepileptics	Valproate sodium	17,850	12	17,838	47.1 (26.2–84.6)	47.1	464.0
	Others			61				
JADER	Total		646,779	30	646,749			
	NSAIDs	Aspirin	9052	5	9047	14.1 (5.4–36.8)	14.1	40.2
		Diclofenac	3793	7	3786	51.7 (22.2–120.5)	51.6	228.7
		Ibuprofen	535	3	532	135.0 (40.8–446.2)	134.2	247.1
		Loxoprofen	7276	5	7271	17.6 (6.7–46.0)	17.6	51.9
		Mefenamic acid	373	4	369	269.5 (93.6–776.0)	266.6	701.5
		Salicylic acid	206	1	205	–[a]	–[b]	–[b]
	Antipyretic Analgesic	Acetaminophen	5358	5	5353	24.0 (9.2–62.6)	23.9	73.3
	Antiepileptics	Valproate sodium	3334	2	3332	13.8 (3.3–57.9)	–[b]	–[b]
	Others			11				

CI: confidence interval; FAERS: FDA Adverse Event Reporting System; JADER: Japanese Adverse Drug Event Report.
[a]Number of cases <2.
[b]Number of cases <3.

aspirin, diclofenac, ibuprofen, loxoprofen, acetaminophen, and valproate sodium were 14.1 (5.4–36.8, n = 5), 51.7 (22.2–120.5, n = 7), 135.0 (40.8–446.2, n = 3), 17.6 (6.7–46.0, n = 5), 24.0 (9.2–62.6, n = 5), and 13.8 (3.3–57.9, n = 2), respectively (Table 1). The PRRs (95% CI, number of cases) of aspirin, diclofenac, ibuprofen, loxoprofen, mefenamic acid, and acetaminophen were 14.1, 51.6, 134.2, 17.6, 266.6, and 23.9, respectively (Table 1). In the 30 reports, 11 patients were male and 19 were female, with 2 males and 7 females aged 30–39 years (Figure 2(b)). The reported number was the highest in the stratified age group of 30–39 years for females. Administration of over-the-counter (OTC) drugs was observed in three reports. The primary illnesses (clinical background) in the cases reported in the JADER database were influenza (23.3%, n = 7/30), upper respiratory tract inflammation (16.7%, n = 5/30), and bronchitis (6.7%, n = 2/30), and missing data (36.7%, n = 11/30).

The total number of suspected drugs for RS in JADER was 42, and the drug name and age were included in 40 cases. The ratio of NSAIDs in patients aged 30–39 years was 85.7% (12/14) (Figure 3(b)). Moreover, the percentage of NSAIDs administered to females aged 30–39 years was 72.7% (8/11 reports) (data not shown).

We used a mosaic plot to summarize the outcome profiles of RS stratified with age group (Figure 4). Incidence of outcome by age was significantly different in the FAERS database (p = 0.0159). The fatal outcome of RS is a major clinical problem. Death is a common objective outcome in both FAERS and JADER databases. The reporting ratio of death due to RS was 42.7% (70/164 cases) in the FAERS database. Incidence of outcome by age was significantly different in the JADER database (p = 0.1528). The reporting ratios of outcomes for death to all RS was 46.4% (13/28 cases).

Discussion

According to "The Manual for Handling Disorders due to Adverse Drug Reactions" distributed by the PMDA, several drugs such as antipyretic analgesics (aspirin, mefenamic acid, diclofenac), xanthine preparations (theophylline), antihistamines, calcineurin inhibitors (ciclosporin, tacrolimus), and glyceol may cause childhood acute encephalopathy.[13] The ROR signals of aspirin, diclofenac, ibuprofen, and valproic acid were detected in FAERS and JADER (Table 1). These are reasonable results in the context of the literature available.[4–10] Our study indicates the importance of evaluating the safety profiles of drugs using post-marketing real-world data.

From December 1980 to November 1997, the percentage of females was 51.9% (618/1190 reports) in a survey on RS in the United States.[29] In an RS survey conducted in Northern Ireland in 1979–1982, the total number of cases was 23, with the number of females being twice that of males.[30] The percentages of females in the FAERS and JADER databases were 50.5% and 60.7%, respectively.

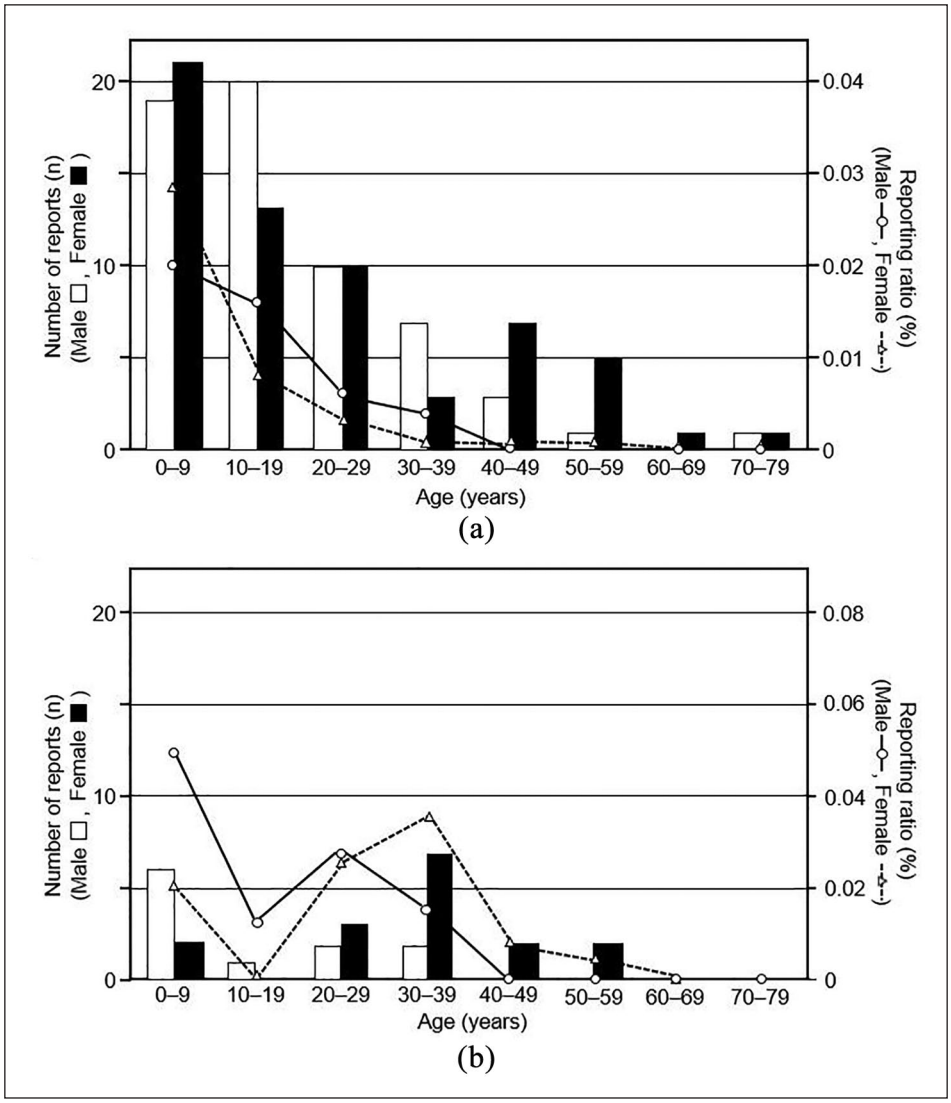

Figure 2. Number of reports and reporting odds ratio associated with Reye's syndrome stratified by age and sex: (a) FAERS and (b) JADER.

The incidence of RS is less than 3 per million,[31] observed almost exclusively in children.[32–34] Less than 2% of these cases were reported in adults.[31] There are several reports of patients who contracted RS in their late teens or 20s in North America.[32,35–37] In contrast with the results from FAERS, the reported number of female patients aged 30–39 years was the highest in JADER even after removing duplicate reports (Figure 2(a) and (b)). Therefore, although RS is often regarded as a childhood disease, reports of RS in adult females cannot be ignored.

It is reported that the usage of aspirin and the occurrence of RS in Japan are lower compared with those in the United States.[13] The share of NSAIDs in the analgesic drug market is approximately 21.3% in the United States and 33.5% in Europe, while it is high at 80.7% in Japan.[38,39] Acetaminophen, which is considered safer than other NSAIDs, is mainly used in the United States and Europe.[40] In contrast, more than 95% of the doctors prescribe NSAIDs for musculoskeletal diseases in Japan, with only 10% prescribing acetaminophen.[40] The percentage of patients aged 30–39 years who were prescribed NSAIDs was 85.7% (12/14) (Figure 3(b)). Therefore, the percentage of NSAIDs within the age group of 30–39 years was higher in JADER than in FAERS. Overuse of NSAIDs in Japan might be one of the reasons for the high reporting rate of RS in 30- to 39-year-old females in the JADER database. Because the reports of RS mentioned administration of OTC drugs including NSAIDs, we believe that attention should be paid to the proper use of OTC drugs in adult females.

Because of the warning by PMDA, it is considered that Japanese healthcare professionals are well aware of the risk of RS in children. Therefore, RS onset in children might be well suppressed in Japan. In the JADER database, few reports of RS in children were observed, and, apparently, the

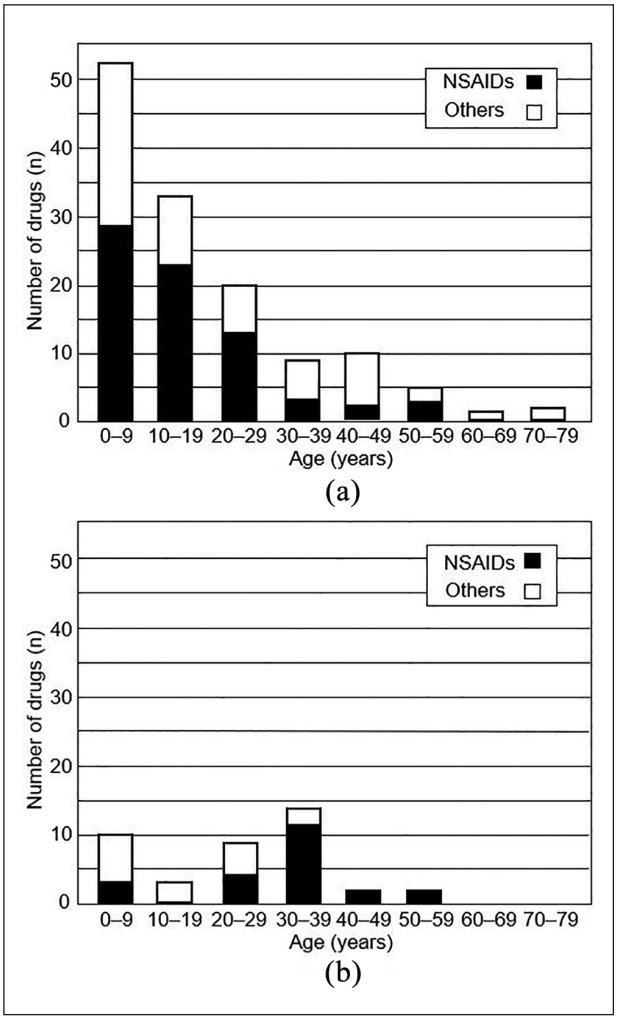

Figure 3. Number of reports associated with Reye's syndrome stratified by the type of suspected drugs: (a) FAERS and (b) JADER.

number of adult female reports seemed high. The objection will no doubt be raised that this hypothesis is weak and difficult to prove; however, this may be another thought-provoking reason for the high reporting rate of RS in 30- to 39-year-old females in the JADER database.

RS has a poor prognosis and a high mortality rate. The overall case fatality rate was 31% according to the survey in the United States.[29] From the Adverse Drug Reactions On-line Information Tracking (ADROIT) database in the United Kingdom, 12 fatalities might be associated with the use of an NSAID from 1964 to December 2000.[41] RS was associated with a fatal outcome in five cases. Aspirin was administered in four of these cases.[42] Our results demonstrated that even adults have significant outcomes such as death in the SRS datasets (Figure 4).

The number of spontaneously reported cases is greatly affected by media attention and publicity resulting from regulatory actions such as safety information. The warning by the PMDA might result in increased reporting ratio, which is a phenomenon known as notoriety bias.[43–45] However, the warnings of RS by PMDA were issued in 1998[4] and 2001[5] that were outside the range of 2004–2020 of the JADER dataset in this analysis. Therefore, notoriety bias does not seem to affect our results. The Weber effect is an epidemiological phenomenon describing substantial AE reporting peaks when the drug is first approved by the regulatory authority, which then plateaus and eventually declines.[46–48] However, the Weber effect is not always observed,[48] and the number of reports generally increases over the first 2 years after approval of a new drug.[49,50] Since NSAIDs and valproic acid are conventional and common drugs, it might be difficult to explain our results based on Weber effect.

Risk factors for RS include inborn errors of metabolism related to fatty acid metabolism.[1–5] There was no such patient in the relevant reports in FAERS and JADER. This suspected risk factor is very interesting, but could not be investigated further.

We restricted reports for analysis in which drugs were recorded as PS in the FAERS or "suspected drug" in the JADER because the calculated RORs and PRRs might vary depending on the selection of the code that was assigned causality by contributors. Moreover, healthcare professionals, pharmaceutical companies, patients, and consumers voluntarily send AE reports to the regulatory authorities according to ICH E2B. It might be difficult to confirm the criteria of causality used to define RS events by volunteers at the time of reporting. With a narrow selection of drugs, the identification of cases is highly likely to represent the condition of interest, and if the code that was assigned causality are selected broadly (SS, C, and I), the identification of cases might contain all possible cases, including some that may prove to be of little or no interest on closer inspection. In the FAERS database, the reporting ratios of NSAID use were as follows: 54.9% (67/122 primary suspect (PS) drugs), 29.5% (43/146 secondary suspect (SS) drugs), and 3.8% (6/158 concomitant drugs). In the JADER database, the reporting ratios of NSAID use were as follows: 55.0% (22/40 suspected drugs) and 13.3% (6/45 concomitant drugs). The "narrow" scope yields "specificity," while the "broad" search yields "sensitivity." Many previous reports using SRS were restricted to reports in which drugs were recorded as a "suspected drug."[16,19,51] The data in the SRS database have been reported by healthcare "professionals." We believe that these results are worthy of evaluation and that these data suggest the association of certain drugs with RS.

There are several limitations to this study. SRSs are subject to over-reporting, under-reporting, missing data, exclusion of healthy individuals, lack of denominators, and presence of confounding factors.[16] External factors such as the release of safety information from regulatory authorities and market trends may affect AE reports. Cases reported in the FAERS database and the JADER database do not always contain sufficient information

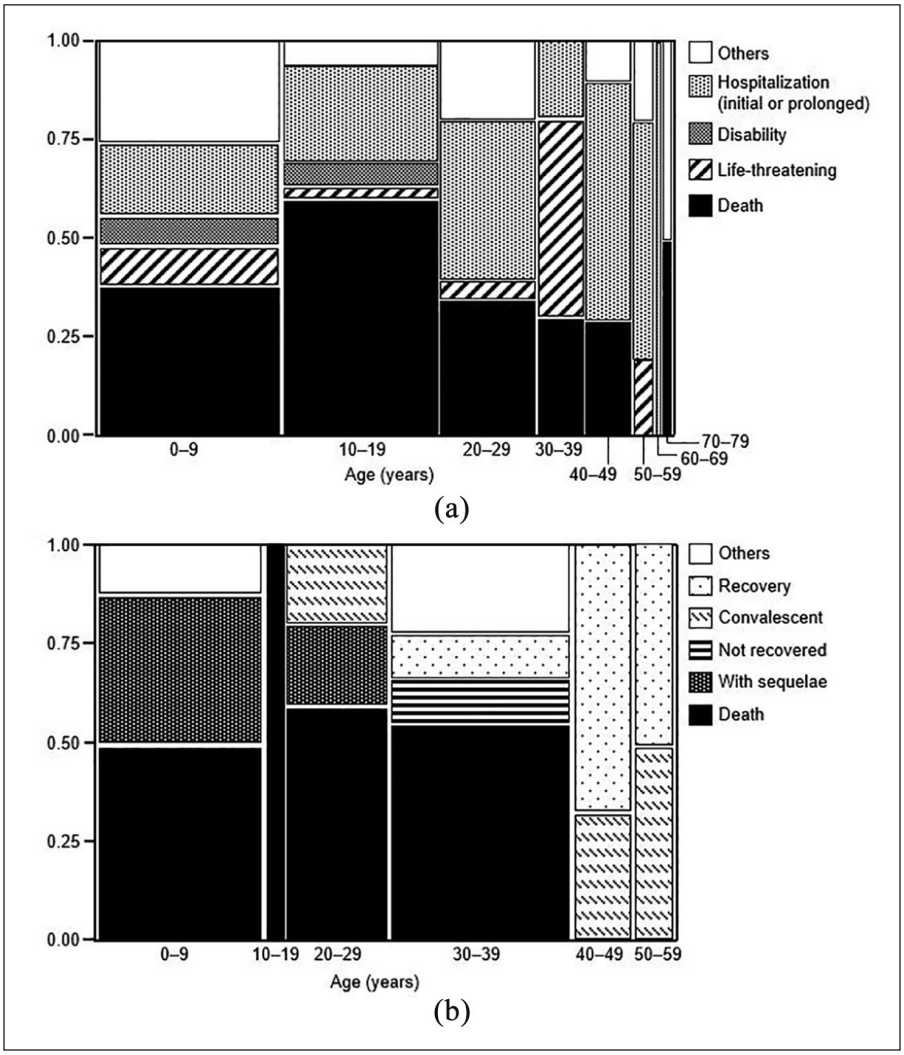

Figure 4. Mosaic plot of outcomes of Reye's syndrome stratified by age. A mosaic plot is divided into rectangles where each vertical length represents the proportion of each level of the Y variable within each level of the X variable: (a) FAERS and (b) JADER.

about patient background such as comorbid condition and concomitant drug administration to allow for proper evaluation. We evaluated primary illness and concomitant drugs (e.g. antibiotics (azithromycin, cefcapene, cefdinir), oseltamivir, phenobarbital, etc.). However, we could not find a convincing tendency. More detailed analysis focusing on these factors is a subject for future investigation.

Conclusion

The ROR and PRR signals of aspirin, diclofenac, ibuprofen, and valproic acid were detected in both databases. Although its frequency is exceptionally low, the possible risk of RS in women must not be overlooked.

Author contributions

KM, SH, SN, and MN contributed to the overall concept and design of the study. KM and MN wrote the main manuscript. KM, KS, RM, MT, RS, YY, FG, and MI carried out data extraction and statistical analysis. HI, KI, and TH revised the article critically for important intellectual content. All authors have reviewed the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our research does not fall within the purview of any of the following laws and guidelines: "Clinical Trials Act (Act No. 16 of April 14, 2017)," "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Law number: Act No. 145 of 1960, Last Version: Amendment of Act No. 50 of 2015)," "Guideline for good clinical practice E6 (R1), https://www.pmda.go.jp/int-activities/int-harmony/ich/0076.html," "Ethical guidelines for human genome and gene analysis research, https://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/genome/0504sisin.html," and "Ethical Guidelines for Medical

and Health Research Involving Human Subjects, https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/index.html#HID1_mid1." Therefore, it is not subjected to ethical examination.

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Informed consent

Ethical approval was not sought for this study because it was a retrospective observational study and no research subjects were enrolled. All the results were obtained using data openly available online from the FDA and PMDA websites. All data from the FAERS and JADER databases were fully anonymized by the regulatory authorities before we accessed them.

Trial registration

Not applicable.

ORCID iD

Mitsuhiro Nakamura https://orcid.org/0000-0002-5062-5522

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