Drugs - Real World Outcomes (2022) 9:315–319
https://doi.org/10.1007/s40801-022-00306-6

SHORT COMMUNICATION

Itraconazole Contaminated with Rilmazafone in Japan: A Retrospective Analysis Using the Japanese Adverse Drug Event Report Database

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Accepted: 26 April 2022 / Published online: 23 May 2022

Abstract

Background In early December 2020, the antifungal medication, itraconazole (ITCZ), was mistakenly contaminated with rilmazafone in Japan. Healthcare professionals reported adverse drug reaction reports associated with ITCZ and included central nervous system-depression symptoms such as dizziness, lightheadedness, loss of consciousness, and intense drowsiness.
Objective We examined ITCZ-associated suspicious cases using the Japanese Adverse Drug Event Report (JADER) database to determine the impact of adverse drug reaction reporting on post-marketing safety measures.
Methods Adverse drug reaction reports in which the suspicious or concomitant medication was ITCZ or fluconazole (FLCZ) were extracted from the JADER dataset. The number of adverse drug reaction reports associated with central nervous system-depression adverse drug reactions were counted, and chronological changes were compared with ITCZ and FLCZ.
Results Of the 713,893 adverse drug reaction reports in the JADER database, 5048 cases were associated with ITCZ and 6007 cases with FLCZ. When ITCZ contamination occurred, the number of adverse drug reaction reports associated with ITCZ increased rapidly, while those with FLCZ did not. In addition, the proportion of central nervous system-depression adverse drug reactions increased only in the ITCZ-associated report.
Conclusions An incident of ITCZ contamination with rilmazafone was detected on the JADER retrospectively. This case highlights the importance of spontaneous adverse drug reaction reporting, even if the causal relationship between the drug and adverse drug reaction is unknown.

Key Points

In early December 2020, the antifungal medication, itraconazole, was mistakenly contaminated with rilmazafone in Japan.

This incident was discovered as a result of healthcare professionals' adverse drug reaction reporting associated with itraconazole and included central nervous system-depression symptoms.

Voluntary adverse drug reaction reporting might be the only method for detecting unexpected adverse drug reactions associations for post-marketing safety measures.

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1 Introduction

In early December 2020, the antifungal medication, itraconazole, (ITCZ; tablet 50 mg; 'MEEK') was discovered to be mistakenly contaminated with rilmazafone [1]. The pharmaceutical company informed the Ministry of Health, Labour, and Welfare of the incident on 4 December. On the evening of the same day, the company announced a Class I voluntary recall of the single applicable batch (92,900 tablets). The drug was contaminated with rilmazafone hydrochloride hydrate, a sleep-inducing ingredient, at a concentration of 5 mg per tablet. The regular clinical dose of rilmazafone is 1–2 mg per day according to the package insert in Japan. Therefore, if the contaminated ITCZ was taken four times a day, the dosage would be 20 mg; this means that the drug was contaminated with as much as 10–20 times the usual daily dosage. According to the Ministry of Health, Labour, and Welfare letter [2], after 1 December, 2021, pharmacies in Gifu, Osaka, and Saga (Prefectures in Western Japan) reported several cases of adverse reactions after taking ITCZ-MEEK tablets. Adverse drug reaction (ADR) reports included dizziness, lightheadedness, loss of consciousness, and intense drowsiness. In addition, there were damage reports of automobile accidents, emergency transport, hospitalization, and falls due to psychiatric and neurological symptoms [2]. Finally, the pharmaceutical company admitted that the problem was caused by "human error in operations" and a problem with the checking system in the manufacturing process [3]. As of 11 December, 2021, contaminated ITCZ tablets were prescribed to 344 patients, and 324 were administered. Of these, 245 people reported health implications, including two fatalities, 38 traffic accident cases, and 41 emergency transport and hospital admission cases [3].

An ADR reporting system is fundamental to post-marketing drug safety measures. Direct ADR reporting from healthcare professionals plays an essential role in providing detailed ADR cases and implementing rapid safety measures [4, 5]. In addition, the ADR reporting system is also designed for hypothesis generation; therefore, these databases are often used for statistical screening in the detection of signals of harm caused by drugs [6–9]. The ADR reports from the pharmacies and hospitals to the pharmaceutical company or the regulatory authority occurred at the beginning of the revelation of this incident. A spontaneous ADR reporting system is important in detecting unexpected ADRs much earlier. The current study aimed to reveal the role of spontaneous ADR reporting in ITCZ-associated incidents in Japan, retrospectively through the analysis of the Japanese Adverse Drug Event Report (JADER) database. We examined ITCZ-associated suspicious cases using the JADER database to determine the impact of ADR reporting on post-marketing safety measures.

2 Methods

2.1 Source of Data

The JADER202110 dataset (consisting of ADR reports received by the Pharmaceuticals and Medical Devices Agency from April 2004 to June 2021) was downloaded and analyzed. The JADER database uses a report format based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E2B-M2 (R3) and consists of four tables: (1) case list table (demo); (2) drug information table (drug); (3) ADR information table (reac); and (4) underlying disease table (hist). From the JADER202110 dataset, the data for suspicious or concomitant medications and the data for the ADRs were extracted and connected. All ADRs and underlying diseases were coded using the Medical Dictionary for Regulatory Activities/Japanese version terminology (Version 24.1) preferred terms. To observe the trend in ADRs associated with ITCZ, we also extracted ADR reports in which the suspicious or concomitant medication was ITCZ or fluconazole (FLCZ) from the connected dataset. Fluconazole is also widely used as an antifungal medication and was therefore used as a negative test. In Japan, ITCZ and FLCZ are approved as oral and injection forms. Therefore, we have no restrictions on the route of ITCZ or FLCZ. Thus, the data analyzed were a mixture of oral and injection forms. Because the reported ADRs included the central nervous system (CNS)-depression-related ADRs, we focused on the CNS-depression-related preferred terms as follows: somnolence, amnesia, dizziness, memory impairment, altered state of consciousness, loss of consciousness, falls, depressed level of consciousness, and traffic accidents.

2.2 Statistical Methods

Data obtained from each ADR report were synthesized by providing descriptive tables reporting ADRs. The findings were presented chronologically. A chi-square test and Fisher's exact test were used to compare the observed proportions of CNS-depression ADRs. All p-values were two-sided, and statistical significance was set at $p < 0.05$. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA; RRID:SCR_008567) was used for all analyses.

3 Results

Of the 713,893 ADR reports in the JADER database, 5048 cases (0.7%) were associated with ITCZ and 6007 cases (0.8%) with FLCZ. After the connection with ADR data and deletion of duplication, 10,500 reports associated with ITCZ and 13,300 reports associated with FLCZ were finally analyzed.

A comparison of the number of ADR reports between ITCZ and FLCZ is shown in Fig. 1. In the third and fourth quarters of 2020, when ITCZ contamination occurred, the number of ADR reports associated with ITCZ increased rapidly. Before the incidental period, the trend in the number of ADR reports was similar for both antifungal medications.

In the incident, ITCZ tablets were contaminated with rilmazafone, a sleep-inducing ingredient. We focused on the CNS-depression ADRs. Table 1 describes the number of CNS-depression ADR reports associated with ITCZ and FLCZ in each time period based on the reporting date. In the third and fourth quarters of 2020, the proportion of CNS-depression ADRs increased only in the ITCZ-associated report. Figure 2 shows the detailed first onset date of

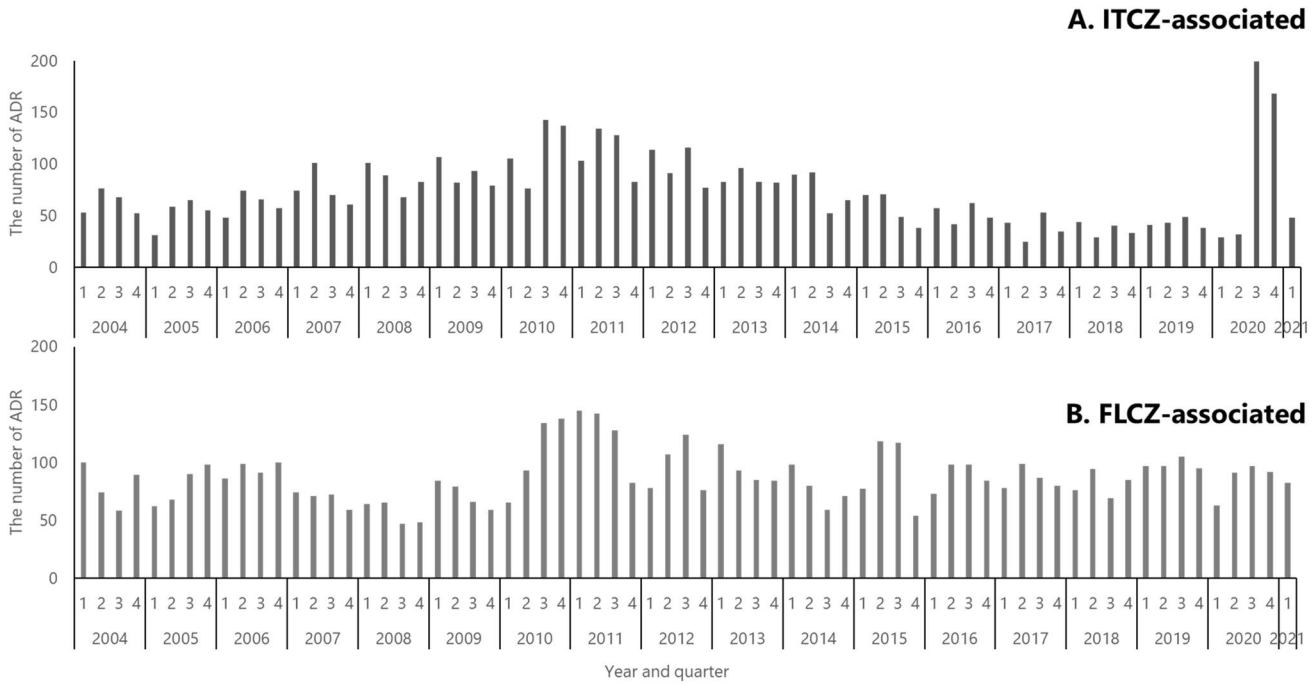

Fig. 1 Comparison of the number of adverse drug reaction (ADR) reports associated with itraconazole (ITCZ) or fluconazole (FLCZ). **A** ITCZ-associated cases, **B** FLCZ-associated cases

Table 1 Number of ADR reports associated with ITCZ and FLCZ in each time period (based on report date)

	–2019 4th quarter (–2020/3)	2020 1st quarter (2020/4–6)	2020 2nd quarter (2020/7–9)	2020 3rd quarter (2020/10–12)	2020 4th quarter (2021/1–3)	2021 1st quarter (2021/4–6)
ITCZ-associated cases ($n = 5048$)	4572	29	32	199	168	48
Including CNS-depression ADRs ($n = 334$) (Reference)	59 (1.3%)	1 (3.4%)	0 (0%)	150 (75.4%)	121 (72.0%)	3 (6.3%)
FLCZ-associated cases ($n = 6007$)	5582	63	91	97	92	82
Including CNS-depression ADRs ($n = 101$)	92 (1.6%)	0 (0%)	1 (1.1%)	2 (2.1%)	3 (3.3%)	3 (3.7%)
P value	0.1385*	0.3152**	1.0000**	< 0.0001*	< 0.0001*	0.6692**

ADR adverse drug reaction, *CNS* central nervous system, *ITCZ* itraconazole, *FLCZ* fluconazole

*Chi-square test

**Fisher's exact test

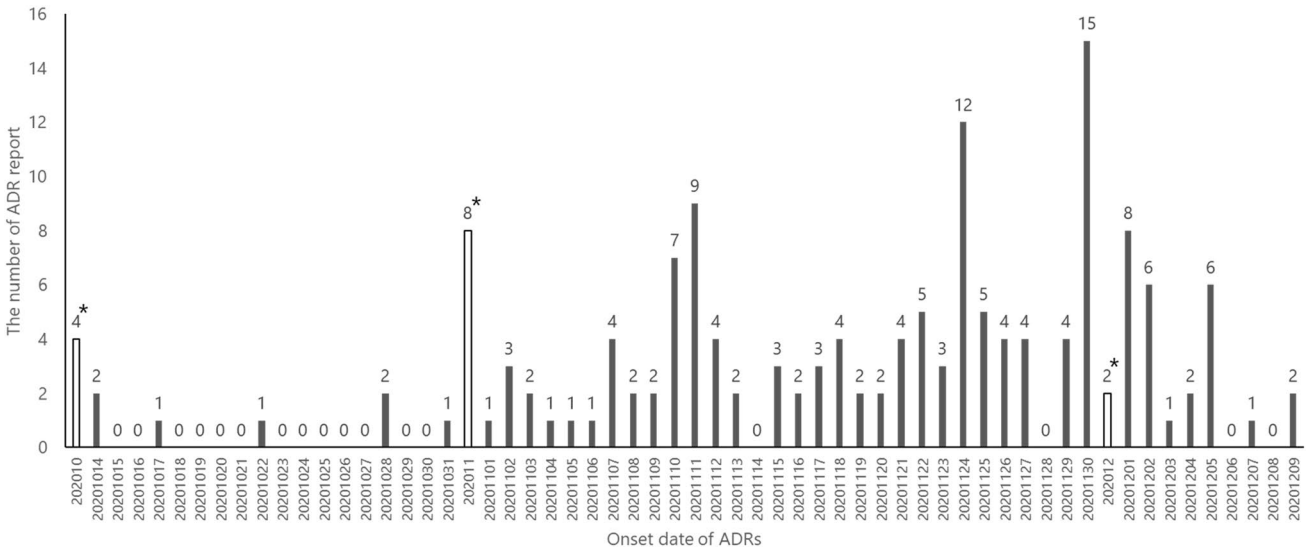

Fig. 2 Detailed first-onset date of itraconazole (ITCZ)-associated adverse drug reaction (ADR) cases with central nervous system (CNS)-depression ADRs. *White rectangles represent the number of ADR reports in which the onset date includes only the year and month

ITCZ-associated ADR reports with CNS-depression ADRs from October 2020. The number of ITCZ-associated ADR reports with CNS depression increased gradually in November 2020 and reached a peak on 30 November, 2020.

4 Discussion and Conclusions

The number of reports of CNS-depression ADRs associated with ITCZ decreased as soon as the recall announcement was made (Fig. 2). An appropriate safety measure could be executed because of ADR reporting on unexpected ADRs. This approach may be helpful to detect a contamination problem associated with a very noticeable and immediate event. However, other more long-term or not-so-apparent events would surely go unnoticed and indeed require different approaches [10].This study had some limitations. The exact date of ADR reporting could not be obtained because of the restriction on data use and provision (the reporting date was rounded off by quarter). The exact reporting date will facilitate the analysis of the relationship between reporting date and ADR onset more precisely. Multiple reports registered in the database in duplicate were deleted based on case information, and each case was regarded as one report as far as possible. However, there remains the possibility of duplicated reports, whereby one case might be reported multiple times and with multiple sources. This possibility cannot be excluded completely because there are no identifiers for the same case [11]. Most CNS-depression ADRs associated with ITCZ may have been reported after the announcement or news. Furthermore, without an a priori hypothesis, broader Medical Dictionary for Regulatory Activities queries or groups should be used to detect safety signals in routine pharmacovigilance measures. To contribute more to post-marketing safety measures, close monitoring and rapid ADR reporting by healthcare professionals should be encouraged to identify potential safety concerns and generate hypotheses [12].

This is the first report to reveal the role of spontaneous ADR reporting in ITCZ-associated incidents in Japan, retrospectively. The primary methods to avoid harm associated with quality failures includes regulatory authorities inspecting manufacturers routinely (i.e., Good Manufacturing Practices audit) and pharmaceutical companies performing internal and external quality controls. If these methods do not work well, voluntary ADR reporting might be the only means to detect drug-unexpected ADR associations for post-marketing safety measures. Of course, these reactive approaches should not be considered primary systems but complementary. Using pharmacovigilance databases for detecting these problems indicates that primary systems have failed and harm can no longer be avoided. This case highlights the importance of ADR reporting, even if the causal relationship between the drug and ADR is unknown. A spontaneous ADR reporting system will continue to play an important role in detecting drug and ADR associations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-022-00306-6.

Acknowledgements This research was partially funded by the Japan Agency for Medical Research and Development (22mk0101228h0001) as a part of the Research on Regulatory Harmonization and Evaluation of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics Project.

Authors' Contributions All authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by MT and TO. The first draft of the manuscript was written by MT and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Funding This study was partially funded by the Japan Agency for Medical Research and Development (Grant no. 22mk0101228h0001).

Conflicts of interest/competing interests Masami Tsuchiya and Taku Obara declare that they have no conflicts of interest that are directly relevant to the content of this article. Nariyasu Mano received consultation fees from Daiichi Sankyo Co., Ltd.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data are available upon reasonable request from the authors.

Code availability Not applicable.

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