Regular Article

Adverse Drug Events Caused by Drugs Contraindicated for Coadministration Reported in the Japanese Adverse Drug Event Report Database and Recognized by Reporters

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The "INTERACTIONS" section of package inserts aims to provide alert-type warnings in clinical practice; however, these also include many drug–drug interactions that occur rarely. Moreover, considering that drug–drug interaction alert systems were created based on package inserts, repeated alerts can lead to alert fatigue. Although investigations have been conducted to determine prescriptions that induce drug–drug interactions, no studies have focused explicitly on the adverse events induced by drug–drug interactions. We, therefore, sought to investigate the true occurrence of adverse events caused by drug pair contraindications for coadministration in routine clinical practice. Toward this, we created a list of drug combinations that were designated as "contraindications for coadministration" and extracted the cases of adverse drug events from the Japanese Adverse Drug Event Report database that occurred due to combined drug usage. We then calculated the reporters' recognition rate of the drug–drug interactions. Out of the 2121 investigated drug pairs, drug–drug interactions were reported in 43 pairs, 23 of which included an injected drug and many included catecholamines. Warfarin potassium and miconazole (19 reports), azathioprine and febuxostat (11 reports), and warfarin potassium and iguratimod (six reports) were among the 20 most-commonly reported oral medication pairs that were contraindicated for coadministration, for which recognition rates of drug–drug interactions were high. Although these results indicate that only a few drug pair contraindications for coadministration were associated with adverse drug events (43 pairs out of 2121 pairs), it remains necessary to translate these findings into clinical practice.

Key words adverse drug event; drug–drug interaction; contraindicated combination; interaction recognition; alert fatigue; spontaneous reporting system

INTRODUCTION

Drug–drug interactions (DDIs) refer to phenomena in which the effects of drugs are modified through coadministration and are the cause of adverse drug events (ADEs).[1–4] ADEs that are caused by DDIs can be prevented by avoiding coadministration of relevant drugs. Therefore, some medical institutions have introduced a DDI alert system to alert a prescribing physician whenever prescriptions are entered with known associated DDIs.[1,4–12] Ahn *et al.* reported that the use of a DDI alert system would help reduce medication errors and contribute toward improving patient safety.[1] Meanwhile, Japanese Package Inserts (JPIs) aim to provide alert-type warnings in clinical practice.[13] Therefore, some of the ADEs caused by DDIs described in the "INTERACTIONS" section of JPIs are thought to include those that are rarely expressed. Indeed, increasing the amount of information on DDIs would result in increased frequency of these alerts, while repeated DDI alerts could be time consuming and mentally exhausting for physicians, ultimately causing alert fatigue.[4–6,9–11] Additionally, alert fatigue may result in important DDI alerts being overridden and subsequent ADEs occurring in patients caused by DDIs.[12] For instance, Yeh *et al.* reported that 91% of the 11084 DDI alerts detected over the course of one year in a hospital with a DDI alert system had been overridden. They also mentioned that in 82% of all alerts, the prescribing physicians had recognized that the combination of drugs being used could cause DDIs.[4] Furthermore, Nasuhara *et al.* reported that out of the 170 DDI alerts regarding contraindications for coadministration (CC), and relative CC that were issued over the course of one year at their facilities, 111 alerts were overridden. However, the ADE occurrence was not reported in this study.[5]

Although studies have been performed to investigate prescriptions that can cause DDIs, none have focused on the occurrence of ADEs due to DDIs. Therefore, we sought to investigate the prevalence of ADEs occurring following the administration of drug pairs with CC, and to translate this information back to routine clinical practice. The Japanese Adverse Drug Event Report (JADER) database accumulates and reports cases of ADEs in the country. Currently this database contains more than 400000 registered ADE cases and is widely used for monitoring drug safety.[14–19] Additionally, the recognition of DDIs by prescribing physicians or drug-dispensing pharmacists may affect the occurrence of ADEs due to DDIs. Therefore, we also investigated the incorporation of DDIs into the JADER database.

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MATERIALS AND METHODS

Combination of Drugs Contraindicated for Coadministration In the "INTERACTIONS" section of JPIs, DDIs are described in three categories: "CC," "Relative CC," and "Precautions for coadministration." In this study, we focused on CC. By using the JAPIC Ethical and OTC Drugs (installation version) (07/2018), we listed all CC drug pairs based on the following criteria:

Condition 1: When the JPI for both drugs identify CCs.
Condition 2: When the JPI for only one of the two drugs identifies CCs.

ADEs That Were Caused by DDIs ADEs due to DDIs are listed in the "INTERACTIONS" section of JPIs. However, "increased blood drug concentration," or "enhanced action" may be described instead of ADEs due to DDIs. In these cases, the ADEs described in the "OVERDOSAGE" section of the JPI were considered as the ADEs due to DDIs.

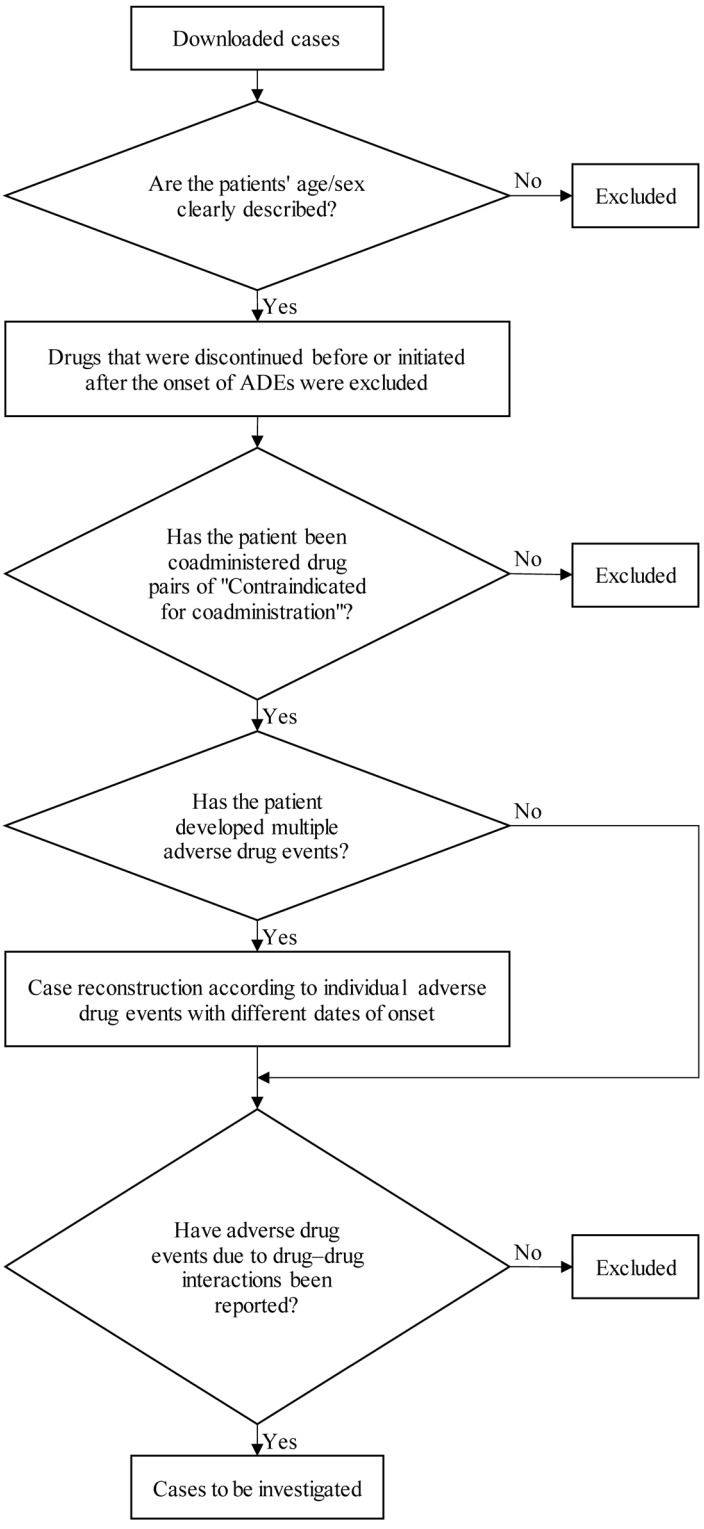

Fig. 1. Flowchart of the Steps Taken to Filter and Extract Suitable Cases for Investigation

Database Information We downloaded information from the JADER database hosted on the Pharmaceuticals and Medical Devices Agency website (https://www.pmda.go.jp/), which collects, analyzes, and provides information related to drug approval reviews and post-marketing safety in Japan. In this study, JADER cases from April 2004 to July 2018 were used. The JADER database consists of four tables, *i.e.*, demo table, drug table, reac table, and hist table, which are linked by a common identification number. The information we extracted included (1) "Sex," (2) "Age," (3) "Qualifications of the reporter," (4) "Drug (non-proprietary name)," (5) "Drug involvement," (6) "Route of administration," (7) "Date of treatment onset," (8) "Date of treatment end," (9) "ADE(s)," and (10) "Date of ADE(s) onset." Items (1) to (3) are listed in the demo table, items (4) to (8) in the drug table, and items (9) and (10) in the reac table. Although many cases that are registered in the JADER database were reported by a single type of healthcare professional (*e.g.*, a physician or pharmacist) as well as a consumer, there were also cases reported by multiple types of healthcare professionals and/or consumers. Additionally, multiple ADEs may be registered under a single identification number in the JADER database. Therefore, we considered ADEs that occurred on the same day as being associated with the same case. Meanwhile, ADEs that occurred on different days were considered as different cases. Since ADEs were listed as per the preferred terms (PT) of the Medical Dictionary for Regulatory Activities/J (MedDRA/J) version 21.0, all the processing was conducted at the PT level.

Extraction of Cases for Investigation The procedure to extract the cases is shown in Fig. 1. First, we extracted the cases in which sex and age were clearly described. Next, drugs that were discontinued before the onset of ADEs, as well as drugs that were initiated after ADE onset, were excluded. We then extracted cases for which drug pairs of CC were used. Thereafter, the cases with ADEs due to DDIs were extracted. However, ADEs that occurred before the JPI revisions as CC, were excluded. To distinguish between DDIs that can occur in routine clinical practice and those that can occur in emergent situations, we divided drug pairs of CC into pairs with injection and pairs without injection.

Reporters' Recognition Rate of DDIs In the "Drug involvement" column of JADER, the "suspected drug," "concomitant drug," and "interaction" are registered for each drug as the involvement of the drug in ADEs. In this study, we surmised that the reporter of a case had recognized the DDIs at the time of reporting when the "Drug involvement" column for both drugs involved in the CC had been registered as "interaction." Among the cases in which DDI-induced ADEs occurred, the proportion of cases registered as "interaction" was defined as the reporters' recognition rate of DDIs.

RESULTS

Drug Pairs Contraindicated for Coadministration and the Number of Cases in the JADER Database A total of 517816 ADEs were downloaded from JADER. After searching through the JPIs, we identified 2121 drug pairs of CC. Of these drug pairs, ADEs caused by DDIs were registered in the JADER database for 43 pairs, of which 20 pairs did not include an injected drug (Table 1), while 23 pairs did (Table 2). Of the 20 pairs, warfarin potassium and miconazole (19 reports), tacrolimus hydrate and cyclosporine (12 reports), azathioprine and febuxostat (11 reports), warfarin potassium and iguratimod (six reports), and tizanidine hydrochloride and fluvoxamine maleate (five reports), were the most commonly reported. In contrast, among the 23 pairs, the most commonly reported pairs included ephedrine hydrochloride and dopamine hydrochloride (14 reports), adrenaline and noradrenaline (10 reports), ephedrine hydrochloride and adrenaline (seven reports), adrenaline and dobutamine hydrochloride (four reports), sodium valproate and meropenem hydrate (three reports), and noradrenaline and sevoflurane (three reports).

Table 1. Drugs Contraindicated for Coadministration, for Which Drug–Drug Interaction (DDI)-Induced Adverse Drug Events Were Reported in the Japanese Adverse Drug Event Report (Injectables Not Included)

Drug 1	Drug 2	Cases (Recognized as DDIs)	Recognition rate of DDIs
Warfarin potassium	Miconazole	19 (15)	78.9%
Tacrolimus hydrate	Cyclosporin	12 (0)	0.0%
Azathioprine	Febuxostat	11 (10)	90.9%
Warfarin potassium	Iguratimod	6 (4)	66.7%
Tizanidine hydrochloride	Fluvoxamine maleate	5 (1)	20.0%
Potassium chloride	Eplerenone	4 (0)	0.0%
Pimozide	Clarithromycin	4 (1)	25.0%
Atazanavir sulfate	Indinavir sulfate ethanolate	2 (0)	0.0%
Tacrolimus hydrate	Spironolactone	2 (0)	0.0%
Triazolam	Telaprevir	2 (0)	0.0%
Bepridil hydrochloride hydrate	Itraconazole	1 (0)	0.0%
Dextromethorphan hydrobromide hydrate	Selegiline hydrochloride	1 (0)	0.0%
Droxidopa	Denopamine	1 (0)	0.0%
Eplerenone	Spironolactone	1 (0)	0.0%
Sildenafil citrate	Isosorbide mononitrate	1 (0)	0.0%
Tadalafil	Nitroglycerin	1 (0)	0.0%
Tadalafil	Riociguat	1 (0)	0.0%
Nisoldipine	Itraconazole	1 (0)	0.0%
Paroxetine hydrochloride hydrate	Selegiline hydrochloride	1 (0)	0.0%
Ramelteon	Fluvoxamine maleate	1 (0)	0.0%

Reporters' Recognition Rate of DDIs The reporters' recognition rate of DDIs was the highest (90.9%; 10/11 reports) for the combination of azathioprine with febuxostat, followed by warfarin potassium and miconazole (78.9%; 15/19 reports), warfarin potassium and iguratimod (66.7%; 2/3 reports), sodium valproate and meropenem hydrate (66.7%; 2/3 reports), pimozide and clarithromycin (25.0%; 1/4 reports), and tizanidine hydrochloride and fluvoxamine maleate (20.0%; 1/5 reports). Across the remaining 37 drug pairs, the reporters had not recognized DDIs in any of the reported cases.

DISCUSSION

Of the 2121 drug pairs with CC surveyed in this study, 43 were reported to JADER as ADEs due to DDIs. Although approximately half of these pairs (23 pairs) included injected drugs, many of them included catecholamines and were associated with cases of arrhythmia/cardiac arrest. These pairs were regarded as permissible combinations in the clinical practice in emergency situations, such as resuscitation.[20] Hence, these should not be assigned to the same category of DDIs as those that occur in routine clinical practice. Moreover, the results of this study (Tables 1, 2) demonstrate that clinical feedback was essential for those CC drug pairs with ADEs that occurred due to DDIs in routine clinical practice. Meanwhile, many pairs were identified for which ADEs due to DDIs did not occur, suggesting that the alert-type warnings issued by JPI have a certain positive effect in preventing DDIs. Incidentally, the reason that ADEs caused by DDIs were not reported for the 2078 pairs may have been due to avoid the coadministrations of these pairs at a clinical setting, or the ADEs caused by DDIs did not occur following coadministration. However, further discussions based on the data hosted on this database are difficult.

The breakdown of the reporters across all of the registered cases in the JADER database that were downloaded for this study, suggests that the most common reporters were physicians (84.2%, where 75.2% of the cases were reported only by physicians) as opposed to pharmacists (13.0%, where 7.0% of the cases were reported only by pharmacists). Therefore, the recognition rate of DDIs obtained in this study was thought to reflect the recognition rate of DDIs by physicians in cases where DDI-induced ADEs occurred. For example, with respect to the combination of azathioprine and febuxostat, which had the highest DDI recognition rate in this study, the Japanese guideline for the management of hyperuricemia and gout states, "new xanthine oxidoreductase drugs are contraindicated for coadministration with azathioprine, but there are not a few reports of medical accidents due to misuse."[21] Therefore, it should be noted that cases occurred in which DDIs were recognized by physicians, yet incorrectly prescribed as drug pairs with a high DDI recognition rate.

The limitations of this study were as follows: (1) the DDI recognition rate determined in this study was that assessed by the reporter and did not necessarily reflect that recognized by the prescribing physicians and the drug-dispensing pharmacists; (2) a reporting bias exists in the JADER database, indicating that many severe cases, such as those of hemorrhage and bone marrow suppression, have been reported, while mild cases may not have been reported; (3) the JADER database contained a limited number of reports on ADEs, such as decreased blood drug concentration, attenuation of drug action, and decline in the pharmacological effect of the drug, indicating limited investigations regarding the DDIs that reduce the pharmacological effects of drugs; (4) missing data, duplicate cases, and erroneous entries were found in the JADER data-

Table 2. Drugs Contraindicated for Coadministration, for Which Drug–Drug Interaction (DDI)-Induced ADEs Were Reported in Japanese Adverse Drug Event Report (Injectables Included)

Drug 1	Drug 2	Cases (Recognized as DDIs)	Recognition rate of DDIs
Ephedrine hydrochloride	Dopamine hydrochloride	14 (0)	0.0%
Adrenaline	Noradrenaline	10 (0)	0.0%
Ephedrine hydrochloride	Adrenaline	7 (0)	0.0%
Adrenaline	Dobutamine hydrochloride	4 (0)	0.0%
Sodium valproate	Meropenem hydrate	3 (2)	66.7%
Noradrenaline	Sevoflurane	3 (0)	0.0%
Noradrenaline	Isoflurane	2 (0)	0.0%
Medroxyprogesterone acetate	Estradiol	2 (0)	0.0%
Foscarnet sodium hydrate	Pentamidine isetionate	2 (0)	0.0%
Adrenaline	Haloperidol	1 (0)	0.0%
Adrenaline	Levomepromazine maleate	1 (0)	0.0%
Amiodarone hydrochloride	Disopyramide	1 (0)	0.0%
Amiodarone hydrochloride	Nifekalant hydrochloride	1 (0)	0.0%
Cyclophosphamide hydrate	Pentostatin	1 (0)	0.0%
Distigmine bromide	Suxamethonium chloride hydrate	1 (0)	0.0%
Neostigmine methylsulfate	Suxamethonium chloride hydrate	1 (0)	0.0%
Noradrenaline	Desflurane	1 (0)	0.0%
Noradrenaline	Dobutamine hydrochloride	1 (0)	0.0%
Medroxyprogesterone acetate	Hydroxyprogesterone caproate	1 (0)	0.0%
Medroxyprogesterone acetate	Estradiol valerate	1 (0)	0.0%
Medroxyprogesterone acetate	Prednisolone	1 (0)	0.0%
Medroxyprogesterone acetate	Methylprednisolone	1 (0)	0.0%
Adenosine	Dipyridamole	1 (0)	0.0%

base, indicating that it is necessary to consider methods to clean the data[15,18,19,22–24]; (5) deciphering why CC drug pairs were co-administered is difficult based solely on the information provided for individual cases in the JADER database.

Of the 2121 CC drug pairs, only 43 were associated with the occurrence of ADEs. The results of this study must be translated to clinical practice as the actual state of ADEs due to DDIs.

Conflict of Interest The authors declare no conflict of interest.

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