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Original Article

Analysis of Prescriptions Not Recommended for Concomitant Use

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Abstract : In accordance with the drug utilization review program developed in 2004, a single general hospital of 2,400 beds instituted prescription control of the drug combinations to avoid (DCA) in 2006. However, in order to treat certain patients, it is necessary to use some of these drugs together. Therefore, this study was conducted for the purpose of guiding safe drug use by analyzing prescriptions, monitoring rates, and the incidence of personal injury for DCA selectively allowed by the hospital's Committee of 'Medication Management and Use'.

This study was conducted on patients administered DCA during a hospitalization period from August 1, 2016, to July 31, 2017, in a single general hospital in Korea. Prescription status, monitoring status, and the occurrence of drug interactions were reviewed in the medical records retrospectively.

As a result, among the DCA designated by the MFDS (Korea Ministry of Food and Drug Safety), 306 cases of 17 combinations were used during the one-year study period. Of the total prescriptions, follow-up monitoring occurred in 110 cases (35.9%) and there were 42 (13.7%) adverse drug events (ADE). However, since 176 cases (57.5%) were not monitored, ADEs were not identified in those patients. In addition, the DCA prescription rate for children and the elderly, who have a high probability for ADEs, was 38.2% (117 cases) and 12.1% (37 cases), respectively, and accounted for 50.3% of all cases.

Prescribing DCA is highly likely to cause harm to patients. Although it should be accompanied by follow-up monitoring, a low monitoring rate was observed in this study. Therefore, additional measures are needed, such as follow-up by the pharmacist. In particular, it is necessary to concentrate on children and the elderly. This study has significance, not only in its analysis of DCA prescriptions but also for post-management, which offers a basis for safer drug use.

[Key words] Drug utilization review, Drug interaction, Adverse drug event, Pharmacist, Monitoring

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According to the national health and nutrition survey of the US Centers for Disease Control and Prevention (CDC), the medication use rates for five or more drugs in adults increased more than three times from 2013 to 2014 compared to 1988 to 1994.[1] As a result of a comparative analysis including over the counter drugs and health supplements, the risk of serious drug interactions due to concomitant medication use was 1.8 times higher in 2010 to 2011 than in 2005 to 2006.[2] Since the risk of drug interactions has increased as the number of drugs used by patients has increased, managing patient safety related to drug interactions has become important.

The Korea Ministry of Food and Drug Safety (MFDS) has introduced a Drug Utilization Review system (DUR) to ensure the safe use of drugs at the national level. The DUR system is defined as a system to ensure the appropriateness of medicines being used and that their use does not lead to inappropriate medical results, by providing safety information in real-time.[3] It was developed by the National Health Insurance Review and Assessment Service (HIRA) and was announced by the Ministry of Health and Welfare in 2004. It is conducted under the supervision of the MFDS.[3] In 2018, the checkpoints of the DUR system in Korea included drug combinations to avoid (DCA); age prohibitions; pregnancy prohibitions; efficacy duplication; and dose, duration, elderly, split, and blood donation precautions. DCA is a combination of drugs which should not be prescribed or prepared at the same time due to the risk of serious adverse drug events (ADE) or decreased drug efficacy.[4]

Drug interactions by a combination of drugs, such as by DCA, have serious consequences. According to a study by Pirmohamed et al., 6.5% of hospital visits were due to ADE, 80% of which required hospitalization.[5] The estimated cost of the morbidity and mortality associated with US pharmaceuticals amounts to $136.8 billion,[6] with approximately 100,000 deaths due to fatal drug reactions.[7] In Korea, according to a press release from the HIRA in January 2017, the cost of medical treatment due to ADEs increased from 174.5 billion won in 2010 to 273.8 billion won in 2014, an annual average increase of 11.9 percent. In addition, in terms of socioeconomic costs, the total amount was estimated to be 535.2 billion won.[8] As such, drug interactions cause socioeconomic burdens. Therefore, appropriate preventive measures for safe drug use are needed.

Since 162 DCA were announced in January 2004, additional drugs have been added. As of December 2017, the lists were expanded to a total of 954 ingredient combinations, and a pop-up window is used to provide the contents to medical institutions.[9] As the safe prescription and administration of drugs become more important, self-examination of DCA by medical institutions prescribing them became mandatory in April 2008. In December 2016, an obligation clause was introduced.[10]

The introduction of the DUR system helps medications to be used safely.[11] However, from standpoint of the prescribers, the excessive reminders given when prescribing lead to a high chance of warning ignorance and fatigue. As a result, important drug interactions can be overlooked. Indeed, according to a multinational study conducted by Slight et al. in the United States, Korea, and the United Kingdom, 60% of the drug warnings were disregarded by doctors.[12] According to a single country study conducted in Korea, 79.6% of the drug interaction warnings were disregarded by doctors, which included 0.3% of highly-important drug interactions.[13] Therefore, important combinations that are very likely to be harmful the patients when used

together require different management than general prescriptions.

However, an unconditional prohibition of prescriptions, which does not reflect the patient's clinical situation and individual characteristics, may limit treatment choices. In addition, the reason for prohibiting the use of DCA is not present in all patients. Therefore, it has been suggested that patients and clinicians should be informed about the risk of concomitant use and be allowed to judge the risks and benefits of using DCA.[4] In this context, a single general hospital in Korea instituted a computerized program in 2006 which prevents the prescription of DCA in order to ensure patient safety. However, when the combination is required, the doctor in charge has the authority to prescribe the drug with approval from the 'Committee of Medication Management and Use (MMU).'

However, in spite of the high risk, studies on DCA have been limited to analysis of the prescriptions, with a lack of data on the effect on patients.[11),13)-15)] Therefore, this study was conducted to guide the safe use of medications and to contribute to patient safety by analyzing the excepted uses of DCA.

METHODS

1. Data collection

1) Inclusion criteria

This study was conducted on inpatients who were prescribed DCA at a single general hospital of 2,400 beds in Korea during the one-year period from August 1, 2016, to July 31, 2017.

2) Exclusion criteria

Emergency situations, such as cardiopulmonary resuscitation, were excluded.

3) Collected items

To identify the patients' baseline characteristics, data on gender, age, and medical department were collected.

A. Age was classified into three categories: children (under 18 years old), adults (18 to 65 years old), and the elderly (65 years or older).
B. Medical departments were classified into four categories: internal medicine, surgery, pediatrics, and others.

In order to analyze the prescription status, data on prescribed DCA, reasons to avoid DCA, reasons for using DCA, and duration of DCA use were collected.

To evaluate safety, data on monitoring rates, the incidence of drug interactions, and hospital length of stay were collected. All the data were retrospectively collected.

2. Definition

The criteria for the implementation of monitoring and the occurrence of ADEs were defined as follows:

1) The presence of medical records or relevant test results to monitor the occurrence of ADE.

2) The occurrence of drug interactions: Cases assessed as above 'possible' according to the World Health Organization-Uppsala Monitoring Center (WHO-UMC) criteria.

A. The occurrence of ADEs is listed in Table 1.
B. All the drug interactions have been clas-

Table 1 Criteria for the occurrence of drug interactions

ADE	Definition of ADE occurrence
GI bleeding	Hematemesis (vomiting of blood or coffee ground like material) or melena (black, tarry stools) or endoscopic findings with GI bleeding
Hyperkalemia*	Serum potassium > 5.5 mmol/L
Seizure	Cases recorded as a 'seizure' in the electronic medical records, regardless of seizure type
Nephrotoxicity†	Increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours or ≥ 50% within 7 days or urine output of < 0.5 mL/kg/hour for > 6 hours
Ototoxicity	Cases recorded as 'ototoxicity' like cochlear and vestibular impairment in the electronic medical records
QTc prolongation‡	QTc > 470 ms for men and > 480 ms for women
Decreased blood pressure*	Systolic blood pressure < 90 mmHg or mean blood pressure < 65 mmHg or a drop in systolic blood pressure > 40 mmHg
Renal stones	Kidney stones confirmed by diagnostic imaging
Increased blood pressure§	Systolic blood pressure/diastolic blood pressure > 135/85 mmHg

ADE, adverse drug event; GI, gastrointestinal
*Hyperkalemia; Decreased blood pressure: Lexi-comp
†Nephrotoxicity: 2012 Kidney Disease Improving Global Outcomes guideline
‡QTc prolongation: 2011 American Heart Association/American College of Cardiology guideline
§Increased blood pressure: 2013 Korean Hypertension Society guideline

sified according to the definition of serious ADEs by the Korea Institute of Drug Safety and Risk Management (KIDS).

i. If it causes death or threatens life
ii. If an extension of hospitalization or hospitalization is required
iii. If it causes persistent or significant disability or impaired functioning
iv. If it causes birth defects or abnormalities
v. Other medically important situations

3. Data analyses

The data were collected using medical records and analyzed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA). Gender, the medical department, age distribution, monitoring rate, and the incidence of drug interactions were expressed as absolute values and percentages. Continuous variables, such as age, duration of DCA use, and hospital length of stay were expressed as medians and quartiles. The incidence of gastrointestinal (GI) bleeding according to the use of GI protective agents was analyzed by the chi-squared test.

4. Subject protection

This study was a retrospective study conducted in a single general hospital in Korea and was approved by the Institutional Review Board (IRB) of the hospital concerned (IRB number: 4-2017-1042).

Table 2 Demographic and clinical variables in the study population

Variables	Value
Male, no. (%)	146 (47.7)
Median age, yr (q1-q3)	31 (4-52)
Age classification, no. (%)	
Children*	117 (38.2)
Adults	152 (49.7)
The elderly†	37 (12.1)

*Children: under 18 years old; Korea child welfare law
†Elderly: 65 years or older; Korea elderly welfare law

RESULTS

1. Patient information

From August 1, 2016, to July 31, 2017, a total of 306 patients were prescribed DCA during their hospital stay at a single general hospital in Korea.

One hundred forty-six (47.7%) males and 160 (52.3%) females were included in the study. More than 50% of the DCA were administered to the elderly and children. The median age of the participants in the study was 31 years old (quartile, 4 to 52) (Table 2).

2. Prescription status

A total of 306 DCA were collected during the period, which consisted of 17 combinations based on the ingredient involved and eight combinations based on contraindications.

The most common DCA, found in 177 cases (57.8%), was the combined use of ketorolac and nonsteroidal anti-inflammatory drugs, which has the potential to cause GI bleeding. In order of frequency, other dangerous combinations with a risk for hyperkalemia, seizure, nephrotoxicity and ototoxicity, QTc prolongation, decreased blood pressure, increased blood pressure and renal stone risk combinations were prescribed. The median duration of using DCA was 2 days (quartile, 2 to 3) (Table 3).

The results of the analysis by the medical departments were as follows: 106 cases (34.6%) in pediatrics, 82 cases (26.8%) in surgery, 58 cases (19.0%) in internal medicine, and 60 cases (19.6%) in other departments (Fig. 1).

In all cases, the doctors requested DCA use after they considered the risks and benefits to the patient's condition. In five out of eight DCA, the doctors stated that they planned to carry out close monitoring (Table 3).

3. Safety

The monitoring rate was analyzed to assess patient safety. The overall monitoring rate was 35.9%, provided in less than half of the DCA prescriptions. In particular, combinations associated with GI bleeding risks had the lowest monitoring rates (12.4%). The monitoring rate for drug combinations associated with seizure risks was 25.9% and 71.2% for drug combinations associated with a risk for hyperkalemia. All other combinations were monitored (100%).

The incidence of drug interactions was analyzed to confirm the safety of the DCA. As a result, the total incidence of drug interactions was 13.7% and no drug interactions were observed in 28.8% of the DCA prescriptions. However, drug interactions in 57.5% of the DCA prescriptions could not be confirmed due to the lack of monitoring or insufficient recording.

According to the analysis, the use of DCA showed a high incidence of ADEs. The incidence of QTc prolongation and increased blood pres-

Table 3 Analysis of prescription status

DCA		ADE	Number of prescription N (%)	Duration of use median (q1-q3)	Reason for using DCA	Monitoring plan
Total prescription			306 (100.0)	2 (2.0-3.0)		107 (35.0)*
Ketorolac	NSAID	GI bleeding	177 (57.8)	2 (2.0-2.0)	This combination is used only for a short period after surgery.	No
Spironolactone	KCL or Amiloride	Hyperkalemia	73 (23.9)	2 (1.0-5.0)	This combination is used to increase the diuretic effect in patients with hypokalemia.	Yes
Valproic acid	Carbapenem	Seizure	27 (8.8)	4 (2.0-7.0)	Carbapenem is indispensable for the control of infection in patients receiving valproic acid.	Yes
Furosemide	Gentamicin	Nephrotoxicity Ototoxicity	21 (6.9)	3 (1.0-5.0)	Gentamicin is needed to treat infective endocarditis. Furosemide is also needed to treat acute pulmonary edema.	No
Amiodarone	Dronedarone or Sotalol	QTc Prolongation	4 (1.3)	1 (1.0-4.5)	Amiodarone is needed for cardioversion in patients who already taking dronedarone or sotalol.	Yes
Acetazolamide	Topiramate	Renal stones	1 (0.3)	1	The addition of topiramate is necessary because of the increased epileptic seizure.	Yes
Sildenafil	Isosorbide or Nicorandil	Decreased blood pressure	2 (0.7)	2.5 (1.0-2.5)	It is used for vasodilation in patients with pulmonary hypertension. It is used only when the benefit is larger than the risk, taking into account the systemic blood pressure and pulmonary artery pressure.	Yes
Nifedipine	Rifampicin	Increased blood pressure	1 (0.3)	1	Patients receiving rifampicin for active tuberculosis treatment need nifedipine for coronary artery dilatation to prevent acute cardiac death.	No

* No. (%)
DCA, drug combinations to avoid; ADE, adverse drug event; NSAID, non-steroidal anti-inflammatory drugs; LOS, length of stay; KCL, potassium chloride

sure, which can be life-threatening, was 100% each. The incidence of seizures and nephrotoxicity and ototoxicity, which can cause permanent functional impairment, was 40.7%, 23.8%, and 4.8%, respectively (Table 4).

As a result of classifying the severity of ADEs according to the KIDS criteria, severe ADEs accounted for 31% of the total ADEs. Drug com-

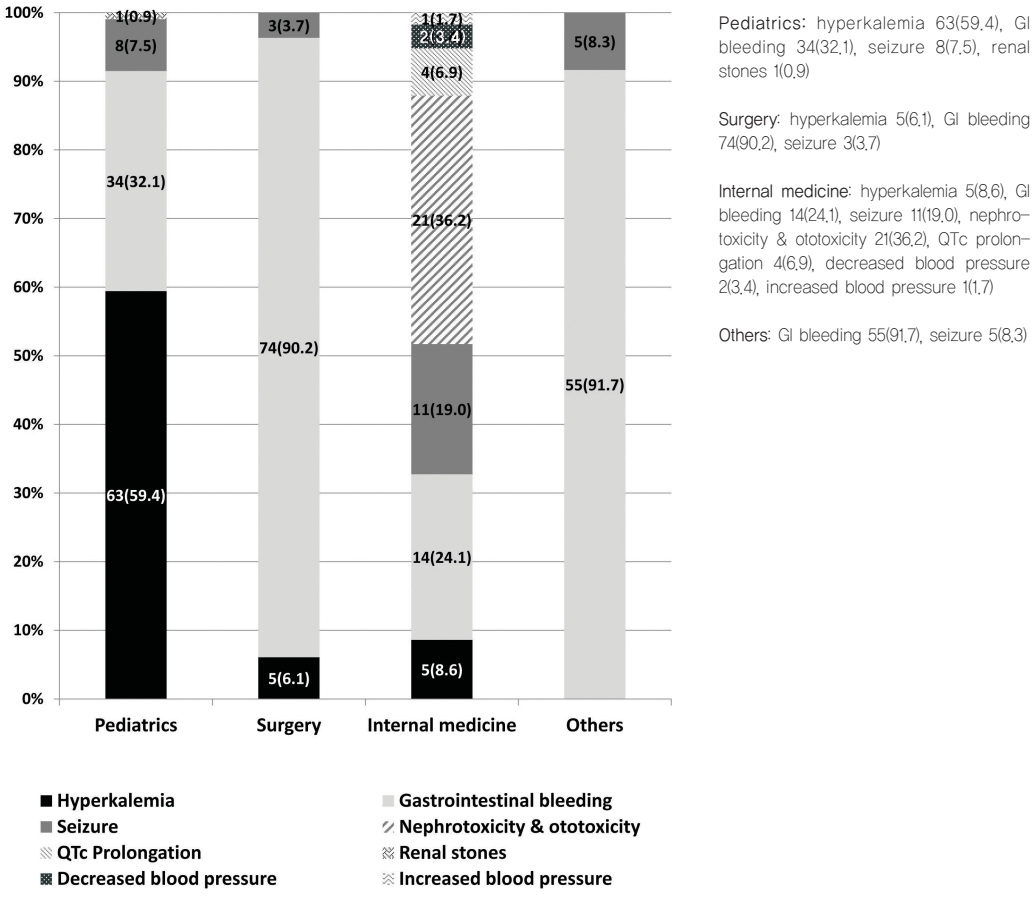

Fig. 1 DCA status classified by medical department, N (%)

binations with seizure risks had the highest incidence (72.7%), followed by nephrotoxicity and ototoxicity risks (66.7%) and QTc prolongation risks (25.0%) (Table 4).

Higher rates of drug interactions were observed in the vulnerable study population, children and the elderly, than in adults. The incidence of ADEs in children was 19 out of 117 (16.2%) and the incidence in the elderly was 8 out of 37 (21.6%), which were significantly higher than that of the adults 15 out of 152 (9.9%).

The median hospital length of stay was 14 days (quartile, 6.0 to 33.0) (Table 4). In further analysis, 54.1% of the elderly patients administered DCA were given drugs listed in Beer's criteria, a list of medications not suitable for the elderly. The drugs included dronedarone, amiodarone, ketorolac, ibuprofen, mefenamic acid, and naproxen. The most frequently used drug not recommended for elderly was ketorolac.

DISCUSSION

The purpose of this study was to establish the basis for safe medication use by analyzing the status of follow-up management after the pre-

Table 4 Analysis of safety profile

DCA		Number of prescription N (%)	Monitoring N (%)	ADE N (%)	Serious ADE*	LOS, days Median (q1-q3)
Total prescription		306 (100.0)	110 (35.9)	42 (13.7)	13 (31.0)	14 (6.0-33.0)
Ketorolac	NSAIDs	177 (57.8)	22 (12.4)	9 (5.1)	0 (0.0)	8 (5.0-16.8)
Spironolactone	KCL or Amiloride	73 (23.9)	52 (71.2)	11 (15.1)	0 (0.0)	27 (15.0-51.0)
Valproic acid	Carbapenem	27 (8.8)	7 (25.9)	11 (40.7)	8 (72.7)	72 (35.5-159.0)
Furosemide	Gentamicin	21 (6.9)	21 (100.0)	6 (28.6)	4 (19.0)	27 (10.0-41.0)
Nephrotoxicity				5 (23.8)	3 (60.0)	
Ototoxicity				1 (4.8)	1 (100.0)	
Amiodarone	Dronedarone or Sotalol	4 (1.3)	4 (100.0)	4 (100.0)	1 (25.0)	7 (9.0-38.0)
Sildenafil	Isosorbide or Nicorandil	2 (0.7)	2 (100.0)	0 (0.0)	0 (0.0)	4.5 (3.0-12.0)
Acetazolamide	Topiramate	1 (0.3)	1 (100.0)	0 (0.0)	0 (0.0)	52
Nifedipine	Rifampicin	1 (0.3)	1 (100.0)	1 (100.0)	0 (0.0)	41

*Incidence of serious ADE (%) = Serious ADE/ADE x 100
DCA, drug combinations to avoid; ADE, adverse drug event; LOS, length of stay; NSAIDs, non-steroidal anti-inflammatory drugs; KCL, potassium chloride

scription and administration of DCA.

Among a total of eight DCA, five DCA (with risks for renal stones, decreased blood pressure, reduced blood pressure, QTc prolongation and nephrotoxicity and ototoxicity) showed 100% monitoring rates. However, the overall monitoring rate was decreased because the monitoring rate for frequently used combinations with GI bleeding, hyperkalemia, and seizure risks was low. In addition, even after post-monitoring, ADEs occurred in 33.6 % of the DCA. Therefore, careful monitoring for immediate treatment is required. However, in this study, the monitoring rate was low, at 35.9%, and the frequency of monitoring was an average of 0.38 times per day.

According to a previous study by McDonnell et al., 26% of the admission-causing ADEs were due to drug interactions. The study also found that 25.0% of all ADEs were serious ADEs.[16] In this study, the incidence of serious ADEs by DCA was 31.0%, higher than the previous study. Therefore, unlike other prescriptions, using DCA is more dangerous and the risks and benefits should be considered before prescribing. Also, clinicians should consider using alternative medications before using DCA but careful monitoring is essential if they must be used. It is also necessary to establish more systematic management at the level of the MMU, rather than leave it to the physician's autonomous discretion after approval to use DCA. Humphries et al. noted that pharmacists' intervention and collaboration with the prescriber reduced the number of critical drug interactions up to 31%, complementing an electronic critical drug interaction alert pro-

gram.[17] Therefore, the active involvement of the pharmacists is necessary.

As a result of analyzing the prescriptions of each department with a high number of DCA prescriptions, 59.4% of the DCA prescribed in pediatrics were potassium-containing TPN-related hyperkalemia combinations, and 90.2% of the DCA prescribed in surgery were GI bleeding risk combinations associated with NSAIDs after surgery. The majority of the DCA used in internal medicine were nephrotoxicity and ototoxicity risk combinations (36.2%) and GI bleeding risk combinations (24.1%). As such, there was a tendency to use specific DCA in certain departments (Fig. 1). Therefore, pharmacists who are experts in various drug interactions should provide customized education for each department, considering different DCA prescription patterns.

Further analysis of GI bleeding risk combinations, which were the most commonly prescribed but had the lowest monitoring rate, showed that the prescription rate for GI protective agents in the combinations was 80.2 percent. Therefore, the suggested reasons for the low monitoring rate are as follows: First, the combination was used for a relatively short period of time (median, 2 days; quartile, 2 to 3). Second, the prescribers may have felt psychological relief because they prescribed GI protective agents together with the DCA. However, there was no statistically significant difference in the incidence of GI bleeding with or without the use of GI protective agents (p=0.503) and clinicians should retain their alertness. In addition, the incidence of ADEs in the combination was three times higher in children and 4.72 times higher in elderly patients than in adults. Therefore, DCA associated with GI bleeding risks should not be used for children or the elderly.

As the average age of the population increases, the accompanying diseases increase and so do the drugs used to treat them. Therefore, the frequency of exposure to drug interactions increases and the incidence of ADEs also increases.[1),18)-20)] According to the 2017 HIRA report, claims by the elderly population aged 65 or older in Korea were about 4.7 trillion won (36.8% of the total) in 2013 and 6.5 trillion won (40.1% of the total) in 2017.[21)] Therefore, this is especially important for the elderly as drug interactions due to polypharmacy can increase.[18)-20)] On the other hand, because many medication profiles for pediatric patients have not been not well established, they are more likely to be exposed to ADEs.[22)] However, in this study, 50.3% of the patients given DCA were children and the elderly. Furthermore, 54.1% of the elderly were using medications potentially inappropriate for the elderly according to Beer's criteria. This can ultimately affect morbidity and mortality. The incidence of drug interactions between children and the elderly was 1.6 times and 2.2 times higher, respectively, than that of adults, consistent with previous studies.[19),20),22),23)]

However, at the time of prescription, doctors often do not recognize the prescriptions of other doctors. Therefore, pharmacists should manage the patient's medication history and check the appropriateness of the prescriptions. According to a study by Hanlon et al., pharmacists' interventions reduce the inappropriate prescribing to 25% and the incidence of ADE to 75.5% compared to the study controls.[24)] Furthermore, Kaur et al., noted in their systemic review that communication between pharmacists and the responsible prescriber was essential to reduce medication errors. Therefore, pharmacists should work as complements to the medical staff to promote patient safety.[25)] In particular, inten-

sive management for children and the elderly is needed through methods, such as categorizing drug interactions between medications which are frequently prescribed to children and the elderly.[13),18)-20),22)]

Inpatients are relatively easy to monitor and can be treated promptly compared to outpatients.[20)] Therefore, in this study, we selected hospitalized patients where intervention could be properly provided. However, given the HIRA statistics showing that the outpatient DCA prescribing change rate informed the drug interaction in 2017 was only 32.3%, the incidence of ADE is likely to increase if outpatients are included. Therefore, for patient safety, comprehensive management, including inpatients as well as outpatients, is necessary.

The limitations of this study are as follows: First, the research was conducted by a single institution and may not reflect the characteristics of all medical institutions. Second, the data are limited to inpatients and did not include outpatients. Third, there is a possibility that some records were missed because it was a retrospective study which relied on electronic medical records. Fourth, the effects of underlying diseases and other factors cannot be totally excluded in the ADEs. Fifth, because the number of prescriptions was small, the data may be insufficient to generalize the incidence of ADEs by DCA.

Despite these limitations, this study has significance in that it analyzed, not only the current use but also the results of the prescription of excepted combinations. In addition, this study suggested that post-monitoring is important for patient safety because ADEs may occur, even when combined with clinical necessity. This can help clinicians to decide whether to use DCA in consideration of the risks and benefits. These efforts will raise awareness about drug interactions and emphasize the importance of careful post monitoring, ultimately contributing to patient safety. However, in order to overcome the limitations of this study, prospective studies with multicenter involvement are needed.

CONCLUSIONS

The use of DCA is highly risky and should be considered in conjunction with the patient's clinical situation, taking risks and benefits into consideration. In addition, patients should be monitored continuously by using additional measures, such as pharmacist follow-up. In particular, it is necessary to focus on children and the elderly who are vulnerable to ADEs. This study has significance in its analysis, not only of DCA prescriptions but also their post-management status, including monitoring rates and the incidence of ADEs. This will serve as the basis for safer drug use. Further, more comprehensive, multi-center studies are needed.

DISCLOSURES

There are no conflicts of interest to disclose.

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