Original Article
Yonsei Med J 2017 May;58(3):564-569
https://doi.org/10.3349/ymj.2017.58.3.564
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Signal Detection of Imipenem Compared to Other Drugs from Korea Adverse Event Reporting System Database

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Purpose: To detect signals of adverse drug events after imipenem treatment using the Korea Institute of Drug Safety & Risk Management-Korea adverse event reporting system database (KIDS-KD).

Materials and Methods: We performed data mining using KIDS-KD, which was constructed using spontaneously reported adverse event (AE) reports between December 1988 and June 2014. We detected signals calculated the proportional reporting ratio, reporting odds ratio, and information component of imipenem. We defined a signal as any AE that satisfied all three indices. The signals were compared with drug labels of nine countries.

Results: There were 807582 spontaneous AEs reports in the KIDS-KD. Among those, the number of antibiotics related AEs was 192510; 3382 reports were associated with imipenem. The most common imipenem-associated AE was the drug eruption; 353 times. We calculated the signal by comparing with all other antibiotics and drugs; 58 and 53 signals satisfied the three methods. We compared the drug labelling information of nine countries, including the USA, the UK, Japan, Italy, Switzerland, Germany, France, Canada, and South Korea, and discovered that the following signals were currently not included in drug labels: hypokalemia, cardiac arrest, cardiac failure, Parkinson's syndrome, myocardial infarction, and prostate enlargement. Hypokalemia was an additional signal compared with all other antibiotics, and the other signals were not different compared with all other antibiotics and all other drugs.

Conclusion: We detected new signals that were not listed on the drug labels of nine countries. However, further pharmacoepidemiologic research is needed to evaluate the causality of these signals.

Key Words: Imipenem, KIDS-KAERS database, signal, pharmacovigilance, pharmacoepidemiology

INTRODUCTION

A signal in pharmacovigilance was defined by the World Health Organization Uppsala Monitoring Centre (WHO-UMC) as a "Reported information on a possible causal relationship between an adverse event (AE) and a drug, the relationship being unknown or incompletely documented previously."[1]

Data mining, a signal detection method, uses a spontaneous reporting system to detect AE signals and has had an important role in pharmacovigilance for the last four decades.[2] Physicians, pharmacists and consumers are recommended to report AEs that are suspected to be AEs to a spontaneous reporting system.[3] Quantitative analysis methods, such as the reporting odds ratio (ROR), proportional reporting ratio (PRR), and Bayesian confidence propagation neural network (BCPNN) analysis, could reveal important signals by analyzing disproportionately collected reports about drugs and clinical events.[4]

Received: June 10, 2016 **Revised:** October 29, 2016
Accepted: November 29, 2016
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•The authors have no financial conflicts of interest.

Imipenem is a member of the carbapenem class of antibiotics. It is known to have a wide spectrum of activity, and therefore, has commonly been used for Gram-positive and -negative, aerobic, and anaerobic bacteria.[5] In US Food and Drug Administration (FDA) drug label information, imipenem presents severe adverse drug reactions (ADRs), such as potential seizure (0.2%). It also presents common ADRs, such as nausea (2.0%), vomiting (1.5%), diarrhea (1.8%), rash (0.9%), and so on.[6] The drug label information regarding imipenem ADRs from the Ministry of Food and Drug Safety (Korea) is similar to that of the FDA.[7] In Korea, however, signal detection associated with imipenem using the Korean spontaneous AEs reporting system database has never been conducted. Therefore, we first analyzed the Korean spontaneous reporting system database regarding imipenem and compared it with the drug label information of 8 other countries to detect signals that are not currently listed in the labels.

MATERIALS AND METHODS

Korea Institute of Drug Safety & Risk Management-Korea adverse event reporting system database

The Korea Institute of Drug Safety & Risk Management-Korea adverse event reporting system database (KIDS-KD) includes AE data from December 1988 to June 2014. The data were screened for detection of input error, logical error and assigned code by drug information and AEs before performing statistical analysis. This database is managed by KIDS, and anyone authorized by KIDS can use the data, and it is composed of patient information, drug information, AE information, seriousness of AE, reporter information, primary causality assessment, and disease history. These data have information about suspected AEs coded with the WHO Adverse Reaction Terminology (WHO-ART) codes-Preferred Term level (PT).[8] These codes were developed 30 years ago by the WHO and have been widely used.[9] We use the combination of drug ingredients and WHO-ART PT codes (PT) to find signals. It should be noted that information from the KIDS-KD is reported regardless of causal relationship. Thus, AE information from other countries and assessment of patient's underlying disease or medical records are needed.[8]

Table 1. 2×2 for Measures of Disproportionality of Imipenem

No. of reports	Specific adverse events	All other adverse events
Imipenem and enzyme inhibitor	A	B
All other drugs	C	D

Disproportionality measurement for signal detection

Disproportionality measurement is one of the techniques used to detect adverse drug event signals, and Netherlands Pharmacovigilance Foundation, the UK Yellow Card database, and WHO-UMC use this method to find AE signals.[10] To make a 2×2 table, we classified rows with imipenem and other drugs, except imipenem, and categorized columns with specific AEs and all other AEs (Table 1).

We calculated the PRR, ROR, and information component (IC) of BCPNN to detect signals. The criteria of signal detection was a PRR and ROR of at least 2, chi-squared value of at least 4 and 3 or more cases,[11] and that for IC was a larger than zero lower limit of the 95% confidence interval of IC (Table 2).[12]

Statistical analysis

We used three methods for signal detection. Nevertheless, there is no 'gold standard' method for signal detection.[13] We applied three methods to target imipenem and all other antibiotics and drugs. In general, the disproportionality calculating measure compares imipenem with all other drugs.[14,15]

A signal was defined when it satisfied all three methods (PRR, ROR, and IC). We also analyzed the number of AEs reported from imipenem use, all drugs and all antibiotics per year and the characteristics of imipenem AE reports. Finally, we compared the drug label informations from South Korea, Canada, the USA, the UK, Japan, Germany, Switzerland, Italy, and France. All signals have the possibility for disease spill-over (code of treated disease as ADRs), therefore, we considered the clinical aspects.[16] All statistical analyses were performed using SAS (Release 9.4, SAS Institute, Inc., Cary, NC, USA) and Microsoft Excel 2010.

RESULTS

The total number of suspected AE reports to the KIDS-KD from December 1988 to June 2014 was 807582. During the same period, the number of AE reports with all antibiotics was 192510 and with imipenem was 3382. The number of reports continued to increase year after year (Table 3).

The characteristics of reports in KIDS-KD are presented in Table 4. They are presented by gender of the patient, suspected AEs, type of reports, identification of reporter, and report-

Table 2. Definition and Signal Detection Criteria of Disproportionality Calculating Method

Calculating method	Definition in 2×2 table	Criteria of signal detection
PRR	[A/(A+B)]/[C/(C+D)]	PRR≥2, chi-squared≥4 and case≥3
ROR	(A/B)/(C/D)	ROR≥2, chi-squared≥4 and case≥3
IC	Log_2 P (ADRs, drug)/P (ADRs) P (drug)	IC lower limit of 95% confidence interval≥0

PRR, proportional reporting ratio; ROR, reporting odds ratio; IC, information component; ADRs, adverse drug reactions.

Table 3. The Number of AEs Reports in KIDS-KD by Year from December 1998 to June 2014

Yrs	No. of AEs reports (%)		
	Imipenem	All antibiotics	All drugs
'1988.12–'2001.12	0	448 (0)*	756 (0)†
'2002	1	43 (2.33)	81 (1.23)
'2003	1	62 (1.61)	139 (0.72)
'2004	12	125 (9.60)	323 (3.72)
'2005	30	397 (7.56)	924 (3.25)
'2006	24	1403 (1.71)	5153 (0.47)
'2007	298	8635 (3.45)	59332 (0.50)
'2008	180	5542 (3.25)	11802 (1.53)
'2009	263	8148 (3.23)	22385 (1.17)
'2010	476	21919 (2.17)	55972 (0.85)
'2011	369	23591 (1.56)	52148 (0.71)
'2012	465	27546 (1.69)	69929 (0.66)
'2013	909	65646 (1.38)	407149 (0.22)
'2014.06	354	29005 (1.22)	121489 (0.29)
Total	3382	192510 (1.76)	807582 (0.42)

AEs, adverse events; KIDS-KD, Korea Institute of Drug Safety & Risk Management-Korea adverse event reporting system database.
*Proportions of imipenem for all antibiotics, †Proportions of imipenem for all drugs.

Table 4. Characteristics of Imipenem AEs Reports in KIDS-KD

Characteristics of reports*	No. of AEs reports (%)		
	Imipenem	All antibiotics	All drugs
Gender			
Male	1871 (55.3)	93618 (48.6)	391326 (48.5)
Female	1440 (42.6)	94976 (49.3)	407825 (50.5)
Unknown	71 (2.1)	3916 (2.0)	8431 (1.0)
Type of report			
Spontaneous reports		73454 (38.2)	154695 (19.2)
Research (including review)	1491 (44.1)	55060 (28.6)	510885 (63.3)
Literature	47 (1.4)	1279 (0.7)	2704 (0.3)
Unknown	1107 (32.7)	62717 (32.6)	139298 (17.2)
Missing	737 (21.8)		
Identification of the reporter			
Physician	1178 (34.8)	67919 (35.3)	473114 (58.6)
Pharmacist	229 (6.8)	14715 (7.6)	34903 (4.3)
Nurse	323 (9.6)	38195 (19.8)	73743 (9.1)
Consumer		832 (0.4)	1632 (0.2)
Unknown	285 (8.4)	18139 (9.4)	50838 (6.3)
Missing	1367 (40.4)	52710 (27.4)	173352 (21.5)
Reporting institution			
RPVC	1538 (45.5)	119923 (62.3)	256772 (31.8)
Manufacturer	1759 (52.0)	61904 (32.2)	530530 (65.7)
Medical institution	78 (2.3)	9363 (4.9)	17620 (2.2)
Pharmacy	3 (0.1)	522 (0.3)	1158 (0.1)
Public health center		35 (0.0)	56 (0.0)
Consumers		333 (0.2)	888 (0.1)
Unknown	4 (0.1)	428 (0.2)	553 (0.1)
Missing		2 (0.0)	5 (0.0)
Total	3382 (100.0)	192510 (100.0)	807582 (100.0)

RPVC, regional pharmacovigilance center; AEs, adverse events; KIDS-KD, Korea Institute of Drug Safety & Risk Management-Korea adverse event reporting system database.
*All of the characteristics were different between imipenem and all of the antibiotics and between imipenem and all of the drugs (p value<0.001).

https://doi.org/10.3349/ymj.2017.58.3.564

Table 5. AEs Contained in Any One of the Drug Labels about Imipenem AEs Signals Compared with All Other Antibiotics in the KIDS-KD

AEs	WHO-ART code (PT)	No. of reports	PRR	ROR	Chi-squared	IC 95% LCI	AEs in drug label (9 countries)*
Hypokalemia	0391	22	2.78	2.79	23.89	0.87	Korea, Japan
Tachycardia	0224	15	2.13	2.14	8.73	0.42	Korea, USA, UK, Italy, Canada, France
Cardiac arrest	0437	12	6.05	6.06	45.63	1.73	None
Cardiac failure	0496	9	6.45	6.47	37.19	1.73	None
Parkinson's syndrome	0106	4	8.28	8.29	22.32	1.76	None
Prostate enlargement	1926	3	5.41	5.42	9.84	1.18	None
Myocardial infarction	0428	3	5.79	5.79	10.76	1.25	None

AEs, adverse events; WHO-ART code (PT), World Health Organization Adverse Reaction Terminology code-Preferred Term level; PRR, proportional reporting ratio; ROR, reporting odds ratio; IC 95% LCI, information component lower limit of 95% confidence interval; KIDS-KD, Korea Institute of Drug Safety & Risk Management-Korea adverse event reporting system database.
*9 countries: Korea, USA, UK, Germany, Italy, Switzerland, Canada, France, Japan.

Table 6. AEs Contained in Any One of the Drug Labels about Imipenem AEs Signals Compared with All Other Drugs in the KIDS-KD

AEs	WHO-ART code (PT)	No. of reports	PRR	ROR	Chi-squared	IC 95% LCI	AEs drug label (9 countries)*
Tachycardia	0224	15	3.16	3.17	21.91	1.01	Korea, USA, UK, Italy, Canada, France
Cardiac arrest	0437	12	5.73	5.75	45.78	1.79	None
Cardiac failure	0496	9	5.36	5.38	31.26	1.62	None
Parkinson's syndrome	0106	4	4.90	4.91	12.17	1.28	None
Prostate enlargement	1926	3	4.46	4.46	7.90	1.08	None
Myocardial infarction	0428	3	3.40	3.40	5.00	0.70	None

AEs, adverse events; WHO-ART code (PT), World Health Organization Adverse Reaction Terminology code-Preferred Term level; PRR, proportional reporting ratio; ROR, reporting odds ratio; IC 95% LCI, information component lower limit of 95% confidence interval; KIDS-KD, Korea Institute of Drug Safety & Risk Management-Korea adverse event reporting system database.
*9 countries: Korea, USA, UK, Germany, Italy, Switzerland, Canada, France, Japan.

ing institution (Table 4). All of the characteristics are different between imipenem and all of the antibiotics, and between imipenem and all of the drugs (p value<0.001). Drug eruption accounted for highest number of AEs reported with imipenem, 353 (10.4%), followed by nausea (207 reports, 6.1%), sepsis (156 reports, 4.6%), and pneumonia (145 reports, 4.3%) (Supplementary Table 1, only online). We calculated imipenem AEs signals compared with all antibiotics and drugs. Compared with all antibiotics, the number of signals detected by the PRR method was 58, 58 by ROR method, 154, and in more than 3 qualified cases by IC method, and 76 by IC method. Compared to all of the other drugs, the number of signals detected by the PRR method was 53, 53 by ROR method, 143, and in more than 3 qualified cases by IC method, and 71 by IC method. Finally, 58 and 53 signals satisfied all three methods.

We found imipenem signals, compared with all other antibiotics and drugs, in the KIDS-KD. Additionally, the signals that satisfied all three indices in the KIDS-KD were compared with the labels from 9 countries (Table 5 and 6).

DISCUSSION

This study describes signal detections after treatment with imipenem, based on KIDS-KD data. A great deal of research to detect individual adverse effects, such as seizure,[5,17] digestive side effects, electrolyte abnormality, and hematopoietic abnormality, including anemia, have been reported.[18,19] Babinchak, et al.[20] indicated imipenem-associated cardiovascular system AEs. In their study, one each case of angina pectoris and left cardiac failure were reported among 12 imipenem AE cases. Torres found that cardiac arrest occurred in one patient among 34 patients using imipenem.[21] However, cardiac arrest, cardiac failure, myocardial infarction, Parkinson's syndrome and prostate enlargement were detected for the first time when the signal detection methods were used. The exact mechanism of heart disease by imipenem is not clear, but electrolyte exchange, a known ADR of imipenem, is a significant adjuvant marker of acute myocardial infarction.[22] Furthermore, seizure, a serious ADR of imipenem, is associated with an increased risk of sudden cardiac death,[23] and bradycardia or tachycardia is included in the drug label information in some countries. Therefore, the ADRs associated with cardiac problems are thought to be worthy of further study. In the present study, Parkinson's syndrome and prostate enlargement, which have never been reported, were detected as signals, therefore, further AE studies are needed to evaluate the causality of this signal.

The number of detected signals by IC was more than detected by the ROR or PRR criteria. This difference mostly results from the minimum number of cases included in the cri-

teria. Lindquist, et al.[24] developed the BCPNN method, which detected signals with 44% positive predictive values and 85% negative predictive values, indicating that BCPNN is a valuable tool to find early signals. ADR information was derived from data obtained from preclinical studies and clinical trials, however, it may not include rare ADRs, which are caused by interactions with other existing drugs or ADRs observed after a long exposure.[25] Therefore, observational studies using a large computerized database for a long time period after marketing should be encouraged.

Our present study employed disproportionality methods not only to compare imipenem with all other drugs, but also to compare it with all other antibiotics. We found that the results were different when using disproportionality methods were used to compare impenem with the same drug class and all other drugs. Compared with all other antibiotics, signals detected were more than when compared to all other drugs. However, since there is the possibility of a false positive, a validity evaluation is required.

This study has the following strengths. First, this study is focused on imipenem, which has been used in more than 26 million patients[26] and is a part of the carbapenem family, whose worldwide usage increased by 40 percent between 2000 and 2010. This is a large increase compared to all other antibiotics used, which increased by 30 percent during the same period.[27] For many complicated bacterial infections, the use of the carbapenem class of antibiotics is considered to be a "last resort".[28] Furthermore, this study is important, since the imipenem-associated adverse effects will likely continue to increase in the future. Second, this is the first study to analyze imipenem signal detection using the KIDS-KD: this database contains all of the AEs spontaneously reported from December 1988 to June 2014 in Korea.

Like many other studies of AEs using spontaneous reporting systems, our present study has some limitations. First, by using a spontaneous AE reporting system, the detected signals may not have a causal relationship. KIDS-KD contains information of causality assessment. However, causality assessment information of imipenem dealt only 53% and that of all drugs only 47%. Therefore, it is difficult to evaluate causality of the KIDS-KD in terms of content or format, and additional pharmacoepidemiologic (PE) studies are needed to evaluate the causal relationship. Second, the present study has various degrees of underreporting, therefore, the true incidence of signals cannot be estimated.[29] Third, delays in reporting and incomplete information are also factors that degrade the quality of signals from spontaneous reporting systems.[30] Fourth, the WHO-ART codes (PT) and the actual disease may not match. WHO-ART codes (PT) are selected as the preferred term by the user.[31] For example, symptoms with the same morphological aspect, but different clinical aspects cannot be processed appropriately by the WHO-ART system.[32] Fifth, there is no information about the total number of patients who prescribed the drug. Thus, it is necessary to conduct PE studies, including a cohort study, considering the actual number of patients who prescribed the drug.

Early detection of signals is very important to secure patients for drug safety. Recently, the number of reported AEs in South Korea has grown explosively. Academies, pharmaceutical companies and institutions need to cooperate actively to effectively detect signals using the KIDS-KD.

In conclusion, we found signals that have not been mentioned previously. If necessary, a causality assessment is required by conducting well designed PE studies, including a cohort study, case-control study, or case crossover study. Clinicians and pharmacists are expected to be able to better care for patients based on the scientific evidence unraveled in these studies.

ACKNOWLEDGEMENTS

We thank the Korea Institute of Drug Safety & Risk Management.

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