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Spontaneous Reporting of Adverse Drug Reactions through Electronic Submission from Regional Society Healthcare Professionals in Korea

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Purpose: Pharmacovigilance Research Network built a spontaneous reporting system and collected adverse drug reactions (ADRs) by electronic submission (e-sub) in Korea. We analyzed ADRs spontaneously reported through e-sub from regional health professionals. **Materials and Methods:** Nine hundred and thirty three ADR cases were collected and analyzed from January to December in 2008. "A matter" was defined as one symptom matched to one culprit drug included in an ADR case. We collected and analyzed e-sub ADR cases and matters to determine common culprits and organ specified ADR matters. **Results:** There were 3,049 matters in 933 ADR cases for 1 year, and 3.3 matters per case were reported. In organ specific ADR classification, skin reactions which took the first place in 866 matters (28%) included urticaria and rash. The next cases were neurologic symptom (624 matters, 21%) and gastrointestinal symptom (581 matters, 19%). Doctor (53%) and pharmacist (31%) were the most important participants in e-sub spontaneous reporting system, and 3% of ADR cases were reported by patients or their guardians. WHO-Uppsala Monitoring Center causality assessment results showed certain 10.6%, probable 37.7%, possible 41.7% and below unlikely 10.0%. Culprit drugs were antibiotics (23.4%), neurologic agents (14.7%) and non-steroidal anti-inflammatory drugs (9.4%). **Conclusion:** In our study, antibiotic was most common culprit drug, and skin manifestation was most common symptom in e-sub ADRs collected from regional healthcare practitioners in Korea.

Key Words: Adverse drug reaction, spontaneous reporting, internet electronic submission, regional primary practice

INTRODUCTION

Adverse drug reaction (ADR) is a serious hazard in patient care. It sometimes leads to marked socioeconomic loss. Therefore, to understand actual status and to

establish a preventive measure about ADRs are urgent.[1] Lazarou, et al.[2] reported approximately 6.7% of total in-patients in the USA experienced serious ADRs within one year and 0.3% of them died due to ADRs. They expected that about one hundred thousand patients would die due to ADRs. For this reason, the importance of pharmacovigilance (PV) was emphasized. In many countries, specified ADR collecting systems have been established which reflect their cultural bases, medical systems, and socioeconomic status to monitor the occurrence of ADR in their countries. Among various PV systems, the spontaneous reporting system (SRS) played a central role to detect signals from post-marketing surveillance of drugs. Furthermore, this SRS was a widely-used, useful and effective tool to confirm newly developed post-marketing ADRs.[3] Analysis of data collected by SRS could provide information about newly detected ADR that was not shown in phase 2 or 3 clinical trial and risk factors for occurrence of serious ADRs.[4]

The Korea Food and Drug Administration (KFDA) organized a centralized SRS system in 1988. However, they failed to motivate healthcare professionals to spontaneously report ADR.[5] In 2006, KFDA changed their PV system policy to de-centralize SRS, based on nationwide regional pharmacovigilance centers (RPVCs). Total 20 RPVCs are currently working in Korea.

After the application of de-centralized SRS, reporting rate showed exponential growth, but quantity and quality of ADR reports still remain low compared to other developed countries.[4,6] For successful settlement of SRS, development of an easily accessible reporting system is essential. Recently, development of the internet made electronic submission of ADRs possible. Many countries have already collected ADRs by internet electronic submission.[7,8] Internet ADR collection could build a database more effectively than other collecting methods such as telephone, fax and mail because of its accuracy and speed. Moreover, once a database is built, it can be used in statistics and signal detection without specific data conversion process.

Pharmacovigilance Research Network (PVnet) built its homepage (http://www.pvnet.or.kr) and collected ADRs by e-sub from October 2007. Through the PVnet homepage, we were able to collect ADR reports from private clinics, pharmacies, general hospitals in lack of their own PV system, patients and their guardians. In this study, we analyzed and characterized ADRs collected through PVnet homepage for one year 2008.

MATERIALS AND METHODS

Collected adverse drug reactions and reporting sources

A Total of 933 ADRs was collected by PVnet homepage internet e-sub from January 2008 to December 2008. We collected ADRs not only from healthcare professionals working in regional general hospitals, private clinics (oriental medicine clinics were included) and pharmacies, but also from the general public who were patients or guardians of pediatric patients. We defined "A matter" that was the only one symptom matched to one drug. Thus, several matters could be included in the same ADR case. Consequently, total 3,049 matters found from 933 ADRs were analyzed.

Reporting interface of electronic submission

Once a new reporter was connected to PVnet hompage, the PVnet e-sub system requested for sign-in and registered as a new reporter. Mandatory information includes the name of institution, type of providing healthcare (general hospital, private clinic, pharmacy and patient/customer), and profession of reporter (doctor, nurse and pharmacist). The ADR e-sub interface required specific fields about adverse event including responsible RPVC selection, information of suggested culprit drug by reporter with co-administered medications (name, duration of administration, etc.), organ specified adverse reactions (e.g. skin-urticaria, cardiac-palpitation), and final treatment for the ADR (spontaneous recovery, medication, admission, etc.). Finally, reporter pressed the "Report" button on homepage, and then e-sub was completed and be enabled to assess causal relationship.

Assessment and feedback process of e-sub ADRs

These spontaneously reported ADRs were reviewed by the ADR monitoring council in each regional center and submitted to the Korean Food and Drug Administration after the causality assessment according to the WHO-Uppsala Monitoring Center (WHO-UMC) criteria.[9] Finally, WHO-UMC causality assessment was done in all cases. The severity of ADRs was also assessed as serious or non-serious. The serious ADRs included death, life-threatening event, permanent disabilities, prolonged hospitalization, and other important medical events defined by healthcare practitioners. The ADRs were classified with expectancy, culprit drugs, clinical manifestations in the order of body system, and the source of primary reporters such as doctors or nurses working in local private clinics, pharmacists in regional

pharmacies, and general consumers.

Statistical analysis

We analyzed these cases using descriptive statistics. The results were reported as frequency of data. In all statistical calculations, we used SPSS 12.0 program (Statistical Package for the Social Sciences, Chicago, IL, USA).

RESULTS

General characteristics of ADRs collected by e-sub

In 2008, PVnet finally reported a total of 933 ADR cases to KFDA via e-sub SRS after WHO-UMC causality assessment. All of them were collected from regional areas including secondary general hospital, private clinics (medical, dental and oriental medicine), pharmacies and general public. They contained 1,241 culprit drugs and 3,049 symptom-drug matched matters. Numerically 3.3 matters were reported in a case.

Reporting sources of ADRs were doctor (491 cases, 53%), pharmacist (290 cases, 31%), nurse (119 cases, 13%), general public (patients or their guardian) (30 cases, 3%), dentist (2 cases) and oriental medical doctor (1 case) (Fig. 1). The causality assessment showed certain causality 10.6%, probable causality 37.7%, possible causality 41.7% and others (including unlikely, conditional and unclassifiable) 10.0% (Fig. 2). About one fourth of e-sub ADRs (24%) were serious case, and 9% of ADRs were not expectable.

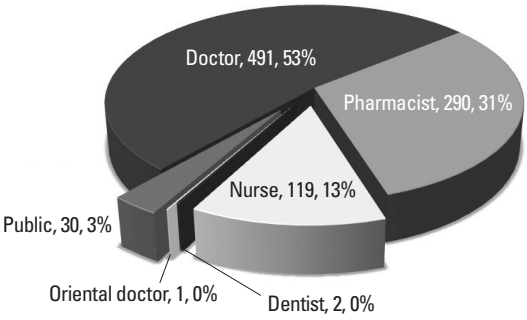

Fig. 1. Number and the proportion of reporting sources of electronically submitted adverse drug reactions from regional society.

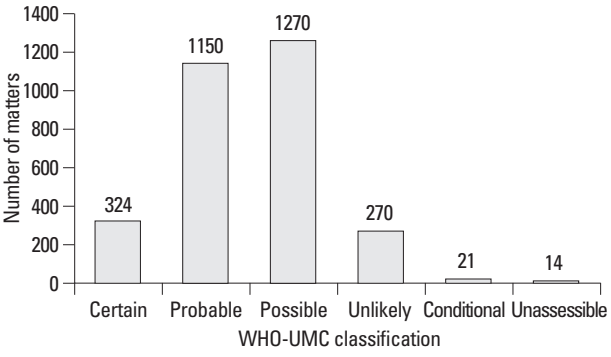

Fig. 2. WHO-UMC cause-relationship classification of collected matters of electronically submitted adverse drug reactions from regional society. WHO-UMC, WHO-Uppsala Monitoring Center.

Table 1. The Culprit Drugs of ADRs Collected by E-Sub (1,241 Drugs/933 Cases)

Drug	No.	%
Antimicrobials	290	23.4
Penicillin	28	2.3
Cephalosporin	72	5.8
Quinolone	28	2.3
Macrolide	9	0.7
Sulfa	2	0.2
Other antibiotics	11	0.9
Antituberculotic	132	10.6
Antifungal	4	0.3
Antiviral	4	0.3
CNS drugs	182	14.7
Antidepressant	72	5.8
Anticonvulsant	39	3.1
Antiparkinsonian	6	0.5
Antipsychotics	54	4.4
Antidemential	11	0.9
NSAIDs	117	9.4
Conventional	103	8.3
Oxicam	6	0.5
Coxib	8	0.6
Cardiovascular	96	7.7
Respiratory	79	6.4
Antineoplastic	41	3.3
Opioid	45	3.6
Antiulcer drug	35	2.8
GI modulator	32	2.6
Antithrombotic	28	2.3
Lipid lowering agent	26	2.1
Muscle relaxant	21	1.7
Hormone	16	1.3
Oral hypoglycemic	15	1.2
Antiosteoporotic	15	1.2
Antihistamine	15	1.2
Xanthine	12	1.0
Steroid	8	0.6
Vitamin	8	0.6
Immunosuppressant	3	0.2
Contrast media	85	6.8
Others	72	5.8

ADR, adverse drug reactions; e-sub, electronic submission; CNS, central nervous system; NSAID, non-steroidal anti-inflammatory drug; GI, gastrointestinal.

The culprit drugs and clinical manifestations of e-sub ADRs

Systematic classification of 1,241 culprit drugs is presented in Table 1, including antibiotics (23.4%), which include anti-tuberculosis agents, the most common culprits, followed by drugs for neurologic symptoms (14.7%). Non-steroidal anti-inflammatory drugs (NSAIDs) (9.4%) were the third, followed by cardiovascular drugs (7.7%), radiocontrast media (RCM) (6.8%), respiratory drugs (6.4%) and opioid drugs (3.6%).

According to the subclass of culprit antibiotics, anti-tuberculotic agents (10.6%) were the most common culprit drug of e-sub ADRs, followed by cephalosporins (5.8%), penicillins (2.3%) and fluoroquinolons (2.3%). Among the neurologic agents, the proportion of anti-depressants (5.4%) was over one third, followed by anti-psychotics (4.4%) and anti-convulsants (3.1%). Conventional NSAIDs (8.3%), not oxicam or coxibs, comprised the main proportion of ADRs caused by NSAIDs. Among 3,049 matters included in 933 ADR cases, skin symptoms (28.4%) such as rash and urticaria were the most frequent clinical manifestations, followed by neurologic symptoms (20.5%), gastrointestinal symptoms (19.1%), generalized symptoms (11.1%) and cardiovascular symptoms (5.3%) (Table 2).

DISCUSSION

In 1998, KFDA built the framework of SRS with a centralized system in Korea, however, its settlement was not easy, and the organization of PVnet with de-centralized SRS of private RPVCs participation influenced PV activities in Korea. There was no reliable data about ADRs before 2006, but nation-wide survey was possible after the foundation of the PVnet.[10] In the early phase of Korean PV activity reinforced by RPVCs, most collected ADRs were internal reports from the tertiary hospitals where RPVCs were settled. It was difficult to grasp the situation of ADRs in primary healthcares which are quite different from the tertiary hospitals, reflecting the different type of patient, disease and disease severity.[11-14]

From October 2007, PVnet opened its homepage to more easily and effectively collect ADRs occurring at private clinics in regional society via internet e-sub. Among the five thousands of ADRs reported to KFDA, 18% were reported from regional areas and 85% of regional ADRs were submitted electronically. After the use of homepage internet e-sub, the number of ADR reports increased rapidly, compared with other conventional reporting methods such as phone, fax and the post. In Korea, infrastructure for internet is relatively well constructed, and all educated people can easily access to internet. It was thought that the proportion of e-sub in collecting regional ADRs will increase in the future.

In this study, we used 933 ADRs collected from regional society and they were thought to reflect the reality of the primary healthcare field. It was expected that doctors were the main reporting source of ADRs of regional society, followed by pharmacists and nurses. First of all, patients or their guardians comprised 3% of reported ADRs, however, some of those reports were concerned with secondary gains such as claims and medical suits, and causality assessments in these cases need a great deal of caution. Nevertheless, spontaneous reporting systems must be open-minded towards public reporters, therefore, continuous education and public relations about PV and SRS are thought to be needed. van Hunsel, et al.[15] reported that the public ADR reporting rate could increase by the broadcast of a consumer program, whereas, increment of oriental doctor's reporting rate is in need because 7,500 oriental doctors are in practice in Korea. However, oriental or herbal medicines are not easily classifiable, because they are frequently used in combination with each other or include several effective components in a prescription. For these reasons, there is a limitation in objective causal relationship assessment.[16,17]

Since our study was based on SRS, we were not able to calculate incidence or prevalence of specific ADR symptom on specified drug. We only observed frequent culprit drugs and clinical manifestations of ADRs from regional areas. The most frequent culprit drug class was antibiotic,

Table 2. Clinical Manifestations Collected by E-Sub (3,049 Matters/933 Cases)

Involved organs	No. of matter	%
Skin	866	28.4
Neurologic	624	20.5
Gastrointestinal	581	19.1
Generalized symptom	338	11.1
Cardiovascular	162	5.3
Respiratory	131	4.3
HEENT	116	3.8
Liver & Biliary	67	2.2
Hematologic	51	1.7
Musculoskeletal	49	1.6
Nephrologic	34	1.1
Endocrine	30	1.0

HEENT, head, eye, ear, nose and throat; e-sub, electronic submission.

and anti-tuberculotic agent comprised a large proportion. We already reported similar results. Shin, et al.[10] reported that cephalosporin was the most frequent culprits among antibiotics, however, we found that anti-tuberculotic agents take the first place (10.6%) in antimicrobial agent section. The proportions of cephalosporin and quinolone were lower in our results, and these could be explained by high prevalence of tuberculosis in Korea. Especially, regional primary clinics reflected this more effectively than tertiary hospitals,[18] and RCM showed a smaller proportion compared with previous results.[10] It is quite likely that this would be related with the difference in the number of imaging studies in tertiary hospitals, private clinics and secondary general hospitals. In fact, a majority of imaging studies such as computerized tomography and magnetic resonance imaging were performed in tertiary hospitals in Korea.[19]

Second frequent culprit class was neurologic agents. Anti-depressants were reported frequently, supporting the fact that the usage of neurologic agents is high in Korea. Kim, et al.[20] reported that 50.3% of Korean elderly people have prescribed benzodiazepine in their out-patient clinics, and their result was higher than other studies in other developed countries,[21,22] reflecting high prevalence of psychiatric diseases in Korea. Further study would be needed what neurologic agent could cause specified symptoms. NSAID class was the third culprit, which is similar to the previous report.[23] The conventional NSAIDs usage is more popular prescription pattern in Korea rather than oxicams or selective COX-2 inhibitors.

In clinical manifestations of regional society ADRs, skin involvement such as rash, urticaria and angioedema was the most frequent symptom related to the usage of antibiotics and NSAIDs. Neurologic symptoms took the second place with 20.5% frequency that was higher than our previous report.[10] As mentioned above, these results would be related with drug usage pattern in Korea.

Surprisingly, 24% which was almost one fourth of regional society ADRs were serious cases. Although 22 admissions were identified in this study, most of the serious cases were considered as important medical accidents defined by reports themselves. In general, the patients visiting private clinic complained of lighter or milder symptoms than patients visiting tertiary hospitals. In a meta-analysis of articles about SRS between 1966 and 1996, Lazarou, et al.[2] reported that the frequency of serious ADR was 6.75% and their mortality rate was 0.32%. In the 21st century, however, many new drugs were released to market and the ADRs also might accordingly increase. We previously reported that 17.7% of ADRs were serious, but the report included ADRs mainly from tertiary hospitals that are visited by patients with more severe symptom or disease status.[10] Ufer, et al.[24] showed that 31% of ADRs was serious in the study which was based on SRS during one year observation of pediatric out-patient clinics where under 16-year-old patients visited. Although the patients visited the out-patient clinic with relatively mild symptoms, they are vulnerable populations to ADR because of being children and elderly people. Thus, serious ADRs could occur in those labile classes, and continuous warnings of alerts for PV and comprehensive educations about ADRs to healthcare practitioners would be necessary.

In this study, 9% unexpected ADRs were observed. This is in support of the fact that post-marketing ADR surveillance might be essential to detect newly developed ADRs that were not shown in pre-marketing clinical trials. However, decisive limitation of SRS is its low reporting rate. Lopez-Gonzalez, et al.[25] reported that low reporting rate was related to physicians in 76% articles in their bibliographic study using 45 articles about SRS. Other influencing factors included ignorance of mild ADRs (95%), diffidence to report ADRs (72%), lethargy for reporting (77%) and indifference and insecurity of individual doctor (67%). Among these various factors, the lethargy had close relation with accessibility to ADR reporting system. In this view point, computerized rapid access to ADR SRS by using internet would be helpful to improve reporting rate of SRS. Actually, the participation of regional society was quite poor at the beginning of PVnet in 2006. We thought that the lack of understanding the importance of ADR reporting was the main influencing factor to participate, but inconvenient reporting systems were also important. After the opening of homepage, ADR reports from regional society were increased appreciably. The internet e-sub reporting system also included validation and assessment process by experts, and assessed cases were finally fed back to healthcare professionals who reported the ADR case by e-mail. We thought that this system could effectively reinforce the motivation of ADR reporting. In the future, the upgrades with user-friendly interface, and real-time statistics and monitoring function showed be included, and then this internet e-sub SRS will be a very useful tool to collect ADRs from regional society. Further studies with a larger number of designated RPVCs and their network, and settlement of active surveillance system of ADRs as well as SRS like signal detection method are needed to understand more objectively

exact status of ADRs in Korea.

In conclusion, we analyzed 933 electronically submitted ADRs via PVnet homepage from regional society including private clinics and pharmacies rather than tertiary hospitals in Korea, and observed that antibiotics, neurologic agents, and NSAIDs were the most frequent culprits and skin involvement was the most frequent clinical manifestation.

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