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Analysis of Hospital Admissions Related to Adverse Drug Events Using ADE Signals

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Abstract – Adverse drug events (ADEs) are the most common type of adverse events in medical practice. Hospital admissions related to ADEs cost high and should be monitored to prevent them. While concerns about the ADEs are increasing, the frequency and characteristics of admissions related to ADEs have not been reported in Korea. The objective of the study was to assess the rate of hospital admission related to ADEs and their characteristics through ADE signal-based retrospective reviews of medical records. As results, a total of 1,420 patients had ADE signals suggesting potential ADEs from 3,494 patients who discharged from an academic medical center over one month period. Six pharmacists independently assessed the presence of ADEs after the review of patients' medical records. Among the 3,494 discharges, 62 admissions (1.8%) were found to be realted to ADEs. Of admissions with ADEs, 83.9% were moderate (category F by the NCC MERP classification), 37.2% were preventable, and 85.5% were type A reaction. The most frequent suspected drugs causing ADEs were antineoplastics (48.9%), and the most frequent ADE signal detecting hospital admissions related to ADEs was white blood cell count (24.2%). Hospital admissions related to ADEs were found through screening the ADE signals. The ADE signal-based retrospective review could be a practical approach for identifying hospital admissions related to ADEs.

Key words □ ADEs, signals, surveillance, hospitalization

INTRODUCTION

Adverse drug events (ADEs) could be responsible for significant morbidity and mortality in hospitalized patients. Nearly 20% of adverse events are related to drugs as the Harvard Medical Practice Study (HMPS) and the Utah Colorado Study (UCS) demonstrated (Brennan *et al.*, 1990 ; Thomas *et al.* 2000). The occurrence of ADEs in hospitalized patients after admission has been found to be at rates of 0.2 to 6.5 per 100 admissions depending on the identification technique used and the population examined (Bates *et al.*,1995; Faich *et al.*, 1986 and 1991; Melmon *et al.*,1971; Keith *et al.*,1989). In the U.S., the additional length of stay (LOS) was 1.7 to 2.2 days for overall ADEs, the increase in cost associated with ADEs was from $2,000 to $2,500, the annual cost attributable to ADEs was estimated to be $5.6 million in a 700-bed teaching hospital based on the costs and the incidences of ADEs, and the national cost of the preventable in-hospital events alone has been estimated to be $2 billion (Bates *et al.*,1997; Classen *et al.*,1997). More serious problem is that about 80% of ADEs were not detected by clinicians (Leape *et al.*, 1991).

While ADEs in inpatients have received considerable recent attention, ADEs in outpatients are less well understood for incidence, severity, preventability, and risk factors for ADEs (Honigman *et al.*, 2001). ADEs in outpatients occur at rates of 3.0 to 5.5 cases per 100 persons annually. Especially, among the patients over 65 years old, 5.1 ADEs occur per 100 persons per year, and the incidence of preventable ADE is 1.4 cases per 100 persons per year (Gurwitz *et al.*, 2000 and 2003). The reported common causes of ADEs were prescription errors (58.4%), monitoring errors (60.8%), and noncompliance (21.1%)(Gurwitz *et al.*, 2000). ADEs also caused 0.5 to 21.0% of all admissions to the hospitals in the U.S. depending on the method of data collection and the definition of ADEs used

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(Levy *et al.*, 1979; Col et al., 1990; Miller *et al.*, 1974; Ives *et al.*, 1987; Lakshmanan *et al.*, 1986; Bero *et al.*, 1991; Dartnell *et al.*, 1996). One recent study at a major Australian academic hospital estimated the rate of ADE-induced admissions to be 5.6% and the annual cost at that hospital to be an approximately 3 million dollars (Dartnell *et al.*, 1996).

There are three methods used to identify ADEs: voluntary reporting, intensive chart-review, and computer-based monitoring. Chart-review identified much more ADEs than did stimulated voluntary report (Bates *et al.*, 1993). Because a computer-based monitoring is much less expensive than chart-review, a computer-based monitoring system could be an efficient approach for measuring ADE frequency and evaluating the effectiveness of ADE prevention programs (Jha *et al.*, 1998). Because ADEs occurred outside the hospital often have signals similar to those associated with ADEs of inpatients, a computer-based ADE monitoring can also detect admissions related to ADEs (Jha *et al.*, 2001; Classen *et al.*, 1991). Most hospitals in Korea have used voluntary reporting system that is insensitive to detect ADEs. The more effective system should be developed to identify, report and prevent ADEs in outpatients and inpatients in Korea.

The objective of the study was to assess the rate of hospital admission related to ADEs through the ADE signal-based retrospective review of medical records. The hospital admissions related to ADEs were also reviewed for severity, preventability, suspected drug, clinical manifestations, causality and the mechanism of ADE.

METHODS

Setting

Samsung Medical Center (SMC) is a 1,300-bed tertiary academic medical center. SMC has been operating its information system, the Samsung Medical Information System (SMIS) since May 2003. The SMIS stores information at a patient level, and includes demographics, medical problem lists, allergic history, medication orders, discharge diagnoses code using ICD-10 (WHO, 1994), pertinent laboratory data, and care providers for patients.

Patients

All the patients discharged over one-month period from February 1st to 29th 2004 were included in this study. The discharged patients from three departments: pediatrics, psychiatrics, and obstetrics and gynecology, were excluded from the study. ADE signal-based retrospective review was conducted and the Institutional Review Board (IRB) of SMC approved the protocol of this study.

Outcomes

The main outcome measure of this study was the rate of hospital admissions related to ADEs. The definition of ADE used in this study was the same as the definition used in Bates et al (1995). They defined an ADE as "an injury resulting from medical intervention related to a drug" They defined that an ADE was different from an adverse drug reaction (ADR) since the definition of ADR by The World Health Organization (WHO) was that "an effect which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis, or therapy." This definition by WHO is restrictive because it considered only incidents in which the use of a drug is appropriate, whereas many ADEs are related to error (Jha *et al.*,1998). An ADE if an error in the medication process could be identified was considered preventable and was considered non-preventable when there were no errors in the medication process.

The characteristics of admissions related to ADEs were also determined: causality, severity, preventability, mechanism of ADEs, suspected drugs, ADE signals, and clinical manifestations of ADEs.

Development of ADE signals

ADE signals to detect ADEs were developed from reported studies: the LDS Hospital study (Classen *et al.*, 1991), the Brigham and Women's Hospital study(Jha *et al.*, 1998), the Good Samaritan Regional Medical Center study in Arizona (Raschke *et al.*, 1998), and the VHA research(VHA, 2002). The ADE signals could be classified into five categories: 1) orders for known antidote (e.g., naloxone as a narcotic antagonist), 2) laboratory abnormalities (e.g., elevated white blood cell counts), 3) laboratory abnormalities occurring in the presence of certain drugs (e.g., falling platelets in patients on heparin infusion), 4) vital signs, 5) documentation in nursing records (e.g., rash, anaphylaxis).

With the advice of six physicians, 46 unique signals to detect ADEs were adapted from the signals of the previous studies. A database was constructed to review medical records and collect data effectively using the Microsoft® Access 2000. The database enabled to import information on the patients with ADE signals and to enter the data related to verification of ADE and

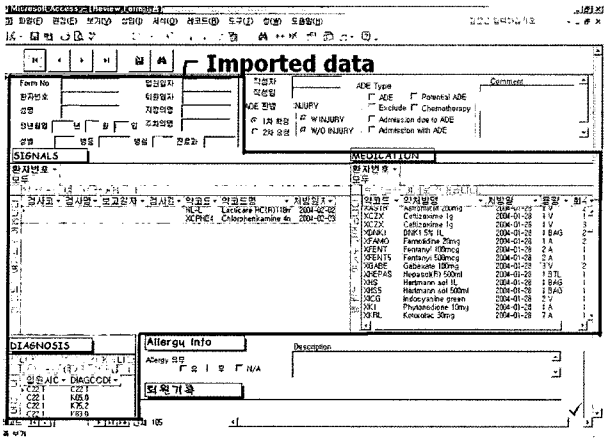

Fig. 1. Review form prepared by Microsoft® Access: Imported data

its characteristics (Fig. 1).

Identification and classification of ADE cases

When a patient's information met the condition of ADE signals, the computer generated alerts for that patient. One patient could have multiple ADE alerts, and one ADE could be associated with multiple ADE alerts. The report generated retrospectively by the computer ADE monitoring included the patient's medical record number, bed location, date of event, and the specific condition. Six pharmacists conducted chart review for the patients with one or more ADE signals to assess whether the patients experienced an ADE. The pharmacists trained in evaluating ADEs reviewed each medical chart of patients from the SMIS. The reviewers discussed about questionable cases at the conference for consensus biweekly, and consulted physicians when they could not reach a consensus.

Once ADEs were identified, the causality of ADEs were assessed based on the Naranjo algorithm (Naranjo *et al.*, 1981). The causal relationship was classified into 4 groups: 1) definite, if the total score is more than 9; 2) probable, if the total score is between 5 and 8 inclusive; 3) possible, if the total score is between 1 and 4 inclusive; and 4) doubtful, if the total score is zero or less. If the causality was greater than possible, the event was regarded as an ADE.

Once causality was assigned, each ADE was characterized by severity. Each ADE was classified by the modified National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) categories (USP, 2001). The category was defined as the error, but in this study it was modified by the injury. Out of 8 NCC MERP categories, 5 categories greater than category E were included for assessment of severity. If an event was classified as category E, F, G, H, or I, it was considered as an ADE. The Shumock & Thornton's criteria[41] was used to determine the preventability of ADEs: answering yes to one or more in the questions of these criteria suggests that the ADE in question may be determined as preventable (Schumock *et al.*, 1992).

ADEs were further classified into 6 different types of ADE mechanism(Miller *et al.*, 1974; deShazo *et al.*, 1997) :1) pharmacological side effect (e.g., dry mouth from antihistamines); 2) drug toxicity or over dose (e.g., hepatotoxicity from methotrexate, seizure from excessive lidocaine; 3) drug-drug interaction (e.g., bleeding with simultaneous use of warfarin and cimetidine); 4) intolerance (e.g., tinnitus after small dose of aspirin); 5) idiosyncratic reaction (e.g., coumarin-induced skin necrosis with protein C deficiency); and 6) hypersensitivity (immunologic) reactions (e.g., anaphylaxis to penicillin or radio-contrast media). Type A reaction included the mechanism of ADEs 1) to 3), and type B reaction included 4) to 6). Type A reactions were caused by known toxicities of drugs and were related to the drug's pharmacology and/or dose.[45] Therefore, type A reactions were considered predictable and early recognition of type A events could permit interventions to prevent more severe manifestations of toxicity. ADEs classified as type B reactions were allergic or idiosyncratic in nature. Type B reactions that resulted from first-time use of a drug were not considered preventable (Evans *et al,* 1994).

Table I. Patient Demographics

Characteristics	n (%), (total, n=62)
Age group, yr	
20	3 (4.9)
21~30	6 (9.7)
31~40	6 (9.7)
41~50	12 (19.4)
51~60	15 (24.2)
61~70	12 (19.4)
≥ 71	8 (12.9)
Gender	
Male	39 (62.9)
Female	23 (37.1)
Departments	
Internal medicine	
Hemato-oncology	19 (30.7)
Infection	12 (19.4)
Gastroenterology	9 (14.5)
Others	15 (24.2)
General surgery	3 (4.8)
Others	4 (6.5)

Statistical analysis

The rate of hospital admissions related to ADEs and their characteristics were mainly presented as frequencies and percentage. The positive predictive value (PPV) of each ADE signal was analyzed for identifying ADE. Comparisons between categorical variables were performed using ordinary Chi-square test and the Fisher's exact test.

Patients' age was categorized into 2 groups (≥65, <65yrs), and severity of ADEs was divided into severe (category F and G) and mild group (category E). The *p*-value less than 0.05 was considered significant.

% MAGREE macro® was used to determine the value of agreement on ADE identification, causality, severity, preventability, and mechanism of ADE. All reviewers independently reviewed the medical charts of 15 patients which were randomly selected to determine the rater reliability. Based on the kappa-value, the degree of agreement was determined as following (Landis *et al.*, 1977): 1) less than 0 points is poor, 2) 0 to 0.2 points is possible, 3) 0.2 to 0.4 points is fair, 4) 0.4 to 0.6 is moderate, 5) 0.6 through 0.8 is substantial, and 6) 0.8 to 1 is perfect. All analyses were performed using SAS program, version 8.1 (SAS Institute Inc, Cary, NC).

RESULTS

Rates of Hospital Admissions Related to ADEs

A total of 3,494 patients were discharged from February 1st to 29th 2004 and a total of 1,420 patients were detected by ADE signals. Overall 394 ADEs were identified among inpatients.

Admissions related to ADEs were 62 cases occurred in 61 patients among 3,494 discharged patients and the rate was 1.8 ADEs in 100 admissions. The kappa-value of raters was 0.79 for agreement in reviewing the cases. Sixty-three percent of the patients admitted with ADEs were male, and 27.4% of the patients were older than 65 years old. The average age was 52.2 years (range, 0 to 91 years). Six patients had allergic history with some materials including medicine (9.7%). And thirty-two patients with hospital admissions related to ADEs were caused by the chemotherapy (51.6%). (Table II)

Characteristics of the Admissions related to ADEs

Causality

Causality assessment using the Naranjo algorithm (average score = 6.6) revealed that definite causality was established in 14 (22.6%) of the ADEs, probable causality in 40 (64.5%), and possible causality in seven (11.3%). There was no case of doubtful causality. One ADE could not be assessed for the causality because the suspected drug had not been described in the medical chart when the patient was admitted to the hospital. (Table II)

Table II. Characteristics of the identified adverse drug events

	n (%) (total, n=62)
Naranjo scale	
Possible (1~4)	7 (11.3)
Probable (5~ 8)	40 (64.5)
Definite (≥9)	14 (22.6)
Don't know	1 (1.6)
Severity (NCC MERP scale)	
E (error, harm)	5 (8.1)
F (hospitalization)	52(83.9)
G (permanent harm)	5(8.1)
Preventability	
Preventable	23 (37.1)
Non-preventable	39 (62.9)
Mechanism of ADE	
Type A	53 (85.5)
Pharmacological side effect	36 (58.1)
Drug overdose or toxicity	15 (24.2)
Drug-drug interaction	2 (3.2)
Type B	9 (14.5)
Idiosyncratic reaction	4 (6.5)
Hypersensitivity (immunologic) reaction	5 (8.1)

Severity and preventability

The severity of ADE was determined by the modified NCC MERP category. Among 62 ADEs were detected, 52 (83.9%) were classified as category F. Both category E and G included 5 ADEs respectively (8.3%). The degree of agreement on severity judgment was considered moderate based on the kappa-value of 0.42.

The preventability of ADE was determined by the Shumock & Thornton's criteria. Among 62 ADEs, 23 (37.1%) were identified as preventable and 39 (62.9%) were non-preventable. (Table II)

Mechanism of ADE

The majority (53 ADEs, 85.5%) of ADEs were type A reactions (predictable) and 9 ADEs (14.5%) were type B reactions (not-predictable). In the type B reactions, all were category F. The most common mechanism of ADEs was pharmacological side effect (58.4%). Fifteen ADEs (24.2%) were caused by the drug overdose or toxicity and two ADEs (3.2%) were the drug-

drug interaction. There were no ADEs whose mechanism of ADEs was intolerance. Four ADEs (6.5%) were classified as idiosyncratic reaction, and five ADEs (8.1%) were caused by hypersensitivity reactions. (Table II)

Suspected drugs causing ADEs

Agents associated with the 62 ADEs tended to cluster in a few therapeutic classes (Table III). Ninty four drugs were identified as suspected drugs causing ADEs because one ADE could be related to multiple drugs. Antineoplastics were the most common agents resulting in admissions related to ADEs than other class of drugs. With 46 ADEs, antineoplastics were primarily or partly responsible for the ADEs, and seven of which were related to irinotecan. Irinotecan was the most common individual medication implicated in ADEs that caused admissions. Other common drug classes related to admissions related to ADEs were antimicrobials (11 ADEs), and cardiovascular drugs (10 ADEs).

Table III. Suspected drugs for the adverse drug events

	n (%), (total n=94)
Antineoplastic	46 (48.9)
Irinotecan	7 (7.5)
5-fluorouracil	6 (6.4)
Doxorubicin	5 (5.3)
Others	28
Antimicrobials	11 (11.7)
Ciprofloxacin	2 (2.1)
Levofloxacin	1 (1.1)
Others	8
Cardiovascular drug	10 (10.6)
Warfarin	2 (2.1)
Atenolol	1 (1.1)
Others	7
Herbs	7 (7.5)
Immunosuprresant	6 (9.6)
Cisplatin	2 (2.1)
Infliximab	1 (1.1)
Others	3
NSAIDs	4 (4.3)
Talniflumate	1 (1.1)
Celecoxib	1 (1.1)
Others	2
Anticonvulsant	3 (3.2)
Carbamazepine	1 (1.1)
Others	2
Others**	7 (7.5)

**One ADE was caused by hypoglycemic drug, 1 was antiviral agent, 2 were stegoid agents, 1 was inhaler material.

Clinical manifestations of ADEs

For among the 62 ADEs detected, 97 clinical manifestations were elicited with the patients admitted related to ADEs because one ADE could have multiple clinical manifestations. The most frequent clinical manifestations were leucopenia, occurring 25 ADEs (25.8%). Symptoms less frequently observed were fever (18.6%), abnormal LFT (14.4%), and rash or itching (8.3%). (Table IV)

Frequency and PPV of ADE Signals

The most frequent ADE signal detecting hospital admissions related to ADEs was white blood cell counts (WBC), 24.2%. Less frequently observed were alanine aminotransferase (ALT) (12.1%), aspartate aminotransferase (AST) (9.9%), and diagnosis code (9.9%). Other signals accounted for the remaining 43.9% of ADE signals. Activated partial thromboplastin time (APTT) was observed in 1 patient, and the change of serum creatinine was noted in one. (Table V)

During the study period, the computer monitor generated 3,017 alerts of which 85 were associated with 62 admissions related to ADEs. The PPV of the alerts for detecting admissions related to an ADE was 5.3%. The highest PPV of ADE signal was generated by diagnosis code (32.1%), and total bilirubin was the next highest PPV of signals (25%). (Table VI)

Relationship between Categorical Variables of ADEs

There was no significant relationship between patients' age and preventability of ADEs (p=0.86), and patients' age and mechanism of ADEs (p=0.30) (Fig. 2, 3). There was no signif-

Table IV. Clinical manifestations of the adverse drug events

Clinical symptoms	n (%), n=97
Leukopenia	25 (25.8)
Fever	18 (18.6)
Abnormal LFT	14 (14.4)
Rash, itching	8 (8.3)
Anorexia/ weight loss	5 (5.2)
Renal failure	5 (5.2)
Diarrhea	4 (4.1)
Dizziness	3 (3.1)
Nausea or vomiting	3 (3.1)
Pain	2 (2.1)
Hyperkalemia	2 (2.1)
Hypokalemia	2 (2.1)
Arrhythmia	1 (1.0)
Dyspnea	1 (1.0)
Hypoglycemia	1 (1.0)
Others	3 (3.1)

Table V. Frequency of the adverse drug event signals

Signals	n(%), (total n=90)
White blood cell (WBC), blood	22 (24.2)
Alanine aminotransferase (ALT), serum	11(12.1)
Aspartate aminotransferase (AST), serum	9 (9.9)
Diagnosis code	9 (9.9)
No signal	5 (5.5)
Total bilirubin, serum	4 (4.4)
Alkaline phosphatase (ALP), serum	3 (3.3)
Blood urea nitrogen (BUN), serum	3 (3.3)
Chlorpheniramine	3 (3.3)
International normalized ratio (INR)	3 (3.3)
Polystyrene sulfonate calcium	3 (3.3)
Metoclopropamide	3 (3.3)
Platelet count (PLt), blood	3 (3.3)
Clostridium difficile	2 (2.2)
Hydrocortisone	2 (2.2)
Potassium (K), serum	2 (2.2)
Activated partial thromboplastin time (APTT)	1 (1.1)
Creatinine, serum	1 (1.1)
Haloperidol	1 (1.1)

Table VI. Positive predictive value of the adverse drug event signals

ADE signals	No. alerts (N)	No. associated with ADEs (A)	PPV (A/N, %)
Diagnosis code	28	9	32.1
Total billirubin, serum	16	4	25
PT (INR)	17	3	17.6
WBC, blood	153	22	14.4
ALT, serum	90	11	12.2
AST, serum	86	9	10.5
Potassium, serum	22	2	9.1
Hydrocortisone	26	2	7.7
APTT	14	1	7.1
BUN, blood	46	3	6.5
ALP, serum	57	3	5.3
Polystyrene sulfonate cal.	65	3	4.6
Haloperidol	22	1	4.5
Platelet count, blood	83	3	3.6
Clostridium difficile	90	2	2.2
Creatinine, serum	46	1	2.2
Metoclopropamide	329	3	0.9
Chlorpheniramine	426	3	0.7
TOTAL	1,616	85	5.3

icant relationship between severity (mild-category E, severe-category F, G) and preventability (p=0.36), and severity and mechanism of ADE, either (p=0.44) (Fig. 4, 5).

DISCUSSION

ADE signals identified hospital admissions related to ADEs.

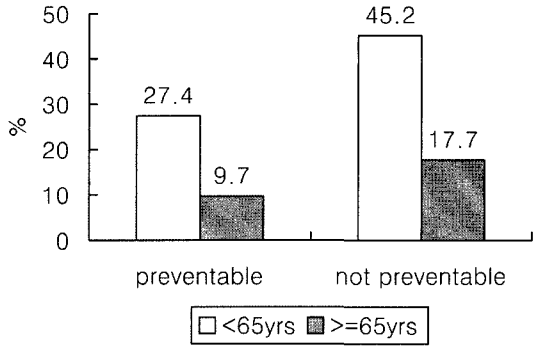

Fig. 2. Preventability of the adverse drug events.

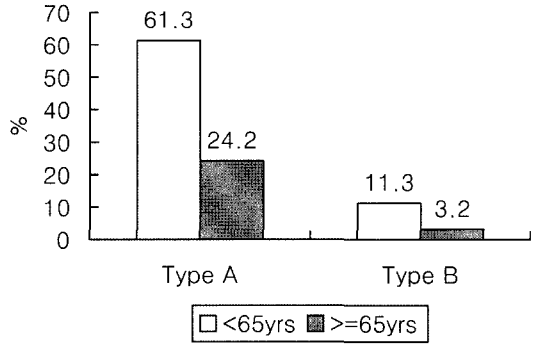

Fig. 3. The mechanism of the adverse drug events.

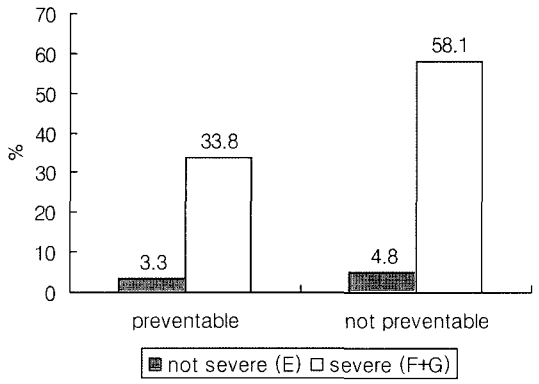

Fig. 4. Severity (NCC MERP) and preventability.

The rate of admissions related to ADEs in this study was 1.8% which was approximately 10-fold higher than 0.14% reported by Classen (1991). Classen and colleagues used a computer-based monitoring to detect ADEs in hospitalized patients as well as admissions related to ADEs at LDS (Latter-day Saints) hospital. Using computer-based monitoring and voluntary report, they found that 52 cases of the 36,653 admissions (0.14 %) in LDS hospital were related to ADEs. Though they were effective in finding ADEs of inpatients, their rates of admissions related to ADEs were very low. However, other studies

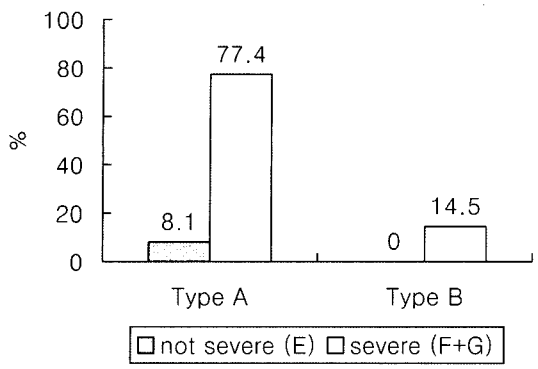

Fig. 5. Severity (NCC MERP) and the mechanism of the adverse drug events.

that have used chart-review method found the rates between 2.9 and 15.4%. Since other studies used different definition of ADEs and review methods, and the hospital circumstances were different from this study conditions, the results of this study could not be directly compared with the results of other studies. Studies from academic hospitals reported the rates between 3.0 to 6.0% (Miller *et al.*, 1974; Lakshmanan *et al.*, 1986; Caranasos *et al.*, 1974). Higher rates of ADEs were reported in other studies including the patients admitted for drugs abuse such as alcohol and narcotics(Levy *et al.*, 1979), and intentional overdoses(Lakshmanan *et al.*, 1986; Caranasos *et al.*, 1974), and in the study with patients in non-academic settings(Colt *et al.*, 1989). A recent meta-analysis of ADRs, which excluded events caused by errors in the prescription and the administration of drugs, found that 4.7% of admissions to hospitals were related to serious ADRs (Lazarou *et al.*, 1998). The data of meta-analysis study was derived by combining many small studies, which mostly used the chart-review method in detecting ADEs; also these studies might have preferentially been performed in medical sites with high rates of admissions caused by ADEs (Jha *et al.*, 2001). One reason that the rate determined in this study might be lower than in other studies was that the computer-based monitoring might miss some admissions caused by ADEs. In one report, the incidence of in-hospital ADEs detected by the computer-based monitoring was compared with the incidence identified by chart-review. The study found that 45% more events were detected by chart-review method. And the overlap between events detected by chart-review and the computer-based monitoring was low, although both sets of events were valid events (Jha *et al.*, 1998).

Most cases were severe, preventable and unpredictable reactions in other studies (Honigman *et al.*, 2001; Jha *et al.*, 2001). But in this study, most cases were moderate (category F by the NCC MERP classification), non-preventable, and predictable reactions with higher dosage and pharmacological reaction. Most patients were improved with the intervention to treat ADE (88.7%). These results could be explained by that over one half of studied patients were related to chemotherapy in the studied hospital. In Korea, tertiary hospitals have much cancer related patients. Antineoplastic agents and immunosuppressants were the most common drug classes to cause ADEs. WBC counts and abnormal LFT values were the most common signals. In other studies, antibiotics and analgesics were the most common suspected drugs. The computer monitoring of this study might have missed ADEs related to opioids analgesics, nephrotoxic antibiotics or NSAIDs. In the 5 cases of ADEs, no signal was detected. In spite of no signal, events could be identified as admissions related to ADEs by chart-review. Signals should be improved to identify the patients admitted related to ADEs. One of the noticeable facts was the ADEs related to herbal medicine. In addition to prescribed medications, Korean culture of taking medicines could not exclude self-medication, poly-pharmacy, overlapping prescriptions of different hospitals, nuraceuticals and oriental herbal medicine. Seven percent of ADEs occurred due to herbal medicine, and they showed electrolyte disturbances and abnormal liver functions in the laboratory level.

We used the information obtained from the electronic medical records and reviewed each chart to identify incidents associated with ADEs. Most other studies about outpatient ADEs used chart-review method and self-report in cohorts of patients and extrapolated their findings on the basis of total annual visits (Honigman *et al.*, 2001). Comparing with other studies, the method of this study to estimate an ADE rate was faster and much less expensive. However, a potential weakness of the study was the lack of information about patients to classify an ADE into admissions related to ADEs because of a retrospective study design with review of electronic medical chart. Even though the causality of all cases was assessed, it was impossible to be absolutely certain of a causal link between the suspected drug and an ADE.

Several risk factors were identified in other studies predisposing patients to admissions related to ADEs; old age, female sex, polypharmacy, impaired renal function, and history of ADEs (Caranasos *et al.*, 1974; Levy *et al.* 1980; Bergman *et al.*, 1981; Wu *et al.*, 2003). Noncompliance was often associated with the admissions in two studies (McKenney *et al.*, 1976). In our study, over 65 years were 27.4% and female were 37.1%. Age and sex were not significant factors to the admission rates

related to ADEs. Patients over 65 years olds were 27.0% in this study compared to 63.0% in the Wu study. Female were 37.1% compared to 56.0% in the same study (Wu *et al.*, 2003). There could not be complete information about compliance and polypharmacy in the retrospective study method. The overall PPV of ADE signals detecting the admissions related to ADEs was also determined to be 5.3%. There are several reasons for the low PPVs of many of ADE signals: 1) though the system was designed to emphasize the sensitivity in detecting ADEs, many alerts were generated, which were not associated with ADEs. 2) Many of the alerts were duplicated. For example, multiple alerts could be generated for one ADE in several days if a patient was on several nephrotoxic agents and had renal failure from any cause. However, once a determination was made that the etiology of the renal failure could not be easily attributable to a single cause and all the subsequent alerts could be ignored. 3) There were often spurious and easily determinable as such. One rule triggered an alert for a patient on an angiotensin converting enzyme inhibitor (ACEI) and elevated serum potassium. That rule was often triggered by spurious hyperkalemia related to laboratory error, 4) many of alerts were low because those alerts were associated with in-hospital ADEs.

Since ADEs are both costly and frequent as the important factors of the quality of care, many attempts to provide a better ADE monitoring at lower cost have been made. To prevent and reduce hospital admission related to ADEs, the efforts on improving the safety of medication used in outpatient care would be necessary. Systems that have computerized allergy checking, tracking of serum medication levels as well as checking of drug-drug and drug-laboratory interactions reduced ADEs in another study, and decreased the rate of ADE-induced admissions. In a past study, an information system decreased the serious medication error rate by 55% in hospitalized patients. Monitoring approaches in routine care had an important role (Evans et al., 1998; Bates *et al.*, 1998). Implement of the computer monitoring system reduced admissions related to ADEs. In the U.S., the Joint Commission on Accreditation of Health Care Organizations (JCAHO) required hospitals to monitor the rates of adverse events as an important marker of the quality of medical care (Faich *et al.*, 1987; Sills *et al.*, 1986).

A spontaneous voluntary reporting system was the only method to detect ADEs in Korea, but it has been rarely used. The routine chart-review method of all medical records is very expensive to use. Therefore, a computer-based approach with chart-review could be cost effective, and could improve the safety and the quality of care. This study could be used to develop ADE signals and to evaluate the performance of them for a computer-based ADE monitoring system in Korea.

This was the first trial to study the current status about admissions related to ADEs using ADE signals by computer-based monitoring system. There were some studies about ADEs in Korea, but it is difficult to be compared directly since the purposes and including patients were different (Choi *et al.*, 2001; Choi *et al.*, 2003). This study had several limitations. First of all, it was performed in only one institution for only one month, so the results might not be generalized to other outpatient setting. Secondly, all the information of patients prior to admission could not be complete since this study was performed by retrospective method, with possible missed data on the medical chart. Over-the-count medications and drugs prescribed from other hospitals might have also caused the adverse events. In addition, six reviewers were participated in this study. There were some difficult cases to reach the consensus, while most studies had 2 reviewers with high degree of agreements.

CONCLUSION

Surveillance of ADE has been important to improve quality of medical care and the computer-based monitoring system has been considered as a good method to detect ADEs. We assessed the rates and characteristics of admissions related to ADEs for the first time in Korea. The rate of hospital admissions related to ADEs was 1.8%. And most of ADEs were moderate in severity by modified NCC MERP category, not preventable type A reaction. Antineoplastics were the most frequent drug class identified as the suspected drug. Clinical manifestations related to chemotherapy presented the most frequently and influenced the characteristics of hospital admissions related to ADEs in this study. In the future, the computerized surveillance system can be developed using improved ADE signals to detect and prevent ADEs for the better quality of medical care.

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Appendix

Signals Used for ADE monitoring

(1) Laboratory test

1) Activated partial thromboplastin time (APTT) > 6 * hospital's upper limits

2) Bilirubin, total > 10 mg/dL

3) Blood urea nitrogen (BUN) > 50 mg/dL

4) *Clostiridium difficille.*

5) Creatinine clearance < 50ml/min and receiving "nephrotoxin" without renal failure.

6) Glucose, fasting < 50 mg/dL

7) Glucose, fasting > 350 mg/dL and diagnosis of diabetes with ketosis or coma.

8) Platelet count, blood < $50*10^3$/ml without leukemia, sepsis, and thrombocytopenia.

9) Prothrombin time (INR) > 3.5 without sepsis, liver disease, hepatitis

10) Serum alanine aminotransferase (ALT) >150 U/L without liver disease

11) Serum alkaline phosphatase (ALP) > 350 U/L without peritonitis, pancreatitis, bone cancer

12) Serum aspartate aminotransferase (AST) > 150 U/L without liver disease

13) Serum creatinine 1.0 over admission baseline and receiving "nephrotoxin"

14) Serum potassium (K) > 6.0 mmol/ without renal failure

15) White blood cell count, blood < $3*10^3$/ml

(2) Drug concentration

1) Serum amikacin peak >25mg/L, trough >10mg/L

2) Serum carbamazepine >10 mg/mL

3) Serum cyclosporine >500 mg/L

4) Serum digoxin >2.0ng/mL

5) Serum gentamicin peak >10mg/L, trough >2mg/L

6) Serum phenobarbital >45ß¹/mL

7) Serum phenytoin >20ß¹/mL

8) Serum tacrolimus (FK506) >30ng/mL

9) Serum theophylline >20 mg/mL

10) Serum tobramycin peak >10mg/L, trough >2mg/L

11) Serum valproic acid >100 mg/mL

12) Serum vancomycin peak >40mg/L, trough >10mg/L

(3) Medication

1) Receiving alteplase without myocardiac infarction.

2) Receiving anti-diarrheal agents without intestinal infectious disease, Crohn's disease, and irritable bowel syndrome.

3) Receiving anti-emetics without post-operation, gastroscopy, etc

4) Receiving anti-histamine without diagnosis of dermatitis, urticaria, erythema, and diseases of the respiratory system.

5) Receiving anti-ulcer drugs and platelet count, blood has fallen to less than 50% previous value not diagnosis of ulcer.

6) Receiving atropine without operation.

7) Receiving benztropine without Parkinson's disease.

8) Receiving Dextrose 50% in water and Glucose, Fasting < 70 mg/dL.

9) Receiving epinephrine without operation and receiving with corticosteroids.

10) Receiving flumazenil.

11) Receiving hydrocortisone without order of "hydrocortisone" within last 7 days, post-transplantation, and autoimmune disease.

12) Receiving methylprednisolone without order of "methylprednis -olone" within last 7 days, post-transplantation, and autoimmune disease.

13) Receiving naloxone.

14) Receiving oral vancomycin.

15) Receiving polystyrene sulfonate calcium without renal failure.

16) Receiving protamine sulfate.

17) Receiving topical steroid without diagnosis of dermatitis, urticaria, erythema.

18) Receiving vitamine K without diagnosis of leukemia, liver disease, gastrointestinal bleeding and order of warfarin within last 14 days.

(4) ICD-10 code

* Receiving ICD-10 code in chief complain or diagnosis indicating adverse drug event (ADE)