Overdose Rate of Drugs Requiring Renal Dose Adjustment: Data Analysis of 4 Years Prescriptions at a Tertiary Teaching Hospital

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OBJECTIVE: To determine the overdose rate of drugs that require renal dose adjustment and factors related with overdose.

SUBJECTS: Total of 23,635,210 records of prescriptions and laboratory data of inpatients at a tertiary teaching hospital for the period from January 2002 to December 2005.

METHODS: A clinical data mart was constructed. A knowledge base containing dose adjusting information about 56 drugs was built. One day dose was compared to the reference dose adjusted to the patient's renal function.

RESULTS: Considering the patient's renal function, 5.3% of drug doses were excessive. The overdose rate in the patients with moderate to severe renal insufficiency was 28.2%. Only 25% of physicians were responsible for 50.6% of the overdoses. Of 56 drugs studied, 10 drugs, including ranitidine, amoxicillin, and piperacillin/tazobactam, were involved in 85.4% of the overdoses. The physicians with high overdose rate had patients with more impaired renal function (correlation coefficient= 0.192, $P<.001$). There were negative correlation between clinical experiences of physician and overdose rate (correlation coefficient=−0.221, $P<.001$) and workload of prescription (correlation coefficient=−0.446, $P<.001$), when excluding interns from the analyses. There was positive correlation between workload of prescription and overdose rate (correlation coefficient=0.361, $P<.001$).

CONCLUSION: A clinical data mart was useful to analyze the vast amount of electronic hospital data. Drug overdose is quite common among inpatients with renal insufficiency. Only a few drugs are responsible for most of drug overdoses. The physicians' clinical experience, workload of prescriptions, and patients' renal function are correlated with drug overdose.

KEY WORDS: adverse drug events; overdose; renal insufficiency; safety; knowledge base; data mart.
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First two authors are equally contributed to this work.

INTRODUCTION

An Institute of Medicine report suggested that 7,000 deaths occur annually in the United States as a result of medication errors.[1] It has been reported that more than half of all preventable medication errors are the consequences of improper physician orders.[2]

Renal insufficiency is relatively common among hospitalized patients, and patients with renal insufficiency are usually taking more than six different medications to manage the symptoms related to their renal impairment.[3,4] The frequency of adverse drug effects increases with the number of medications used, degree of renal dysfunction, age of patients, and number of comorbid conditions.[5,6] As drugs which require renal dose adjustment may cause renal function impairment or accumulate in the body at excessive concentrations, they should carefully be selected and dosed, based on pharmacologic principles and systematic approach for safe and effective patient care.[7]

In a case-control study covering 17,828 patients, Chertow et al. revealed that the inappropriate order rate of nephrotoxic or renally cleared medication for renally impaired patient in a hospital was 70%,[8] and Falconnier et al. reported in a case-control study covering 1,648 patients that 67% of drugs were not adjusted to individual renal function.[9] However, there are a lack of large-scale studies, which have identified the medications most commonly overdosed and the predictive physician factors for these errors. In the present study, we analyzed electronic prescriptions and laboratory data at a tertiary teaching hospital for a 48-month period and determined the overdose rate, overdosed drug, and the physician factors related with overdose for drugs requiring renal dose adjustment by constructing a clinical data mart. To get insight into drug overdoses in a hospital, the physician characteristics, such as clinical experience, prescription workload, and the renal function of patients whom they are in charge of, were further investigated.

METHODS

Study Design

The data on electronic prescriptions and laboratory results are too extensive and distributed on many computer systems in the subject hospital to make them suitable for direct analysis. For the specific purpose of our analyses, therefore, the data had to be gathered, extracted, and reorganized into a clinical

data mart through complex and laborious multistep processes. A knowledge base containing dose-adjusting information based on the creatinine clearance was necessary to determine whether a prescription was an overdose. A daily dose of each prescribed drug was compared with the recommended daily dose adjusted for the patient's creatinine clearance.

Construction of Clinical Data Mart and Renal Dosing Reference Knowledge Base

The subject 1,080-bed tertiary teaching hospital has been using a computerized prescribing system since 1994, however, the prescribing system does not support any drug dosing guideline for physicians, except checking for drugs, which should not be used together. We obtained all the electronic data for 48 months between January 1, 2002 and December 31, 2005 from the subject hospital information system. The hospital information system (HIS) is run on the Caché version 5.0 (InterSystems, Cambridge, MA) database management system (DBMS). The prescription data, serum creatinine values, and information on patients and doctors were selected from the dump data file, and imported into a staging data mart (an intermediate data mart), which is run on the MS-SQL 2000 (Microsoft, Redmond, WA). The identities of patients and doctors were removed from the data. Individual identification data, including name, social security number, and hospital identification number, were deleted and replaced with random serial numbers. The study was approved by the local institutional review boards (AJIR-CRO-06-057). The data cleansing and transformation were performed. The resulting data mart consisted of a drug prescription table, a patient table, a doctor table, a laboratory table, and a renal function table.

We built a renal dosing reference knowledge base by referring to the literature,[10,11] which was subsequently reviewed by a nephrologist. For the purpose of analysis, the maximally allowed daily doses were applied to the knowledge base to prevent overestimation of overdose rate. The knowledge base consisted of three tables: a drug substances table, which contains general information about drug itself; a usual dosage table, which contains dosing data for normal renal function; and a renal dosage table, which contains dosing data for impaired renal function.

The initial knowledge base contained information on 125 drugs, however, drugs requiring patient's body weight or patient's disease state were excluded because the HIS data did not contain patient's body weight or reliable data on patient's disease state. Drugs, which were not used in the subject hospital, were also excluded. The resulting final renal dosing reference knowledge base contained dosage adjustment information on 56 generic drugs by ingredient basis and route of administration. The 56 generic drugs were mapped into 103 brand drugs used in the subject hospital. The bioavailability was not considered in this study.

Estimation of Creatinine Clearance and Overdose Decision

The abbreviated Modification of Diet in Renal Disease equation was used to estimate the creatinine clearance.[12] The highest serum creatinine value was used to estimate the creatinine clearance if two or more serum creatinine values were given in the same day. If no serum creatinine value was shown for a prescription day, the nearest previous serum creatinine value was used to estimate the creatinine clearance.

The 1-day dose of a prescribed drug was calculated by multiplying the unit dose (mg) and frequency. The recommended 1-day dose (mg) for the patient's estimated creatinine clearance was selected from the renal dosing reference knowledge base. An overdose was identified by comparing the 1-day dose of a prescribed drug with the recommend 1-day dose.

Study Selection and Data Extraction

The subject data contained 150,452 individual patient data, 573 individual doctor data, 18,981,276 records of prescription data, and 4,653,934 records of laboratory data (Fig. 1). Patients younger than 18 years or data not associated with

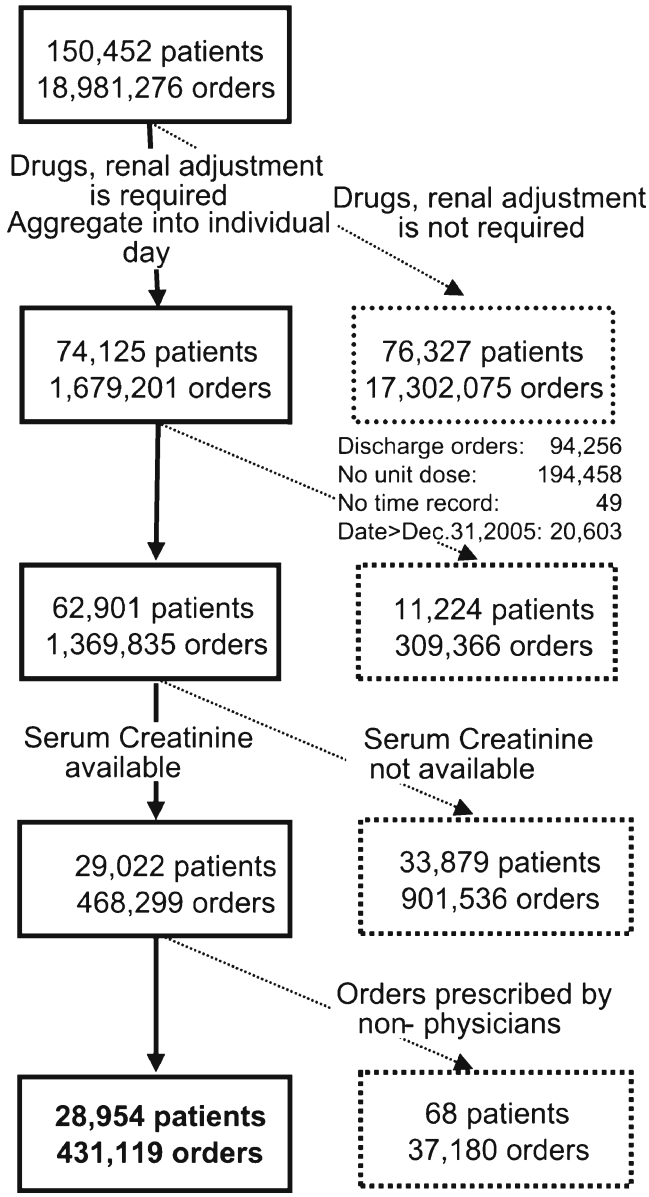

Figure 1. The selected target data for analysis. 28,954 individual patients and 431,119 prescriptions of drugs that require renal dose adjustment were selected.

drugs on the reference knowledge base were excluded. Multiple prescriptions of a same drug to a patient in a same day were aggregated into a record to make individual day order, which contained a total drug dose administrated in a day. Hereafter, a prescription order (or data) means an aggregated individual day prescription order (or data). The resulting database consisted of 74,125 individual patient data and 1,679,201 records of prescription data. The 94,256 records regarding discharge orders, 194,458 records that had no unit dose, 49 records that had no time, and 20,603 records ordered after December 31, 2005 were excluded. In addition, 33,879 individual patient data and 901,536 records of prescription data were excluded because they were not associated with serum creatinine values. The resulting 28,954 individual patient data and 431,119 records of prescription data were finally selected to analyze the overall drug overdose rate, frequency and fraction of overdose drugs, degree of overdose, frequency and fraction of overdose rate by physician groups, and drug overdose rate by physicians' training experience. Physicians were divided into quartiles by their overdose rate: highest overdose group, high overdose group, low overdose group, and lowest overdose group.

Statistical Analysis

The chi-squared test was used to determine the difference in overdose rate by the route of administration. Spearman's correlation test was used to determine the correlation between physician's clinical experience and number of prescriptions requiring renal dosing adjustment; between physician's clinical experience and overdose rate; and between physician group divided by overdose rate and patients' renal function. Kruskal–Wallis test was used to determine the difference in the patients' renal function between the physician groups. All the statistical analyses were carried out by using the SPSS version 12 (SPSS, Chicago, IL). $P<0.05$ was considered statistically significant.

RESULTS

A total of 28,954 patients were evaluated. The age of patients ranged from 18 to 96 years (mean=56.0, SD=16.0). The mean creatinine clearance of patients was 99.6 mL/min (SD=56.4). Patients with normal renal function (CrCl≥80 mL/min) were 55.9%, mild renal insufficiency (50 mL/min≤CrCl<80 mL/min) 22.6%, moderate renal insufficiency (15 mL/min≤CrCl< 50 mL/min) 12.1%, and severe renal insufficiency (CrCl< 15 mL/min) 5.3%. We found 22,981 overdose prescriptions out of 431,119 prescriptions that required renal dose adjustment during 4 years in the subject hospital, and the overall overdose rate was 5.3%. The overdose rates for normal to mild renal insufficiency were relatively low (1.1% and 1.3%, respectively, mean=1.1%). In contrast, as shown in Figure 2, the overdose rates for moderate to severe renal insufficiency were high (27.8% and 29.0% respectively, mean=28.2%), There was significant difference in overdose rates by the route of administration (chi-square, $P<.001$). For the patients with moderate renal insufficiency, the overdose rate of injection type drugs was 37.2%, whereas that of oral type drug was 12.9%. For the patients with severe renal insufficiency, the overdose rate of injection type drugs was 32.1%, whereas that of oral type drug was 23.3%.

Ranitidine was prescribed 97,138 times; 11,092 (48.3% of all overdose prescriptions) were overdoses (Table 1). Amoxicillin was prescribed 2,218 times; 1,595 (6.9% of all overdose prescriptions) were overdoses. Piperacillin/tazobactam was overdosed 1,594 times out of 15,510 prescriptions, and cefotetan was overdosed 1,243 times out of 12,694 prescriptions, and they were responsible for 6.9% and 5.4% of all overdose prescriptions, respectively. Twenty of the 56 drugs studied contributed to 96.2% of all overdose prescriptions, and only 10 drugs (17.8%) caused 85.4% of the overdoses. Amoxicillin, sotalol, and ertapenem had the highest overdose rates in descending order (71.9%, 37.5%, and 34.2%, respectively).

We found that 21,710 overdose prescriptions were 1 to 2 times the recommended dose, which was the most frequent degree of overdose, constituting 94.5% of all overdose prescriptions and that 1,198 overdose prescriptions were 2 to 5 times the recommended dose, which was the second most frequent degree of overdose, constituting 5.2% of all overdose prescriptions. Most overdose prescriptions (99.7%) were 1 to 5 times the recommended dose, although some extreme cases were found: 26 overdose prescriptions were greater than 5 times the recommended dose (fexofenadine 18 orders, cetirizine 2 orders, famotidine 2 orders, etc). Although the use of terbinafine or itraconazole is contraindicated in patients with impaired renal function, they were prescribed 24 and 23 times, respectively, during the study period.

Five hundred fifty individual physicians were responsible for the data on the data mart during the study period. The length of service ranged from 1 to 1,456 days. The physicians with lengths of service less than 6 months were excluded (125 physicians), leaving 425 physicians in the study. Of these physicians, 25.0% (106 of 425) prescribed 31.1% of all drug prescriptions that required renal dose adjustment and caused 50.6% of all drug overdoses (11,567 of 22,867). The top 50% of physicians (first and second quartiles) wrote 75.3% of all drug prescriptions that required renal dose adjustment and were responsible for 92.3% of all drug overdoses (21,111 of 22,867).

Because a greater length of physician employment at the hospital appeared to have prescribed more overdoses, the length of employment was normalized. The annual prescription rate was calculated as follows: (calculated annual prescriptions per physician)=(total number of prescriptions by a physician)×365/[the length of their employment period (days)]. Nevertheless, the analysis by the above calculated annual prescriptions gave similar results: 25.0% of the physicians prescribed 29.0% of all drug prescriptions and were responsible for 51.6% of all drug overdoses.

The overdose rates by physicians' training experience were 2.6% for interns, 8.6% for first year residents, 7.2% for second year residents, 6.1% for third year residents, 6.4% for fourth year residents, and 5.7% for board-certified specialists (Fig. 3). When interns were excluded from the analysis, there was a statistically significant negative correlation between the clinical experience and overdose rate (correlation coefficient=−0.221, $P<.001$). The causes of difference in overdose rates by physician's grade were further analyzed. There was a statistically significant negative correlation between the clinical experience of physicians and number of prescriptions when interns were excluded (correlation coefficient=−0.446, $P<.001$) (Fig. 3). There was a positive correlation between the quantity of prescriptions that require renal dose adjustment and overdose rates (correlation coefficient= 0.361, $P<.001$). Patients' renal function was analyzed by physi-

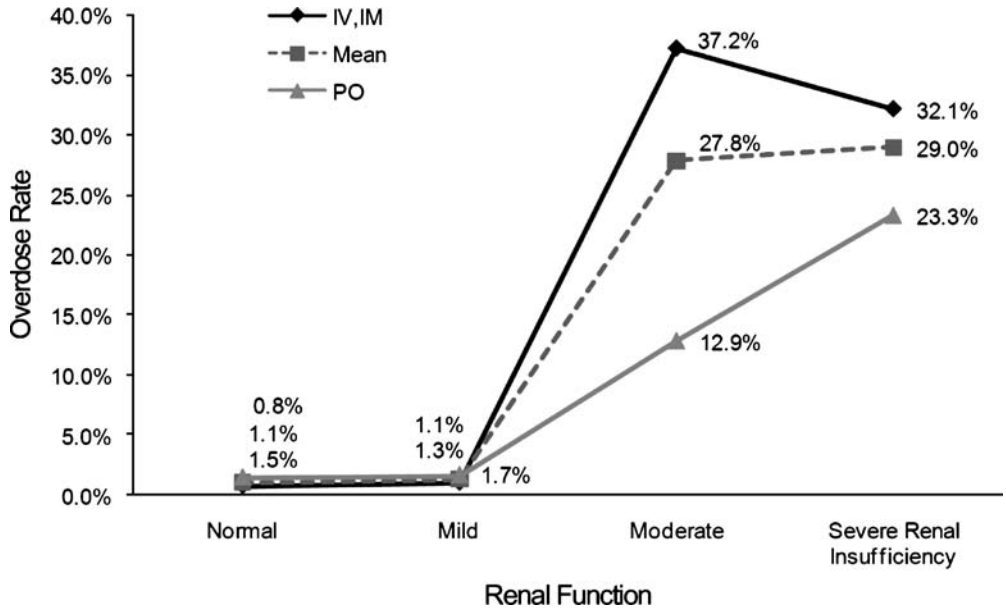

Figure 2. The drug overdose rate according to renal function and route of administration. Injection type drugs have higher overdose rate than oral type drugs for patients with moderate to severe renal insufficiency (estimated creatinine clearance≤50 mL/min).

cians' overdose rate group. The patients' mean creatinine clearance was 86.7 mL/min (SD=20.2) for the highest overdose rate physician group, 97.3 mL/min (SD=13.1) for high overdose rate physician group, 98.9 mL/min (SD=17.0) for low overdose rate physician group, and 99.5 mL/min (SD=24.9) for the lowest overdose physician group. Patients' renal function was significantly different between the physician groups (Kruskal–Wallis test, $P<.001$).

DISCUSSION

The overdose rate of patients with moderate to severe renal insufficiency was significantly higher than that of patients with normal to mild renal insufficiency (28.2% vs 1.1%). The present overdose rate is relatively low compared to previous studies: 70% by Chertow et al.[8] and 67% by Falconnier et al.[9] The low overdose rate in this study might have been because of the fact that we used the maximal daily dose for the cut-off value of overdose. When there is no proven maximal daily dose for a drug, we estimated a maximal daily dose from a loading dose and maintenance dose or from a maximal unit dose multiplied by the maximal frequency for a day. Another possible reason for the low overdose rate in this study might be that we evaluated the overdose rate by daily basis: That is, multiple prescriptions of a drug to a patient in a day were aggregated into a record and counted as one order.

The injection type drugs have higher overdose rate than oral type drugs (Fig. 2). We expected that oral type drugs would

Table 1. The 20 Most Frequently Overdosed Drugs

Drug	Route of administration	Overdoses (*N*)	Total prescriptions (*N*)	Overdose rate (%)	Fraction out of total overdoses (%)
Ranitidine	Oral/injection	11,092	97,138	11.4	48.3
Amoxicillin	Oral	1,595	2,218	71.9	6.9
Piperacillin/tazobactam	Injection	1,594	15,510	10.3	6.9
Cefotetan	Injection	1,243	12,694	9.8	5.4
Ketorolac	Oral/injection	873	52,132	1.7	3.8
Cetirizine	Oral	867	3,238	26.8	3.8
Levofloxacin	Oral/injection	767	15,371	5.0	3.3
Fexofenadine	Oral	667	4,027	16.6	2.9
Ceftazidime	Injection	540	8,643	6.2	2.3
Fluconazole	Oral	391	8,819	4.4	1.7
Ciprofloxacin	Oral/injection	361	30,691	1.2	1.6
Cimetidine	Oral/injection	341	67,509	0.5	1.5
Gabapentin	Oral	336	16,116	2.1	1.5
Amantadine	Oral	288	1,080	26.7	1.3
Cefotaxime	Injection	238	4,032	5.9	1.0
Cefazolin	Injection	221	6,143	3.6	1.0
Cefepime	Injection	219	13,741	1.6	1.0
Imipenem/cilastatin	Injection	169	14,391	1.2	0.7
Amoxicillin/clavulanate	Oral	163	1,515	10.8	0.7
Ampicillin/sulbactam	Injection	137	5,356	2.6	0.6
Total		22,102	380,364	–	96.2

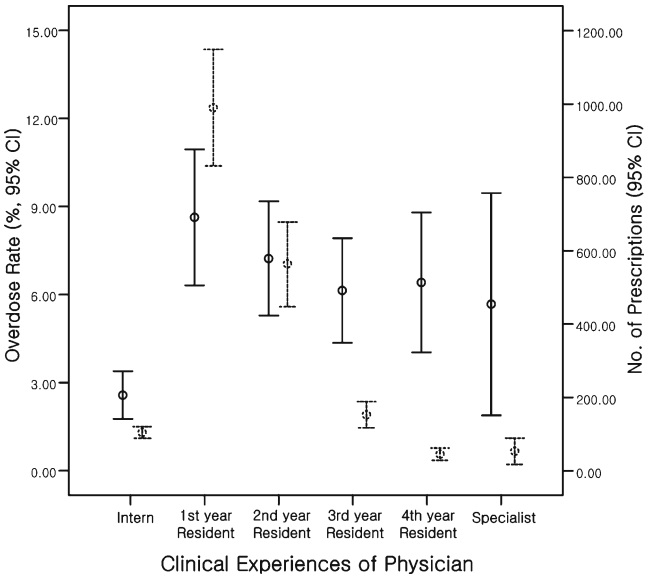

Figure 3. Overdose rate for drugs requiring renal dose adjustment by physicians' clinical experience (*left, lined*). Except interns, physicians' clinical experience and overdose rate inversely correlated (Spearman's correlation coefficient=–0.221, *P*<.001). Number of prescriptions requiring renal dose adjustment by physician's clinical experience (*right, dotted*). Except interns, physician's clinical experience and order count inversely correlated (Spearman's correlation coefficient=–0.446, *P*<.001).

have higher overdose rate than injection type drugs because oral type drugs are fixed in dose and hard to divide. Although we are at a loss to explain this result, it seems interesting and deserves further investigation.

Of the 56 drugs investigated, only 10–20 drugs were found to be the bulk of the problem. Ranitidine was the most frequently overdosed drug (48.3% of all overdoses). As the elimination of ranitidine is reduced in renal insufficiency, it is necessary to adjust the dose in patients with renal insufficiency.[13] Especially adverse reactions of central nervous system such as lethargy, confusion, somnolence, and disorientation have been reported in older patients with renal function impairment.[14] Amoxicillin ranked the highest overdose rate (71.9%). We investigated the reasons and found that much of amoxicillin were used as routine order such as 'Amoxicillin (500 mg) 2 cap q12 h' without renal adjustment. Another routine order for amoxicillin was for gargle solution, directed to be ingested after gargling, for example: 'Amoxicillin 2,000 mg mix with 2,000 cc distilled water, ingest after gargling'. Such 'problematic drugs' should be carefully treated. What about to modify the computerized physician order entry (CPOE) user interface such as displaying the drug names in red or orange color?

Only a quarter of physicians were found to be responsible for half of the overdoses. The factors associated with high overdose rate were found to be patient's renal function, physician's quantity of prescriptions, and clinical experience of physicians. The physicians with the highest overdose rate had patients with low renal function. If we assume that the quantity of prescription partly reflects the workload of physician, it is quite possible that the more a physician is busy and low in clinical experience and the lower the patient's renal function, then the more overdoses may occur. This feasibility could possibly explain why overdose rates of first year and second year residents are so high. However, the overdose rate of interns was significantly lower than that of residents and specialists. The small quantity of prescriptions by interns may be the explanation. As interns more recently completed training, they might be more careful in prescribing drugs and they have even more time to check patient's renal function.

It is well known that medication errors, including overdoses, can be reduced by using CPOE with clinical decision support systems.[15–17] Inappropriate order rate of nephrotoxic drug for renally impaired patients at a hospital was decreased from 70% to 49% by using a guided medication dosing system.[8] Contraindicated drug orders were decreased from 89% to 47% after CPOE with automated decision support alert.[18] It is known that the drug safety alerts generated by CPOE are overridden by physicians in 49% to 96% of cases because of low specificity, low sensitivity, unclear information content, unnecessary workflow disruptions, and unsafe and inefficient handling.[19] However, the drug adjustment information given by renal dosing system are noninterruptive in type and have good compliance. Even with interruptive alerts, the compliance was increased to 67% by using selective knowledge base and minimizing workflow interruption.[20] Whereas education alone had limited effects and waned with time.[21,22] We believe that the adoption of CPOE with decision support system is essential for the safety of patients with renal insufficiency in a hospital.

By constructing a data mart through the multistep processes of cleansing, extraction, transformation, and loading of about 23 million prescriptions and laboratory data into a data mart and subsequent analysis, we unraveled the overdose rate and related factors associated with drugs that require renal dose adjustment in a hospital. The result showed that the overdose rate of patients with renal insufficiency is quite high. Although only a small fraction of physicians are responsible for most of overdoses, we found that associated factors for overdoses included the workload of prescriptions, physicians' clinical experience, and patients' renal function. A small fraction of drugs were responsible for most of drug overdoses.

This study has a number of limitations. The prescribed drug dose was considered the dose actually administered as there were no other reliable data in the database, but the actual dose administered to the patient might have differed from the prescribed dose. Patients' renal function was indirectly estimated by using an abbreviated version of the Modification of Diet and Renal Disease equation. The study was performed in only one hospital and the results might not be generalizable, especially with regards to the physician analysis.

It is highly possible that massive electronic hospital data would exponentially be stacked within the near future because the adoption of CPOEs or electronic medical record systems is rapidly increasing worldwide. We expect that the use of data mining and text mining techniques, which extract and build useful secondary knowledge from massive raw data, would be important tools in the clinical research field.

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Conflicts of Interest: *None disclosed.*

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