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In-hospital Prescription Checking System for Hospitalized Patients with Decreased Glomerular Filtration Rate

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Akihiro Sonoda, Yuki Kondo, Yoshitaka Iwashita, Shoji Nakao, Kazuhisa Ishida, Tetsumi Irie, and Yoichi Ishitsuka

Key Points:

*We introduced a simple in-hospital prescription check system to alert the presence of renally excreted drugs and to support dosage settings.

*The in-hospital prescription checking system reduced the dosage error rate of renally excreted drugs in hospitalized patients.

Abstract:

Background: Clinical decision support systems (CDSS) are reported to be useful in preventing dosage errors in renally excreted drugs by alerting hospital pharmacists to inadequate dosages for hospitalized patients with decreased glomerular filtration rate. However, it is unclear whether CDSS can reduce dosage errors in renally excreted drugs in hospitalized patients. To prevent dosage errors in renally excreted drugs, we introduced a prescription checking system (PCS) for in-hospital prescriptions. This retrospective study aimed to evaluate whether a prescription audit by hospital pharmacists using the PCS reduced the rate of dosage errors in renally excreted drugs. Methods: The target drugs were allopurinol, cibenzoline, famotidine, and pilsicainide. Interrupted time series analysis was used to evaluate trends in the 4-weekly dosage error rates over 52 weeks before PCS implementation and 52 weeks after PCS implementation. Results: Before and after PCS implementation, 474 and 331 prescriptions containing one of the targeted drugs, respectively, were generated. The estimated baseline level of the 4-weekly dosage error rates was 34%. The trend before the PCS implementation was stable with no observable trend. The estimated level change from the last point in the pre-PCS implementation to the first point in the PCS implementation was −20%(p<0.001). There was no change in the trend after PCS implementation. Conclusions: We demonstrated that a prescription audit by hospital pharmacists using the PCS reduced the rate of dosage errors in the target renally excreted drugs in hospitalized patients. Although further studies are needed to confirm whether our results can be generalized to other health facilities, our findings highlight the need for a PCS to prevent the overdose of renally excreted drugs.

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Funding: None

Author Contributions: Akihiro Sonoda: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Visualization; Writing - original draft; Writing - review and editing Yuki Kondo: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Visualization; Writing - original draft; Writing - review and editing Yoshitaka Iwashita: Conceptualization; Methodology Shoji Nakao: Conceptualization; Methodology Kazuhisa Ishida: Conceptualization; Methodology Tetsumi Irie: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Visualization; Writing - review and editing Yoichi Ishitsuka: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Visualization; Writing - review and editing

Data Sharing Statement: The datasets analyzed during this study are available from the corresponding author on reasonable request.

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In-hospital Prescription Checking System for Hospitalized Patients with Decreased Glomerular Filtration Rate

Akihiro Sonoda¹, Yuki Kondo²*, Yoshitaka Iwashita¹, Shojo Nakao¹, Kazuhisa Ishida¹, Tetsumi Irie², and Yoichi Ishitsuka²

¹Department of Pharmacy, Izumi Regional Medical Center, 4513 Akasegawa, Akune, Kagoshima 899-1611, Japan
²Department of Clinical Chemistry and Informatics, Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto 862-0973, Japan

*These authors contributed equally to this study.

*Corresponding author

Yuki Kondo, Ph.D.

E-mail: ykondo@kumamoto-u.ac.jp

Tel: (+81)-96-371-4559
Key Points

• We introduced a simple in-hospital prescription check system to alert the presence of renally excreted drugs and to support dosage settings.

• The in-hospital prescription checking system reduced the dosage error rate of renally excreted drugs in hospitalized patients.

Abstract

Background: Clinical decision support systems (CDSS) are reported to be useful in preventing dosage errors in renally excreted drugs by alerting hospital pharmacists to inadequate dosages for hospitalized patients with decreased glomerular filtration rate. However, it is unclear whether CDSS can reduce dosage errors in renally excreted drugs in hospitalized patients. To prevent dosage errors in renally excreted drugs, we introduced a prescription checking system (PCS) for in-hospital prescriptions. This retrospective study aimed to evaluate whether a prescription audit by hospital pharmacists using the PCS reduced the rate of dosage errors in renally excreted drugs.

Methods: The target drugs were allopurinol, cibenzoline, famotidine, and pilsicainide. Interrupted time series analysis was used to evaluate trends in the 4-weekly dosage error rates over 52 weeks before PCS implementation and 52 weeks after PCS implementation.

Results: Before and after PCS implementation, 474 and 331 prescriptions containing one of
the targeted drugs, respectively, were generated. The estimated baseline level of the 4-weekly dosage error rates was 34%. The trend before the PCS implementation was stable with no observable trend. The estimated level change from the last point in the pre-PCS implementation to the first point in the PCS implementation was −20% ($p<0.001$). There was no change in the trend after PCS implementation.

**Conclusions:** We demonstrated that a prescription audit by hospital pharmacists using the PCS reduced the rate of dosage errors in the target renally excreted drugs in hospitalized patients. Although further studies are needed to confirm whether our results can be generalized to other health facilities, our findings highlight the need for a PCS to prevent the overdose of renally excreted drugs.
Introduction

Chronic kidney disease (CKD) has recently been recognized as a public health problem (1,2). CKD is associated with an increased mortality rate, as well as an increased risk of death and cardiovascular events (3). The estimated overall prevalence of CKD in adults (aged ≥20 years) continues to increase in the older population in Japan (4). CKD patients often show pharmacokinetic changes (5), and patients with decreased glomerular filtration rate (GFR) have a greater risk of plasma concentration above the therapeutic range, leading to adverse drug events (ADEs) (6). Corsonello et al. (7) reported that decreased GFR was substantially more prevalent in patients with ADEs from renally excreted drugs. Therefore, adjustment of drug dosages of renally excreted drugs according to kidney function is necessary for patients with decreased GFR (8). The reported overdose rate for renally excreted drugs in hospitalized patients with decreased GFR is 28.2%–73.6% (9–11). Thus, the prevention of overdose of renally excreted drugs in hospitalized patients with decreased GFR is an important issue.

Clinical decision support systems (CDSS) are useful in preventing dosage errors in renally excreted drugs by alerting hospital pharmacists to exceeded or contraindicated dosages for hospitalized patients with decreased GFR (12–14). However, previous reports have not evaluated whether CDSS can reduce dosage errors. Using dosage errors as the primary endpoint, Bhardwaja et al. showed that a prescription audit using CDSS in
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Outpatients at community pharmacies could reduce dosage errors in renally excreted drugs (15). However, it is unclear whether prescription audit by hospital pharmacists using CDSS in hospitalized patients can reduce dosage errors in renally excreted drugs.

To prevent dosage errors in renally excreted drugs in hospitalized patients, we introduced the following in-hospital prescription checking system (PCS): 1. the label “renal” was added in front of the name of renally excreted drugs on the prescription; 2. the level of the patient’s estimated kidney function was added to the prescription; 3. a check sheet for dosages according to kidney function was used.

In this study, we retrospectively evaluated whether a prescription audit by hospital pharmacists using the PCS reduced the rate of dosage errors in renally excreted drugs in hospitalized patients.
Materials and Methods

Study design

We retrospectively analyzed the medical records of hospitalized patients in the Izumi Regional Medical Center. Patients admitted to the wards of gastrointestinal surgery, neurosurgery, orthopedic surgery, gastrointestinal medicine, ophthalmology, and urology were included. A fact-finding survey to identify those renally excreted drugs that tended to be overdosed was conducted. Prescriptions containing the renally excreted drugs included in the drug dosing guidelines of the Japanese Society of Nephrology and Pharmacotherapy (16) were examined. The target drugs were determined based on the findings of the survey. A dosage error was defined as a prescription dispensing one of the target drugs at dosages that were contraindicated or too high according to the patient’s kidney function. The following data were collected: age, sex, height, body weight (BW), serum creatinine (SCr) levels, and the prescription contents. In the fact-finding survey, kidney function was estimated using the most recent SCr, age, and BW data at the time of the prescription audit.

For kidney function estimates, estimated creatinine clearance (eCCr) was obtained using equation [1] (17)

\[
eCCr (\text{mL/min}) = \left(140 - \text{age (years)}\right) \times \frac{\text{BW (kg)}}{72 \times \text{SCr (mg/dL)}} (\times \text{if female 0.85})
\]

[1]

The eCCr was automatically calculated using the most recent SCr, age, and BW data from
the in-hospital prescription (Fig. 1-A).

The target drug dosages appropriate for different levels of kidney function were determined using a report on allopurinol dosages (18) and the Japanese Society of Nephrology and Pharmacotherapy drug dosing guidelines (16). Dosages of the target drugs according to kidney function are shown in Fig. 1-B.

This study was approved by the ethics committee of Izumi Regional Medical Center (no. 20170629-1).

Pharmacist intervention

A workflow diagram of the physician’s order entry, the pharmacist’s prescription audit using the PCS, and the pharmacist’s dispensation is shown in Fig. 2. When physicians prescribed the drugs using the computerized physician order entry system, the prescription drug information was sent to the VP-Win total prescription analysis system (TOSHO Inc., Tokyo, Japan). Pharmacists printed the in-hospital prescriptions using the VP-Win system (Fig. 1-A). If the label “renal” had been added in front of the name of the renally excreted drug on the in-hospital prescription, pharmacists also printed the check sheet of dosages according to kidney function using the VP-Win total prescription analysis system (Fig. 1-B). Pharmacists checked the dosages of renally excreted drugs using the PCS at the time of dispensation. If the dosage of the target drugs was appropriate, pharmacists dispensed the
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drugs. If the dosage of the target drugs was inappropriate, pharmacists asked the prescriber about the prescription contents before dispensing the drugs.

**Interrupted time series analysis with segmented linear regression**

A quasi-experimental interrupted time series (ITS) analysis with segmented linear regression was used to evaluate the effect of the PCS (19). ITS analysis has been successfully used to evaluate the effect of various quality improvement programs (20–22). Parameters included trend before PCS implementation ($\beta_1$, baseline trend), level change from the last point in the pre-PCS implementation to the first point in the PCS implementation ($\beta_2$), and trend change after the PCS implementation ($\beta_3$). The regression model was $Y_t = \beta_0 + \beta_1T + \beta_2DA + \beta_3PA + e_t$, where $Y_t$ indicates the 4-weekly dosage error rates, $T$ is the time from baseline, $DA$ is a dummy variable for the implementation phase (assumes 0 before the PCS implementation and 1 after the PCS implementation), $PA$ is the period from the PCS implementation, the error term $e_t$ at time $t$ represents the random variability not explained by the model. The PCS was introduced on August 4, 2016. Therefore, two time segments in the ITS analysis with segmented regression were defined as 52 weeks before the PCS implementation (from August 6, 2015, to August 3, 2016) and 52 weeks after the PCS implementation (from August 4, 2016, to August 2, 2017). The autocorrelation of the residuals in the full segmented regression model was examined using
the Durbin–Watson test (23). The periodicity in the 4-weekly dosage error rates of the target drugs was examined using the autocorrelation function (24,25).

**Statistical analysis**

Continuous variables are expressed as mean ± standard deviation or median (range). The normality of the data was assessed using the Shapiro–Wilk test. Univariate analyses to compare two groups were performed using Welch’s $t$ test, the Mann–Whitney $U$ test, or Fisher’s exact test. Significance was set at $p<0.05$ for all analyses. The statistical analyses were performed using Excel 2010 (Microsoft Corp., Redmond, WA, USA) with the add-in software Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan) and the free software R (version 4.0.4) (26).
Results

Results of the fact-finding survey of prescriptions containing renally excreted drugs

Table 1 shows the results of the fact-finding survey of prescriptions containing renally excreted drugs. The number of dosage errors was highest for allopurinol, followed by amantadine and famotidine. Of the drugs with dose errors in 3 or more cases, the dosage error rates were highest for cibenzoline, pilscainide, and disopyramide.

Patient characteristics before and after implementation of the prescription checking system

Patient characteristics are shown in Table 2. The median ages before and after PCS implementation were 81 years and 79 years, respectively. The median SCr levels before and after PCS implementation were 0.86 mg/dL and 0.86 mg/dL, respectively. The median eCCr (mL/min) before and after PCS implementation were 50.2 mL/min and 51.6 mL/min, respectively. There was no significant difference in patient characteristics before and after PCS implementation.

Trend in the 4-weekly dosage error rates before and after implementation of the prescription checking system

Fig. 3 shows the trend in the 4-weekly dosage error rates before and after PCS
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implementation. Table 3 summarizes the parameter estimates from the segmented regression model. The $r$ value for the regression model was 0.9007 and the adjusted $r^2$ value was 0.7855. The estimated baseline level of the 4-weekly dosage error rates ($\beta_0$) was 34%. The trend before PCS implementation ($\beta_1$) was stable with no observable trend. The estimated level change from the last point in the pre-PCS implementation to the first point in the PCS implementation ($\beta_2$) was $-20\%$ ($p<0.001$). There was no trend change after PCS implementation ($\beta_3$).

The Durbin–Watson statistic for the full segmented regression model predicting the 4-weekly dosage error rates of the target drugs was 1.80 ($p=0.1171$), indicating no autocorrelation. The analysis showed no periodicity in the 4-weekly dosage error rates of the target drugs using the autocorrelation function.

Comparison of the dosage error rate before and after prescription checking system implementation

Table 4 shows the comparison of the dosage error rate before and after PCS implementation. The overall dosage error rate of the four target drugs was significantly lower after PCS implementation than before implementation (3% vs 26%, respectively; $p<0.001$). In particular, the dosage error rate for allopurinol was substantially lower after PCS implementation than before (3% vs 29%, respectively; $p<0.001$).
In this study, we demonstrated that a prescription audit by hospital pharmacists using the PCS reduced the dosage error rate of the target renally excreted drugs in hospitalized patients.

In the fact-finding survey of prescriptions containing renally excreted drugs, the number of dosage errors was highest for allopurinol, followed by amantadine and famotidine (Table 1). In addition, the dosage error rate was highest for antiarrhythmic drugs such as cibenzoline, pilsicainide, and disopyramide (Table 1). These drugs have frequently been associated with overdose-related ADEs in CKD patients in Japan (27). These findings suggest that dosage errors frequently occur with high-risk drugs that tend to induce ADEs when overdosed in patients with decreased GFR. Therefore, we recommend the use of interventions to improve this situation. Based on these findings, the target drugs selected to test the PCS were allopurinol, cibenzoline, famotidine, and pilsicainide.

Older hospitalized patients frequently have impaired kidney function despite normal SCr levels and are exposed to an increased risk of ADEs from renally excreted drugs (7). Therefore, considerable care is needed when administering renally excreted drugs to older hospitalized patients, and adjustment of drug dosages according to kidney function is required. In this study, the median age both before and after PCS implementation was approximately 80 years (Table 2). The median eCCr both before and after PCS implementation was approximately 50 mL/min (Table 2). These results suggest that this
study identified a high-risk population for ADEs from renally excreted drugs.

In this study, the ITS analysis showed that the estimated level change from the last point in the pre-PCS implementation to the first point in the PCS implementation was −20% (p<0.001), and the changes in the trend per 4 weeks before and after PCS implementation were −1% and 0.3%, respectively (Table 3 and Fig. 3). These results suggest that the level change was substantially greater than the changes in the trend per 4 weeks before and after PCS implementation. Therefore, we believe that the PCS implementation was strongly associated with a reduction in dosage errors. Furthermore, the dosage error rate after PCS implementation declined for all target drugs compared with before PCS implementation (Table 4). These results suggest that prescription audit by hospital pharmacists using the PCS can reduce dosage errors in the target drugs.

Our PCS had several advantages over other CDSS. First, the concept underlying our PCS was very simple. The aim was to make pharmacists aware that renally excreted drugs had been prescribed by adding a label to the prescription, and to print out information to facilitate dose determination for renally impaired patients. Implementation of this simple concept may be possible regardless of which systems are used by individual hospitals. Second, in our present PCS workflow, pharmacists were always involved in the dosage decisions for the target drugs based on patients’ kidney function. Many previous studies (15,28–30) have reported that hospital pharmacists can contribute to dosage setting and
reduction in the incidence of ADEs in patients with renal impairment. Therefore, this collaboration between prescribers and pharmacists may have increased the number of correct dosage decisions. Indeed, our findings seem to indicate that our PCS reduced dosage errors compared with other CDSS (31–33) that warn prescribers at the time of prescribing (Table 4). However, because pharmacists are involved in the final dosage decision, they must have a certain level of clinical knowledge about pharmacotherapy for renal impairment. Therefore, pharmacists may need to be well educated about renal impairment before introduction of this PCS system.

This study had some limitations. First, we examined changes in the prescription trend before and after PCS implementation. The number of prescriptions containing allopurinol, cibenzoline, and pilsicainide reduced after the PCS implementation compared with before implementation (Table 4). Therefore, we are unable to exclude the possibility that the prescription trend changes affected the reduction in dosage errors. However, the dosage error rate for famotidine significantly declined after PCS implementation although there was no change in prescription trend (Table 4). In addition, the level change from the last point in the pre-PCS implementation to the first point in the PCS implementation was substantially greater than the changes in the trend per 4 weeks before and after PCS implementation (Table 3). Therefore, we believe that the PCS implementation contributed to the reduction in dosage errors of the target drugs. Second, we were unable to investigate
whether the PCS significantly reduced the incidence of ADEs, because the ADE frequency was low in this study. One patient experienced hypoglycemia owing to cibenzoline overdose before PCS implementation, but no patients experienced ADEs after PCS implementation. Therefore, we believe that prescription audit by hospital pharmacists using the PCS reduced the dosage error rate of renally excreted drugs, which helped to prevent ADEs after PCS implementation. Third, we cannot rule out the possibility of misidentification of acute kidney injury (AKI) as CKD in the one-point assessment of kidney function in the prescription audit using the PCS. To resolve this issue, we believe that it is necessary to devise a way to obtain multiple assessments of kidney function. Indeed, there was one case of suspected AKI during this study. In this case, the SCr was elevated before and during the prescription audit, further elevated after the prescription audit, and then returned to near baseline. The pharmacist followed these changes carefully, so there were no problems associated with renally excreted drugs in this case. The safe use of renally excreted drugs in AKI patients may require continuous follow-up by medical professionals, with or without PCS. Fourth, there is limited evidence regarding the dosage of renally excreted drugs in AKI, and SCr levels are not at a steady state during AKI; hence, SCr change lags behind both kidney injury and kidney recovery (34–36). Therefore, it is difficult to determine the dosage of renally excreted drugs in the presence of AKI, even with the PCS. Fifth, this study was performed at a single institution, limiting the generalizability
of our results. Although further studies are needed to confirm whether our findings can be
generalized to other institutions, we believe that PCS implementation in many other
institutions could facilitate the appropriate use of renally excreted drugs.

In conclusion, these findings demonstrated that prescription audit by hospital pharmacists
using the PCS reduced the dosage error rate of the target renally excreted drugs in
hospitalized patients. Although further studies are needed to confirm whether our results can
be generalized to other health facilities, our findings highlight the need for PCS
implementation to prevent the overdose of renally excreted drugs.

Disclosures

Y. Kondo reports the following: Research Funding: Safety Medical System Laboratory
Corporation, AYUMI Pharmaceutical Corporation; Patents or Royalties: Safety Medical
System Laboratory Corporation; and Advisory or Leadership Role: Safety Medical System
Laboratory Corporation, the capacity was not paid. T. Irie reports the following: Patents or
Royalties: Safety Medical System Laboratory Corporation. Y. Ishitsuka reports the
following: Patents or Royalties: Safety Medical System Laboratory Corporation. The
remaining authors have nothing to disclose.
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Author Contributions

Akihiro Sonoda: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Visualization; Writing - original draft; Writing - review and editing. Yuki Kondo: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Visualization; Writing - original draft; Writing - review and editing. Yoshitaka Iwashita: Conceptualization; Methodology. Shoji Nakao: Conceptualization; Methodology. Kazuhisa Ishida: Conceptualization; Methodology. Tetsumi Irie: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Visualization; Writing - review and editing. Yoichi Ishitsuka: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Visualization; Writing - review and editing.
Data sharing statement

The datasets analyzed during this study are available from the corresponding author on reasonable request.
References


of a computer-assisted antimicrobial stewardship intervention on antimicrobial use and length of stay. *J Antimicrob Chemother* 72: 933–940, 2017


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Table 1 Results of the fact-finding survey of prescriptions containing renally excreted drugs from March 2015 to February 2016

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Adequate dose</th>
<th>Dosage errors</th>
<th>Rate of dosage errors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>151</td>
<td>102</td>
<td>40</td>
</tr>
<tr>
<td>Amantadine</td>
<td>81</td>
<td>75</td>
<td>48</td>
</tr>
<tr>
<td>Famotidine</td>
<td>262</td>
<td>46</td>
<td>15</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>235</td>
<td>45</td>
<td>16</td>
</tr>
<tr>
<td>Metformin</td>
<td>93</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>5</td>
<td>33</td>
<td>87</td>
</tr>
<tr>
<td>Risedronate sodium</td>
<td>69</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Levofoxcaxin</td>
<td>304</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Cibenzoline</td>
<td>11</td>
<td>15</td>
<td>58</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>214</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>37</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Pilsicainide</td>
<td>8</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>73</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Bezaflibrate</td>
<td>51</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>22</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Alogliptin-pioglitazone</td>
<td>45</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Entecavir</td>
<td>6</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Tenofovir disoproxil</td>
<td>6</td>
<td>2</td>
<td>25</td>
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<tr>
<td>Edoxaban</td>
<td>85</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
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<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>0</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>52</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>468</td>
<td>1</td>
<td>0.2</td>
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</table>
Table 2 Characteristics of patients before and after implementation of the prescription checking system

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>System implementation of the PCS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>84/49</td>
<td>78/52</td>
</tr>
<tr>
<td>Age (year) (^b)</td>
<td>81 (38-101)</td>
<td>79 (34-102)</td>
</tr>
<tr>
<td>Body weight (kg) (^a)</td>
<td>56.2 ± 13.0</td>
<td>56.1 ± 13.0</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL) (^b)</td>
<td>0.86 (0.31-8.68)</td>
<td>0.86 (0.24-4.74)</td>
</tr>
<tr>
<td>eCCr (mL/min) (^b)</td>
<td>50.2 (5.2-167.2)</td>
<td>51.6 (5.3-216.9)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m(^2)) (^b)</td>
<td>56.2 (5.2-141.0)</td>
<td>60.0 (7.1-233.7)</td>
</tr>
<tr>
<td>CKD stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage G1 (%)</td>
<td>11 (8)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Stage G2 (%)</td>
<td>50 (38)</td>
<td>55 (42)</td>
</tr>
<tr>
<td>Stage G3a (%)</td>
<td>33 (25)</td>
<td>41 (32)</td>
</tr>
<tr>
<td>Stage G3b (%)</td>
<td>20 (15)</td>
<td>17 (13)</td>
</tr>
<tr>
<td>Stage G4 (%)</td>
<td>15 (11)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Stage G5 (%)</td>
<td>4 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Dialysis (%)</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

\(^a\)Data are expressed as mean ± standard deviation, \(^b\)Data are expressed as median (range).

CKD chronic kidney disease, eCCr estimated creatinine clearance, eGFR estimated glomerular filtration rate, PCS prescription checking system.
Table 3 Coefficients, 95% confidence intervals, and $p$ values from full segmented linear regression model predicting 4-weekly dosage error rates of target drugs

<table>
<thead>
<tr>
<th>Parameter Description</th>
<th>Coefficient</th>
<th>Lower limit of 95% CI</th>
<th>Upper limit of 95% CI</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept, $\beta_0$</td>
<td>0.3355</td>
<td>0.2569</td>
<td>0.4141</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trend before the system implementation of the PCS, $\beta_1$</td>
<td>-0.0099</td>
<td>-0.0198</td>
<td>0.00004</td>
<td>0.0509</td>
</tr>
<tr>
<td>Level change from last point in the pre-system implementation of the PCS, $\beta_2$</td>
<td>-0.1989</td>
<td>-0.3042</td>
<td>-0.0937</td>
<td>0.0007</td>
</tr>
<tr>
<td>Trend change after the system implementation of the PCS, $\beta_3$</td>
<td>0.0125</td>
<td>-0.0015</td>
<td>0.0265</td>
<td>0.0776</td>
</tr>
</tbody>
</table>

$\beta_0$ estimates the baseline level of the dosage error rates of the target drugs, at time zero; $\beta_1$ estimates the trend in the 4-weekly dosage error rates of the target drugs before PCS implementation (i.e., the baseline trend); $\beta_2$ estimates the level change in the 4-weekly dosage error rates of the target drugs immediately after PCS implementation; and $\beta_3$ estimates the trend change in the 4-weekly dosage error rates of the target drugs after PCS implementation. CI confidence interval, PCS prescription checking system.
Table 4 Comparison of the dosage error rate of the target drugs before and after implementation of the prescription checking system

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Prescriptions containing dosage errors (%)</th>
<th>Prescriptions containing dosage errors (%)</th>
<th>( p ) value (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>208</td>
<td>105</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Cibenzoline</td>
<td>34</td>
<td>14</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Famotidine</td>
<td>207</td>
<td>204</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pilsicainide</td>
<td>25</td>
<td>8</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Overall</td>
<td>474</td>
<td>331</td>
<td>11 (3)</td>
</tr>
</tbody>
</table>

\(^a\)Fisher’s exact test.

PCS prescription checking system.
Figure legends

Fig. 1. The in-hospital prescription checking system.

(A) Typical example of an in-hospital prescription containing a renally excreted drug, allopurinol. The label “renal” was added in front of the name of the renally excreted drug and the value of eCCr (mL/min) was added to the prescription. (B) The check sheet of dosages according to kidney function for the target renally excreted drug. The value of eCCr was 27.78 mL/min, and the dosage of allopurinol needed to be reduced from 300 mg/day to 50 mg/day.

eCCr estimated creatinine clearance.

Fig. 2. A workflow diagram of the physician’s order entry, the pharmacist’s prescription audit using the PCS, and the pharmacist’s dispensation

The PCS automatic/electronic processes are enclosed in red boxes.

PCS prescription checking system.

Fig. 3. Change in the 4-weekly rates of dosage errors of the target drugs before implementation of the prescription checking system (52 weeks) and after implementation of the prescription checking system (52 weeks).
A)

In-hospital Prescription

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>12345</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient name</td>
<td>Hanako Nippon</td>
</tr>
<tr>
<td>Age</td>
<td>80 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Height</td>
<td>150 cm (10/20/2016)</td>
</tr>
<tr>
<td>Body Weight</td>
<td>50 kg (10/20/2016)</td>
</tr>
</tbody>
</table>

Department | Neurosurgery

Ward | 8F

Prescriber | Taro Nippon

Start date | 10/28/2016

Rx1: 【Renal】
- Allopurinol 100mg 3 tablets
- Teprenone 50mg 3 capsules
- Mosapride citrate 5mg 3 tablets

Sig: Take in 3 divided doses after each meal

14 Days

Rx2: Amlodipine 5mg 1 tablet
- Candesartan 4mg 1 tablet

Sig: Take one tablet once a day after breakfast

14 Days

B)

The check sheet of dosages according to kidney function

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Cut-off values, mL/min</th>
<th>Dosages according to kidney function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>50&lt;eCCr</td>
<td>200-300 mg/day</td>
</tr>
<tr>
<td></td>
<td>30&lt;eCCr≤50</td>
<td>100 mg/day</td>
</tr>
<tr>
<td></td>
<td>eCCr≤30</td>
<td>50 mg/day</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
<td>100mg after dialysis</td>
</tr>
<tr>
<td></td>
<td>60≤eCCr</td>
<td>300-450 mg/day</td>
</tr>
<tr>
<td></td>
<td>30≤eCCr&lt;60</td>
<td>50-100 mg/day</td>
</tr>
<tr>
<td></td>
<td>eCCr&lt;15</td>
<td>25 mg/day</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Famotidine</td>
<td>60≤eCCr</td>
<td>40 mg/day</td>
</tr>
<tr>
<td></td>
<td>30≤eCCr&lt;60</td>
<td>20 mg/day</td>
</tr>
<tr>
<td></td>
<td>eCCr≤30</td>
<td>10 mg/day or 20 mg/2-3day</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
<td>10 mg/day or 20mg after dialysis</td>
</tr>
<tr>
<td></td>
<td>60≤eCCr</td>
<td>150-225 mg/day</td>
</tr>
<tr>
<td></td>
<td>30≤eCCr&lt;60</td>
<td>50 mg/day</td>
</tr>
<tr>
<td></td>
<td>eCCr&lt;15</td>
<td>25 mg/2day</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
<td>25 mg/2day</td>
</tr>
</tbody>
</table>

Fig. 1
Physicians prescribe the drugs using the electronic physician order entry system.

The PCS automatically determines if the prescription contains a renally excreted drug, and calculates creatinine clearance based on the latest serum creatinine levels, age, and body weight of the patient.

If a renally excreted drug is prescribed, the PCS automatically adds the label “renal” in front of the name of the renally excreted drug on the in-hospital prescription (Fig. 1-A) and prints the check sheet to facilitate the dosage check by pharmacists (Fig. 1-B).

Pharmacists check the dosages of the renally excreted drugs using the check sheet.

If the dosage is adequate:
- Pharmacists discuss the dosage with the prescriber.
- Dispensation.

If the dosage is inadequate:
- Pharmacists discuss the dosage with the prescriber.
- Dispensation.

Fig. 2

PCS automated/electronic processes
Before system implementation of the prescription checking system

After system implementation of the prescription checking system

Fig. 3