

Prescription audit of renally excreted drugs and vancomycin dosing for older patients with reduced kidney function

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ABSTRACT

Japan has the largest aging population in the world, and kidney function declines with age. Therefore, when administering renally excreted drugs to older patients, the dosage should be adjusted according to the kidney function. This study addresses the appropriate use of renally excreted drugs in older patients in two topics. The first topic is concerned with the author's experience with cibenzoline overdose, which led the author to conduct a survey of renally excreted drugs and establish an in-hospital prescription checking system for these drugs. The second topic clarifies the usefulness of serum creatinine-based kidney function estimation equations for predicting the area under the concentration-time curve of vancomycin in bedridden older patients. Based on these findings, the importance of pharmaceutical interventions by pharmacists in the pharmacotherapy of older patients with reduced kidney function is discussed.

Key words: older patients, prescription checking system, reduced kidney function, serum creatinine, vancomycin

1. Introduction

Japan has the largest aging population worldwide (Nakatani, 2019). The physiological functions of older patients are more impaired than those of the young (Mangoni and Jackson, 2004). In particular, the most variable physiological function of pharmacokinetics in older people compared with that in young people is decreased kidney function. When renally excreted drugs are administered to patients with impaired kidney function, such as older patients, the risk of adverse drug events (ADEs) increases because the same dose administered to patients with normal kidney function is equivalent to an overdose of the drug (Corsonello et al., 2005). Therefore, dosage should be adjusted in patients with impaired kidney function.

Chronic kidney disease (CKD) is typically associated with several comorbidities, including hypertension, diabetes, and cardiovascular diseases (Levin et al., 2017; MacRae et al., 2021). Therefore, patients with kidney impairment such as those with CKD are prone to polypharmacy, which is a risk factor for kidney failure, cardiovascular events, and all-cause mortality (Kimura et al., 2021). Polypharmacy requires attention to drug-drug interactions, which may lead to increased toxicity of a drug or a reduction in its effectiveness (Błęszyńska et al., 2020). Therefore, pharmacist intervention

for patients with impaired kidney function is necessary to avoid overdosing or underdosing of drugs arising from drug-drug interactions (Dagnew et al., 2022).

Pharmacists have contributed to the prevention of overdose by adjusting dosages according to kidney function during prescription audits (Fernandez-Llamazares et al., 2012; Ishikawa et al., 2021; Shimizu et al., 2017). The usefulness of clinical decision support systems (CDSS) in assisting pharmacists in auditing prescriptions has been previously reported (Bhardwaja et al., 2011; McMullin et al., 1997; Niedrig et al., 2016). However, few studies have reported on the use of overdose as an outcome to evaluate the usefulness of the CDSS. Therefore, the author developed a prescription audit system using in-hospital prescriptions and evaluated its usefulness (Sonoda et al., 2022b). In addition to prescription audits, therapeutic drug monitoring (TDM) is also important for pharmacists. In this study, the author focused on vancomycin (VCM), which requires TDM. Although VCM dosing designs have been studied in patients with normal kidney function and special populations, including those with impaired kidney function, obesity, and children (Matsumoto et al., 2022; Rybak et al., 2020), few studies have focused on bedridden older patients. The author studied the VCM dosing design methods in bedridden older patients (Sonoda et al., 2022a).

Based on the results of previous studies (Sonoda et al., 2022a, 2022b), this study outlines two topics: (1) a prescription audit by hospital pharmacists using the in-hospital prescription checking system for renally excreted drugs and (2) a VCM dosing design for bedridden older patients. Based on these topics, the importance of pharmacist interventions in the pharmacotherapy of older patients with reduced kidney function is discussed.

2. Prescription audit by hospital pharmacists using the in-hospital prescription checking system for renally excreted drugs

The pharmacokinetics are altered in patients with chronic kidney disease (CKD) (Nolin, 2015). The dose of renally excreted drugs administered to patients with normal kidney function is too high for those with a reduced estimated glomerular filtration rate (eGFR), leading to ADEs (Eppenga et al., 2016). The kidney function declines with age (Noronha et al., 2022). Therefore, in older patients, the dosage should be adjusted according to kidney function. The author previously encountered a case of hypoglycemia in an older patient following an overdose of cibenzoline, a renally excreted drug (Sonoda et al., 2022b), which improved when the cibenzoline dosage was reduced according to the patient's kidney function. The author suspected that more cases of overdoses may have occurred. Therefore, the author surveyed prescriptions containing renally excreted drugs. In the fact-finding 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. In the survey, the number of dosage errors was highest for allopurinol, followed by amantadine and famotidine (Sonoda et al., 2022b). Among the drugs with dosage errors in three or more cases, the dosage error rates were the highest for cibenzoline, pilsicainide, and disopyramide (Sonoda et al., 2022b). These drugs have been frequently associated with overdose-related ADEs in Japanese patients with CKD (Kondo et al., 2014). Therefore, the author recommended the use of interventions to improve this situation. To prevent prescriptions with exceeding dosages based on kidney function in renally excreted drugs in hospitalized patients, the author introduced the following in-hospital prescription checking system (PCS) (Sonoda et al., 2022b): (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, and (3) a check sheet for dosages based on kidney function was used. The author demonstrated that a prescription audit by hospital pharmacists using PCS reduced the rate of dosage errors in the target (renally excreted drugs in hospitalized patients) (Sonoda et al., 2022b).

What checkpoints should be in place to prevent overdosing on renally excreted drugs in patients with impaired kidney function? The two key checkpoints are as

follows: (1) physicians prescribe the proper dosage according to kidney function and (2) pharmacists dispense the proper dosage according to kidney function (Figure 1). First, the author describes the following four reports in which physicians used the CDSS to assess whether inappropriate prescriptions of renally excreted drugs were reduced: Chertow et al. constructed a system whereby when the prescribers entered a drug using the electronic physician order entry system, they were guided to the appropriate dose and dosage frequency based on kidney function and evaluated the usefulness of the system on 7490 hospitalized patients (Chertow et al., 2001). The rates of prescriptions deemed appropriate in the intervention and control periods were 67% and 54% ($p < 0.001$) by dose and 59% and 35% ($p < 0.001$) by frequency, respectively. Galanter et al. constructed a system designed to be activated when prescribers attempt to order a potentially contraindicated drug in a patient whose most recent estimated creatinine clearance was below the corresponding safe level for that drug (Galanter et al., 2005). The prescribers are alerted to a "pop-up" recommending that the order not be continued because of the patient's kidney dysfunction. The possibility that a patient would receive at least one dose of a contraindicated drug after order initiation decreased from 89% to 47% after the deployment of the alert ($p < 0.0001$). Field et al. created a system whereby physicians are alerted if they use the computerized provider order entry system to initiate an order for one of the specific medications included in the CDSS for a resident with kidney failure (Field et al., 2009). In the control group, 134 of 257 prescriptions (52.1%) were appropriate, whereas in the intervention group, 172 of 274 (62.8%) were appropriate. Thus, the proportion of appropriate prescriptions was significantly higher in the intervention group ($p < 0.05$). Terrell et al. developed a decision support system that provides physicians with targeted drug dosing recommendations when a patient's

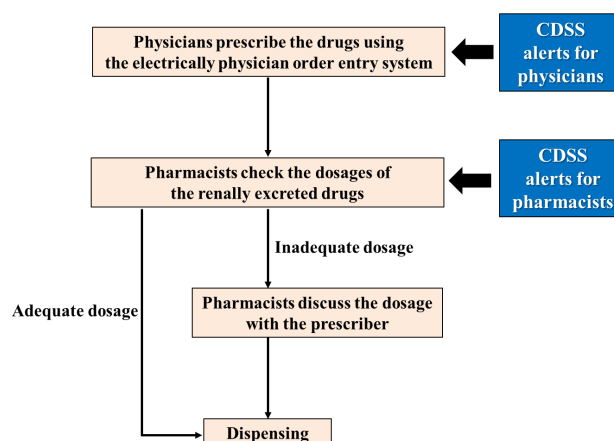


Figure 1. Checkpoints to prevent overdose of renally excreted drugs using CDSS from prescribing to dispensing.
CDSS, clinical decision support systems

estimated creatinine clearance value is below a threshold for dose adjustment (Terrell et al., 2010). In the intervention group, 31 of the 73 prescriptions (43%) were overprescribed. The control group had a significantly higher proportion of overprescribed drugs ($p = 0.001$), with 34 of 46 prescriptions (74%). These reports indicate that the CDSS reduce inappropriate prescriptions; however, despite the implementation of the CDSS, the rates of inappropriate prescriptions are high. Shah et al. designed a selective drug alert system suitable for ambulatory care and examined improving clinician acceptance of drug alerts by minimizing workflow disruption by designating only alerts of high importance in alerts that disrupt the clinician's workflow (Shah et al., 2006). Of the 5,182 interrupted drug alerts, 67% were accepted. The highest acceptance rate was observed in the drug class overlap category (77%), followed by drug-disease alerts (53%). The lowest acceptance rate for drug pregnancy alerts was 10%. Thus, setting selective drug alerts in a manner that does not disrupt the clinician workflow and improves clinician acceptance of drug alerts may further reduce inappropriate prescriptions. In addition, Desmedt et al. suggested the need for collaboration with pharmacists to elevate CDSS compliance (Desmedt et al., 2018), and the author describes reports of pharmacists using the CDSS to reduce overdoses. A system in which pharmacists are alerted when dispensing to the intervention group when exceeding the dose according to kidney function has been described (Bhardwaja et al., 2011). A total of 6125 patients (3025 and 3100 in the intervention and control groups, respectively) were prescribed target drugs. The rates of dosage errors in the intervention and control groups were 33% and 49% ($p < 0.001$), respectively, and were significantly lower in the intervention group. In the author's study, the rate of dosage errors was as high as 26% before the implementation of PCS but decreased significantly to 3% after the implementation of PCS ($p < 0.001$) (Sonoda et al., 2022b). Thus, in respective studies by physicians and pharmacists, the CDSS have contributed to the prevention of overdoses of renally excreted drugs, and collaboration between pharmacists and physicians may further reduce overdoses of renally excreted drugs. Therefore, further research is needed to evaluate physician-pharmacist collaboration using the CDSS to reduce the overdosage of renally excreted drugs.

Is the concept of PCS applicable to individual hospitals? The first is to label "renal" before the name of the renally excreted drug; this can be done by simply adding the label "renal" in the master management. The second is the estimated creatinine clearance (CCr), calculated based on the latest data, which can be easily obtained by setting up a formula in Microsoft Excel, even if it cannot be automatically indicated on the prescription. The third is a check sheet for dosages according to kidney function; efforts such as posting dosages according to kidney function near where prescriptions are audited can be made immediately, even if

the check sheet for dosages according to kidney function cannot be output automatically. Therefore, the PCS concept in this study is simple. Schreier et al. mentioned that the PCS is simple, contains no complex logic, and requires few IT resources (Schreier and Barreto, 2022). Therefore, the implementation of this simple concept may be possible regardless of the systems used by individual hospitals.

Would a PCS prescription audit be acceptable to pharmacists? The PCS automates three necessary pieces of information to confirm the dose according to kidney function. Although adequate education of pharmacists on pharmacotherapy for kidney impairment is necessary for the implementation of the PCS, conducting prescription audits using the PCS is feasible, as it is integrated into the workflow of prescription audits routinely performed by pharmacists (Fernandez-Llamazares et al., 2012; Ishikawa et al., 2021; Shimizu et al., 2017). However, as the PCS outputs a check sheet for dosages based on kidney function when four target drugs are prescribed even when the dosage is appropriate based on kidney function, Schreier et al. (Schreier and Barreto, 2022) pointed out the increased burden on pharmacists to audit prescriptions when the number of target drugs in the system increases. Therefore, the PCS must be improved to output a check sheet of dosages based on kidney function only when the dosage exceeds the kidney function.

However, PCS has several limitations. First, a one-point evaluation of kidney function did not reveal any changes in kidney function. To resolve this issue, it is necessary to devise a method to assess kidney function multiple times. Second, PCS cannot be used to design dosing for patients with acute kidney injury (AKI) because, during AKI, serum creatinine (SCr) is not in a steady state, that is, there is a time lag between changes in SCr and kidney injury and recovery (Thomas et al., 2015; Waikar and Bonventre, 2009). The safe use of renally excreted drugs in patients with AKI requires continuous follow-up by medical professionals with or without PCS. Although PCS has this limitation, the author's findings highlight the need for PCS implementation to prevent overdose of renally excreted drugs.

3. Vancomycin dosing design in bedridden older patients

VCM is a renally excreted drug with a high urinary excretion rate of approximately 90% of the unchanged drug, and an increase in its trough concentration and area under the concentration-time curve (AUC) causes nephrotoxicity (Rybak et al., 2020). Therefore, TDM is essential to ensure the therapeutic efficacy of drugs and avoid ADEs, such as nephrotoxicity (Rybak et al., 2020). In addition, TDM of VCM requires an accurate assessment of kidney function. SCr levels are frequently used as indicators of kidney function in clinical practice (Duncan et al., 2001). Measuring SCr levels is inexpensive; however, in patients with reduced muscle mass such as bedridden older patients, reduced kidney

function is unlikely to reflect an increase in SCr levels (Nakatani et al., 2019). Therefore, kidney function tends to be overestimated when SCr levels are measured in bedridden older patients, leading to VCM overdose. In contrast, the assessment of kidney function using cystatin C (Cys C) is effective in patients with reduced muscle mass, such as sarcopenia (Nakatani et al., 2019). However, Cys C is affected by thyroid function (Jayagopal et al., 2003) and some drugs, including steroids and cyclosporine (Cimerman et al., 2000). It is also expensive to measure and is only permitted once every three months in the Japanese health insurance system. Resolving this problem would be clinically beneficial. Otani et al. (Otani et al., 2018a) reported that consistency between estimated creatinine clearance (eCCr) and measured CCr was the highest when the SCr level was adjusted by adding 0.2 mg/dL to the enzymatically measured SCr value in bedridden older patients. Therefore, we examined whether kidney function assessment could be used to design VCM dosing in these patients (Sonoda et al., 2022a). The author clarified the Bayesian approach using eCCr (SCr + 0.2) calculated by substituting the SCr level + 0.2 mg/dL into the Cockcroft-Gault (CG) equation: it has the highest prediction accuracy for the reference AUC (AUC_{REF}) in bedridden older patients. In the 2022 revision of the clinical practice guidelines for the TDM of VCM, AUC -guided dosing was more strongly recommended than trough-guided dosing to decrease the risk of AKI (Matsumoto et al., 2022). However, few reports are available on dosage design in frail cases (Matsumoto et al., 2022). The author assumes that these findings may assist in the design of VCM dosing in bedridden older patients (Sonoda et al., 2022a).

What equations are appropriate for estimating kidney function when designing VCM dosing regimens in older patients? Okamoto et al. compared the accuracy of the CG equation for SCr and Larsson's equation for Cys C in predicting VCM clearance in older patients (Okamoto et al., 2007). The correlation coefficient ($\rho = 0.883$) between Larsson's equation with Cys C and VCM clearance was significantly higher than that ($\rho = 0.684$) between the CG equation and VCM clearance ($p < 0.05$). Glatard et al. compared the ability of various equations to estimate kidney function and describe VCM pharmacokinetics in older patients (Glatard et al., 2015). This study demonstrated that the methods for estimating kidney function should not be considered interchangeable with pharmacokinetic modeling or model-based estimation of VCM concentrations in older patients. Ling et al. performed a population pharmacokinetic analysis of the most appropriate equation for estimating kidney function to describe VCM pharmacokinetics in older Chinese patients (Ling et al., 2024). Kidney function was estimated using two Berlin Initiative Study equations (BIS-1 and BIS-2), three Chronic Kidney Disease Epidemiology Collaboration equations (CKD-EPIcys-scr, CKD-EPIscr, and CKD-EPIcys), the CG equation, and the Modification of Diet

in Renal Disease equation. The eGFR based on Cys C and Scr (CKD-EPIcys-scr and BIS-2) was significantly improved compared with the other equations in model building, and the CKD-EPIcys-scr and BIS-2 based models reduced the inter-individual variability in VCM clearance from 49.4% to 23.6% and 49.4% to 23.7%, respectively. The VCM clearances and GFR estimated using the EPIcys-scr and BIS-2 equations showed a good correlation ($r = 0.834$ and 0.833 , respectively). These findings suggest that the equation estimating kidney function, which includes both SCr and Cys C, may be useful in VCM dosing design for older patients. The author found that eCCr (SCr + 0.2) was useful in predicting the AUC of VCM in bedridden older patients (Sonoda et al., 2022a). Thus, these reports provide beneficial information for the design of VCM dosing in older patients, which is considered to have been based on minimal evidence in the past.

The predictability of kidney function has been reported to be improved by considering muscle mass in the formula for estimating kidney function using SCr levels in patients with reduced muscle mass (Nakatani et al., 2019; Otani et al., 2018b). Otani et al. (Otani et al., 2018b) reported that adding triceps skinfold thickness (TSF) to eCCr (SCr + 0.2) improved the prediction accuracy of kidney function in bedridden older patients. The measurement of the TSF is noninvasive and can be easily performed using calipers. In addition, the EPIcys-scr and BIS-2 equations described above may accurately estimate kidney function in bedridden older patients. In the future, we plan to evaluate the accuracy of the equations for estimating kidney function that may be useful for the individualized dosing design of VCM in bedridden older patients.

4. Conclusions

In this study, two topics are presented to address the appropriate use of renally excreted drugs in older patients. The author previously reported that prescription audits by hospital pharmacists using PCS reduced the dosage error rate of target renally excreted drugs in hospitalized patients (Sonoda et al., 2022b). In the future, PCS needs to be improved by increasing the number of target drugs and issuing a confirmation sheet based on kidney function only when there is a problem with dosage. In addition, further research is needed to evaluate physician-pharmacist collaboration using the CDSS and PCS to reduce the overdosage of renally excreted drugs. The author also observed that the Bayesian approach using eCCr (SCr + 0.2) had the highest prediction accuracy for AUC_{REF} in bedridden older patients compared with other creatinine-based equations (Sonoda et al., 2022a). Future population pharmacokinetic analyses should clarify the kidney function estimation equations and population pharmacokinetic parameters that best fit the VCM dosing design for older patients in Japan. This study highlights the importance of

pharmaceutical interventions to promote the appropriate use of renally excreted drugs in older patients with reduced kidney function. As the Japanese population ages, collating evidence for pharmacotherapy in older patients should continue.

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Conflict of Interest

The author declares no conflict of interest.

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