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Research Paper

Usefulness of serum cystatin C to determine the dose of vancomycin in critically ill patients

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Abstract

Objectives Serum creatinine (Scr) is not a reliable marker of renal function in critically ill patients because of an enhancement of protein catabolism, which makes it difficult to adjust the dosage of renally eliminated drugs such as antibiotics. This study aimed to investigate whether serum cystatin C (Scys-C) could be used as a reliable marker of renal function.

Methods We investigated whether Scys-C was a reliable marker of renal function in 56 critically ill patients. Subsequently, the usefulness of Scys-C to determine the initial loading and the maintenance dose of vancomycin was examined in 18 patients. Creatinine clearance (Ccr) was assessed from Scr and creatinine in urine collected over 24 h (24-h Ccr).

Key findings There was a good correlation between 24-h Ccr and 1/Scys-C ($r^2 = 0.616$), whereas less marked correlation was observed between 24-h Ccr and 1/Scr ($r^2 = 0.221$). On the other hand, vancomycin concentration was predicted from population pharmacokinetic parameters based on a two-compartment linear model. There were significant correlations between real trough concentrations of vancomycin and the values predicted from Scys-C using various equations ($r^2 = 0.416$–0.488), while less pronounced relationships were observed between real concentrations and the values predicted from Scr ($r^2 = 0.134$–0.187).

Conclusions These findings suggest that Scys-C is a reliable marker reflecting renal function in critically ill patients and is applicable to determine the initial loading dose as well as the maintenance dose of vancomycin.

Keywords creatinine clearance; critically ill patients; cystatin C; loading dose; vancomycin

Introduction

In critically ill patients, renal function fluctuates considerably within a short period during hospitalization in many cases, which makes it difficult to determine the dosage of renally eliminated medicines, such as some antibiotics. Vancomycin, a glycopeptide antibiotic, has been widely used in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection.[1] Vancomycin is mainly eliminated via the kidney, thus its dosage regimens are dependent on renal function.[2] Rybak *et al*.[3] reported that trough concentration of vancomycin recommended by clinical practice guidelines is in the range of 15–20 μg/ml against MRSA infection. They also reported that careful monitoring of vancomycin trough concentration should be carried out in patients who received vancomycin with concurrent administration of other nephrotoxic drugs, such as aminoglycoside, to avoid acute renal failure. Therefore, precise monitoring of renal function is requisite in critically ill patients for the establishment of dosing schedule or therapeutic monitoring of vancomycin and other antibiotic agents, including aminoglycoside antibiotics.

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Glomerular filtration rate (GFR) is the most reliable index of renal function and its calculation is based on the clearance of endogenous (creatinine) or exogenous (iohexol and inulin) substances that are freely filtered by the glomerulus but not reabsorbed or secreted from renal tubules.[4,5] On the other hand, creatinine clearance (Ccr), which is assessed by comparing serum creatinine (Scr) with creatinine in urine collection, is a useful measure for estimating GFR, although the procedure is time-consuming. In the clinical setting Ccr or GFR is commonly estimated from Scr according to several equations, including Cockcroft–Gault,[6] the Modification of Diet in Renal Disease (MDRD)[7,8] and modified MDRD.[9] However, Scr is not a reliable marker of renal function in critically ill patients, since Scr is easily affected by the amount of muscle, gender, age and nutritional status.[4,5] Moreover, Scr is not a sensitive index reflecting changes in renal function, in which the value is almost constant in the GFR range 40–70 ml/min per 1.73 m^2 (the so-called creatinine blind range) and is considered to be an inadequate measure to detect the early phase of acute renal failure.[10] On the other hand, critically ill patients reveal in many cases an abrupt change in Scr because of the loss of muscle protein associated with the enhanced catabolic response to burn injury and sepsis, in which glucocorticoids and pro-inflammatory cytokines, including tumour necrosis factor-α and interleukin-1β, are reported to be implicated.[11,12]

Cystatin-C is an endogenous inhibitor of cysteine protease with a molecular weight of 13 kDa and is produced in all nucleated cells. This substance is freely filtered through the renal glomerulus and fully reabsorbed and catabolized in the renal tubules.[13,14] A number of reports have shown that serum cystatin C (Scys-C) is more sensitive than Scr as a marker of GFR in elderly patients or those with renal dysfunction.[15–18] Villa *et al*.[19] have shown in critically ill patients that Scys-C correlates more closely than Scr with Ccr as assessed by urine collection for 24 h (24-h Ccr), although the concentration of Scys-C is influenced by thyroid function and corticosteroids.[20]

In this study, we investigated the usefulness of Scys-C as a marker of renal function in critically ill patients. We also examined the applicability of Scys-C to the determination of the initial loading dose and the maintenance dose of vancomycin in such patients.

Materials and Methods

Subjects

This study was carried out in accordance with the guidelines for the care for human study adopted by the ethics committee of the Gifu Graduate School of Medicine, and notified by the Japanese government. We obtained written informed consent from the legal guardian of every participant before enrolment. The exclusion criteria were those who underwent haemodialysis, and those under 18 years of age. Fifty-six patients admitted to the intensive care unit of Gifu University Hospital from August 2007 to July 2008 were the subjects of the study. Among them, 13 patients (30 samples) were tested to obtain the laboratory data repeatedly (2–8 times), thus the total number of samples was 86. Patient characteristics are shown in Table 1. Out of the 56 patients, 18 patients were treated with vancomycin, thus trough concentrations of vancomycin were monitored in these patients for initial loading dose (18 samples) and in six patients (12 samples) for maintenance dose.

Table 1 Demographics of patients admitted to the intensive care unit

No. of patients	56
Male	37 (66%)
Female	19 (34%)
No. of blood samples	86
Male	52 (60%)
Female	34 (40%)
Age (years)	65.94 (20–89)
Body weight (kg)	61.33 ± 15.12
Body surface area (m2)	1.63 ± 0.21
24-h Ccr (ml/min)	101.10 ± 53.33 (10.22–221.35)
Serum creatinine (mg/dl)	0.75 ± 0.61 (0.18–3.97) [male: 0.6–1.2; female: 0.4–0.8]
Serum cystatin C (mg/l)	1.14 ± 0.64 (0.42–3.7) [0.53–0.95]
Alanine aminotransferase (IU/ml)	32.02 ± 29.16 [7–40]
Aspartate aminotransferase (IU/ml)	37.72 ± 26.35 [7–35]
Diseases	
Sepsis/septic shock	18 (32.1%)
Multiple trauma	13 (23.2%)
Cardiovascular disease	7 (12.5%)
Pulmonary disease	7 (12.5%)
Severe burn	3 (5.4%)
Gastrointestinal disease	3 (5.4%)
Severe pancreatitis	2 (3.6%)
Neurological disease	2 (3.6%)
Toxicosis	1 (1.7%)

Figures in square brackets represent the normal range. Ccr, creatinine clearance.

Determination of serum cystatin C, serum creatinine and urine creatinine

Serum samples were taken from an arterial line and centrifuged at 1500g for 15 min. Serum was isolated and stored at –80°C until assay. Scys-C was determined by a particle-enhanced nephelometric immunoassay using the Dade Behring N Latex Cystatin C assay kit and evaluated on the Dade Behring Nephelometer II (Dade Behring Diagnostics, Marburg, Germany), as reported earlier.[21] Scr and urine creatinine were determined by the enzymatic method and evaluated on the autoanalysing system (BM-2250; Nihon Denshi, Tokyo, Japan). The 24-h Ccr was calculated from the creatinine excretion into urine collected for 24 h and a single measurement of Scr according to the equation 1:

$$\text{24-h Ccr}\,(\text{ml/min}) = [\text{urine output}\,(\text{ml}) \times \text{urine creatinine}\,(\text{mg/dl})]/[\text{serum creatinine}\,(\text{mg/dl}) \times 60 \times 24] \quad (1)$$

Estimation of glomerular filtration rate or creatinine clearance from serum creatinine or serum cystatin C

Ccr was estimated from Scr according to the Cockcroft–Gault (C&G) formula (equation 2)[6] or from Scys-C by the present method. GFR was estimated from Scr by the modified MDRD (mMDRD) formula (equation 3)[9] and from Scys-C according

to the methods of Hoek *et al*. (equation 4)[22] or Rule *et al*. (equation 5).[23]

$$\mathrm{Ccr} = [140 - \mathrm{age(years)}] \times \mathrm{weight(kg)} / [72 \times \mathrm{Scr(mg/dl)}] \times 0.85[\mathrm{woman}] \quad (2)$$

$$\mathrm{GFR}/1.73\mathrm{m}^2 = 175 \times \mathrm{Scr(mg/dl)}^{-1.154} \times \mathrm{age(years)}^{-0.203} \times 0.741 \times 0.742[\mathrm{woman}] \quad (3)$$

$$\mathrm{GFR}/1.73\ \mathrm{m}^2 = -4.32 + 80.35/\mathrm{Scys\text{-}C\ (mg/l)} \quad (4)$$

$$\mathrm{GFR}/1.73\ \mathrm{m}^2 = 66.8/\mathrm{Scys\text{-}C\ (mg/l)}^{1.30} \quad (5)$$

Moreover, we deduced the formula predicting Ccr from Scyc-C based on the data concerning the relationship between Scys-C and 24-h Ccr. The units of Ccr and GFR were expressed as ml/min and ml/min per 1.73 m^2, respectively, after adjustment with body surface area (BSA) by the method of DuBois and DuBois (equation 6).[24]

$$\mathrm{BSA}\ (\mathrm{m}^2) = 0.007184 \times [\mathrm{body\ weight\ (kg)}]^{0.425} \times [\mathrm{height(cm)}]^{0.725} \quad (6)$$

Relationship between serum trough vancomycin concentrations and p redicted values

Among 56 patients, MRSA was detected, or could be detected, in 18 patients and they were treated intravenously with vancomycin (500–1500 mg/dose, intravenous infusion over 1 h). The dosing intervals were set from 8 to 24 h. Serum samples for measuring the trough concentration of vancomycin were collected on the third day after initiation of administration. On the other hand, serum vancomycin concentrations were predicted from Scys-C or Scr, using population pharmaco- kinetic parameters based on a two-compartment linear model,[25] as shown below:

$$\text{Vancomycin clearance (l/h)} = 0.0478 \times \mathrm{Ccr}\ (0.0425 - 0.0531)(\mathrm{Ccr} \le 85\ \mathrm{ml/min})$$

$$\text{Vancomycin clearance (l/h)} = 3.51(3.09 - 3.93)(\mathrm{Ccr} > 85\ \mathrm{ml/min})$$

$$K_{12}(\mathrm{h}^{-1}) = 0.525(0.452 - 0.598)$$

$$K_{21}(\mathrm{h}^{-1}) = 0.213(0.174 - 0.252)$$

$$\mathrm{Vdss(l)} = 60.7(53.9 - 67.5)$$

The relationship between real vancomycin concentrations and the values predicted from Scr or Scys-C was compared. Serum vancomycin was determined by a particle-enhanced turbidimetric inhibition immunoassay (PETINIA) using Dimension RxL Max (Siemens K.K., Tokyo).

Statistical analyses

The square of coefficient of correlation (r^2) was calculated as a measure showing linearity of the relationship between the two variables. For evaluation of the prediction of serum vancomycin concentration, mean prediction error (ME) was calculated as a measure of bias (equation 7), mean absolute error (MAE) as a measure of accuracy (equation 8), and root mean squared prediction error (RMSE) as an index of precision (equation 9):

$$\mathrm{ME} = 1/\mathrm{n} \sum (\mathrm{C_{pre}} - \mathrm{C_{mea}}) \quad (7)$$

$$\mathrm{MAE} = 1/\mathrm{n} \sum |\mathrm{C_{pre}} - \mathrm{C_{mea}}| \quad (8)$$

$$\mathrm{RMSE} = \left[1/\mathrm{n} \sum (\mathrm{C_{pre}} - \mathrm{C_{mea}})^2\right]^{1/2} \quad (9)$$

Results

Relationship between serum creatinine or serum cystatin C and 24-h creatinine clearance

There was a significant relationship between the inverse of Scys-C and 24-h Ccr ($r^2 = 0.616$, $P < 0.001$). A similar but less pronounced relationship was observed between the inverse of Scr and 24-h Ccr ($r^2 = 0.221$, $P < 0.001$) (Figure 1). Thus, Ccr can be predicted from approximation of the power exponential curve of the scatter plot of Scys-C versus 24 h Ccr, as shown by equation 10:

$$\mathrm{Ccr} = 83.865 \times [\mathrm{Scys\text{-}C\ (mg/l)}]^{-1.2832} \quad (10)$$

As shown in Figure 2, there was a significant correlation between 24-h Ccr and predicted Ccr from Scys-C using the present equation ($r^2 = 0.587$, $P < 0.001$), the Hoek equation ($r^2 = 0.628$, $P < 0.001$) or the Rule equation ($r^2 = 0.601$, $P < 0.001$). Less marked correlation was observed between 24-h Ccr and predicted Ccr from Scr according to the Cockcroft–Gault equation ($r^2 = 0.419$, $P < 0.001$) or modified MDRD equation ($r^2 = 0.293$, $P < 0.001$).

Relationship between real concentrations of vancomycin and predicted concentrations from serum cystatin C or serum creatinine

The estimated Ccr or GFR was applied to the population pharmacokinetic analysis program to predict serum vancomycin concentrations, and the relationship between predicted concentrations and real concentrations was investigated in these patients. As shown in Figure 3, the predicted vancomycin concentrations from Scys-C correlated well with the real concentrations ($r^2 = 0.475$, $P < 0.001$ for the present equation; $r^2 = 0.488$, $P < 0.001$ for the Hoek equation; $r^2 = 0.416$, $P < 0.001$ for the Rule equation). On the other hand, less pronounced correlation was obtained between real concentrations and predicted concentrations from Scr using the Cockcroft–Gault equation ($r^2 = 0.134$, $P < 0.05$) or mMDRD equation

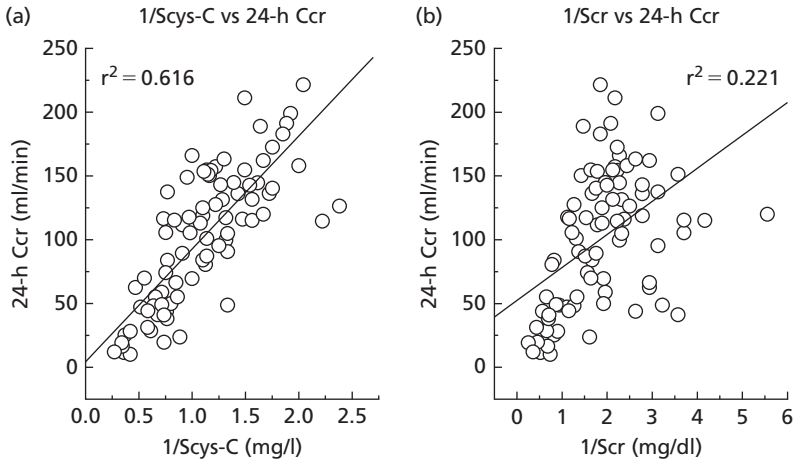

Figure 1 Relationship between 24-h creatinine clearance and the inverse of serum cystatin C (a) or serum creatinine (b) in 56 patients (86 serum samples) admitted to the intensive care unit. The 24-h creatinine clearance (Ccr) was assessed from creatinine concentration in urine accumulated for 24 h and serum creatinine (Scr). Scys-C, serum cystatin C.

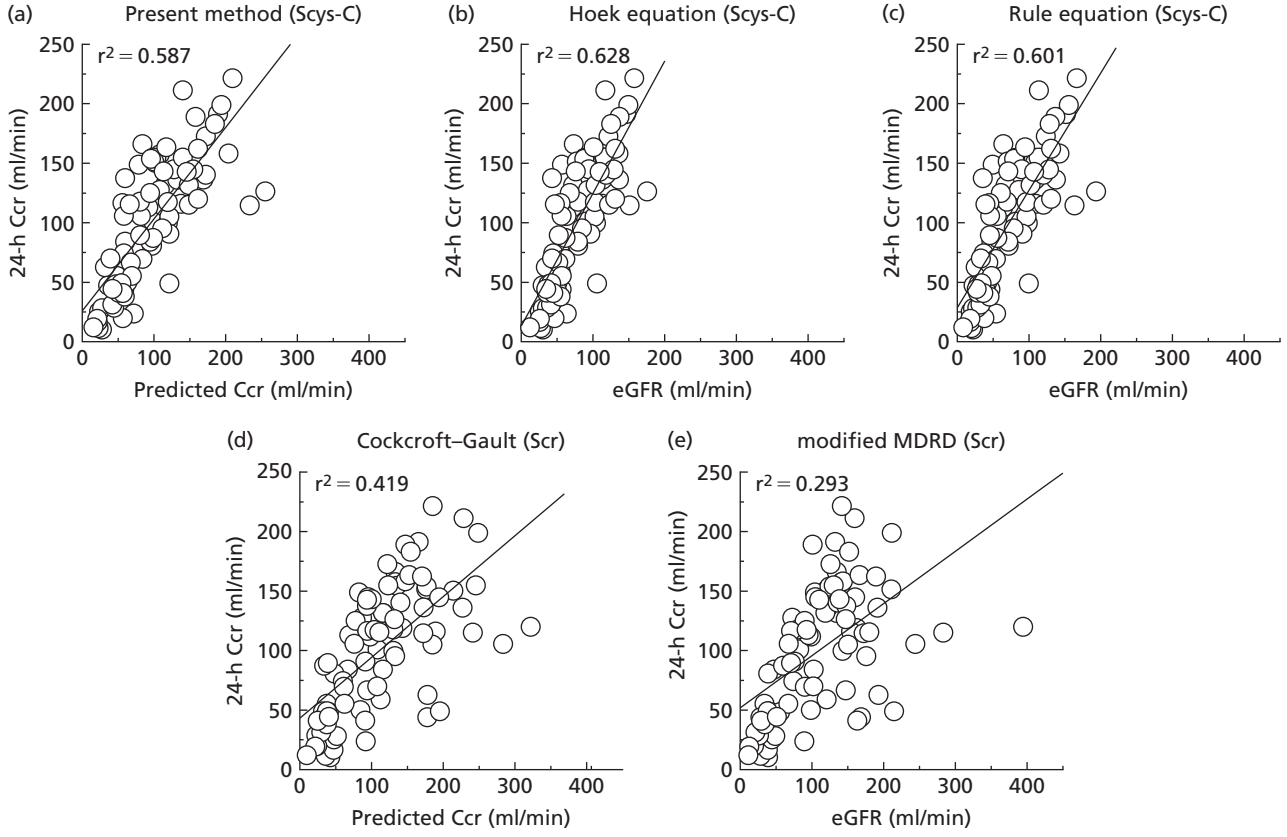

Figure 2 Relationship between 24-h creatinine clearance and predicted creatinine clearance from serum cystatin C. Relationship was determined by the present formula (a), Hoek equation (b) and Rule equation (c), or from serum creatinine (Scr) by Cockcroft–Gault equation (d) or modified MDRD method (e) in 56 critically ill patients (86 serum samples). Ccr, creatinine clearance; eGFR, estimated glomerular filtration rate; Scys-C, serum cystatin C.

($r^2 = 0.187, P < 0.01$). Table 2 shows the ME, MAE, RMSE and 95% confidence intervals (CI) reflecting the performance of the estimation of serum vancomycin concentrations. Both MAE (accuracy) and RMSE (precision) obtained from the data based on Scys-C using the three different equations were low compared with those obtained from the data based on Scr.

Discussion

Cystatin C, an endogenous cysteine protease inhibitor that is produced in all nucleated cells, was filtrated by the glomerulus and catabolized in the renal tubules after reabsorption.[13,14] It has been demonstrated that a small change in renal function

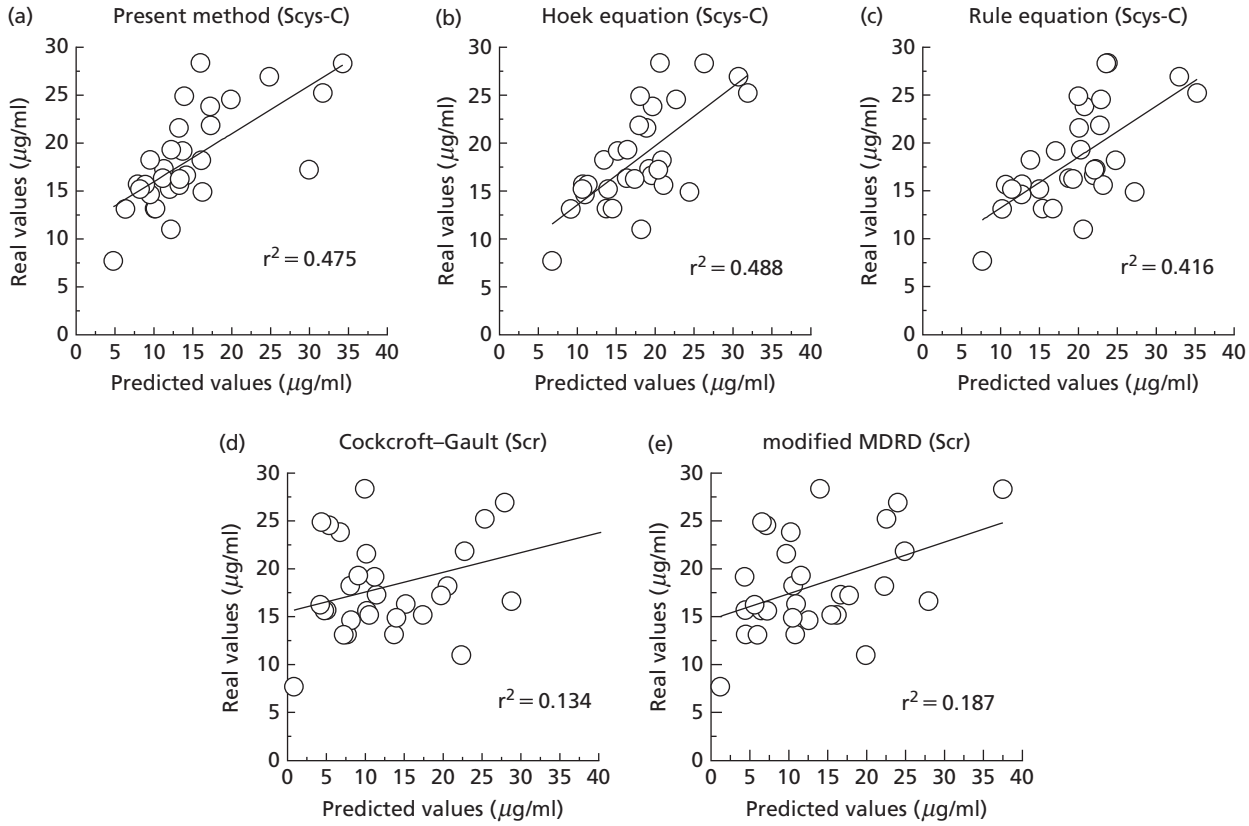

Figure 3 Relationship between serum trough concentrations of vancomycin and predicted concentrations from the population pharmacokinetic analysis using estimated creatinine clearance from various equations. Equations included the present formula (a), Hoek equation (b), Rule equation (c), Cockcroft–Gault equation (d) and modified MDRD method (e) and the relationship was determined in 18 critically ill patients (30 serum samples). Serum vancomycin concentrations were determined by the fluorescence polarization immunoassay. Scr, serum creatinine; Scys-C, serum cystatin C.

Table 2 Comparison of the predictive performance of vancomycin concentrations among several estimates using serum cystatin C or serum creatinine in 18 patients (30 serum samples)

Method	ME (95%CI)	MAE (95%CI)	RMSE (95%CI)
Scys-C			
Hoek	−0.54 (−2.55–1.47)	3.69 (2.62–4.76)	4.32 (2.16–6.47)
Rule	1.28 (−1.04–3.61)	4.14 (2.77–5.51)	5.04 (2.27–7.80)
Present method	−3.60 (−6.04 to −1.17)	5.47 (4.02–6.91)	6.25 (3.22–9.28)
Scr			
Cockcroft–Gault	−4.74 (−8.88 to −0.61)	7.93 (5.13–10.73)	9.86 (4.78–14.95)
Modified MDRD	−4.94 (−8.56 to −1.33)	7.54 (5.13–9.92)	9.04 (4.59–13.49)

Data represent the average and 95% confidence intervals (CI). ME, mean prediction error; MAE, mean absolute error; RMSE, root mean squared prediction error; Scr, serum creatinine; Scys-C, serum cystatin C.

is reflected by Scys-C but not by Scr in patients with mild renal deficiency[15–18] as well as in critically ill patients.[19] Consistent with these findings, Scys-C correlated well with 24-h Ccr ($r^2 = 0.587–0.628$) in our study. In critically ill patients, there would be a muscle loss and relative malnutrition,[26] thus Scr often indicates low values and GFR or Ccr values estimated from Scr indicate higher than the actual levels. Indeed, in our study, Scr of lower than 0.5 mg/dl was observed in 25 patients. Therefore, it is likely that Scys-C is a reliable marker reflecting renal function, especially in such patients.

On the other hand, Scys-C is reported to be influenced by several factors, including glucocorticoids[27,28] and cyclosporin.[28] In addition, Scys-C level is considered to be dependent on the thyroid function, in which Scys-C is lower in the hypothyroid state, while the level is higher in the hyperthyroid state.[29,30] Thus, Wulkan *et al*.[20] argued against the use of Scys-C as the index of renal function in critically ill patients, since most of the critically ill patients reveal a hypothyroid state or they were under treatment with glucocorticoids. Indeed, in our study, estimated Ccr based on Scys-C was

slightly, and not significantly, lower (–21%, P = 0.113, by paired test) than 24-h Ccr in 19 samples obtained from patients with glucocorticoid therapy (70.5 ± 8.7 ml/min vs 89.2 ± 14.9 ml/min) but the values were similar in 67 samples obtained from patients not receiving glucocorticoid therapy (102.9 ± 6.5 ml/ min vs 103.6 ± 6.2 ml/min). On the other hand, we could not evaluate the influence of thyroid function on the Scys-C-based estimation of Ccr because of the lack of data on thyroid function in the present study. Although several drawbacks in the use of Scys-C as an index of renal function have been reported in critically ill patients, the present findings strongly suggest that Scys-C is a more reliable index of renal function than Scr.

Subsequently, we determined whether the Ccr estimated from Scys-C is useful for prediction of serum trough vancomycin concentration in critically ill patients. Predicted concentrations from Scys-C correlated well with the real concentrations of vancomycin, suggesting that Scys-C was applicable to determine the loading dose of vancomycin in critically ill patients. However, the accuracy of the prediction appeared to be less marked in low serum vancomycin concentrations. We do not know the precise reason at present, but such a less-marked precision may result from large variations in urine volume due to the hydration or administration of diuretic agents in critically ill patients. In contrast, the predicted vancomycin concentrations based on Scr were less markedly correlated with real concentrations ($r^2 = 0.134$ or 0.187). Our data were generally consistent with the data reported by Tanaka *et al*.[31] in elderly and non- elderly patients (≥65 and < 65 years old, respectively) in which the predicted vancomycin concentrations based on Scys-C but not on Scr correlated well with the real concentrations in the elderly. They also determined the population pharmacokinetics of vancomycin by the use of GFR estimated from Scys-C.[32] Taken together, these findings suggest that Scys-C is applicable to determine the initial loading dose of vancomycin in critically ill patients.

Conclusions

In critically ill patients, Scys-C reveals a better correlation than Scr with 24-h Ccr. Moreover, the estimated vancomycin trough concentration using GFR predicted from Scys-C but not Scr correlated well with the real concentrations.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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