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Simple and rapid method for analysis of urinary vancomycin using solid phase extraction and fluorescence spectroscopy

Yuki Oshima[1], Mizuki Hori[2], Miyu Matsumoto[2] and Masaru Kato[1,2*]

Abstract

Vancomycin (VCM) is an antimicrobial that is recommended for therapeutic drug monitoring (TDM) for maintaining the efficacy and safety of treatment. The trough monitoring has been used to guide VCM dosing regimens. However, newer guidelines recommend the use of area under the curve/minimum inhibitory concentration (AUC/MIC)-guided vancomycin dosing, and there is a need for easier and more frequent measurements of VCM concentrations. Therefore, in this study, we developed a simple and rapid analytical method for measuring urinary VCM by combining solid-phase extraction and fluorescence analysis. Urine samples are easier and less invasive than blood samples. In addition to the therapeutic range of blood VCM, this method was also able to measure 0.01–1 mg/mL, which is the concentration range of urinary VCM. The accuracy of 10, 20, and 30 μg/mL VCM solutions were between 93.18 and 109.76%. The relative standard deviation (RSD) of intra-day and inter-day analysis were less than 6.25% and 6.28%, respectively. Since this method does not use large equipment, it is expected to be better suited for clinical use.

Keywords Fluorescence analysis, Vancomycin, Urine, Dosing, Therapeutic drug monitoring

Introduction

Vancomycin (VCM), with a broad antimicrobial spectrum, is used as a first-line drug against methicillin-resistant *Staphylococcus aureus* (MRSA) (Cafferkey et al. 1982). However, overdose of VCM may cause nephrotoxicity and acoustic disturbance (Jeffres et al. 2007). Therefore, VCM is recommended for therapeutic drug monitoring (TDM), and its dosage is adjusted based on its blood concentration (Patel et al. 2011).

Based on pharmacokinetic/pharmacodynamic analysis, the most suitable predictor for the efficacy and safety of VCM is area under the curve/minimum inhibitory concentration (AUC/MIC) (Tkachuk et al. 2018; Revilla et al. 2010); however, trough monitoring is still a preferred suitable indicator for the adjustment of VCM dose because of easy measurement (Liu et al. 2011; Kullar et al. 2011). Subsequent studies have reported about trough monitoring not being an ideal substitute predictor, and the latest guidelines recommend AUC/MIC for guiding VCM dosing regimens (Rybak et al. 2020; Mohr and Murray 2007). Accurate determination of AUC requires collecting blood samples numerous times from patients and measuring concentrations over time, which is burdensome on patients and healthcare professionals. Therefore, there is a strong demand for a convenient non-invasive or less invasive technique for collecting samples and obtaining necessary information for guiding VCM dosing regimens.

When VCM is administered intravenously, almost all of it is rapidly excreted in urine as an unaltered drug (Moellering et al. 1981). Therefore, many studies have been reported measuring VCM concentrations in the

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urine instead of blood (Shokouhi et al. 2017; Baranowska et al. 2009, 2010; Cass et al. 2011; Javorska et al. 2017). Thus, VCM can be measured easily and frequently in urine instead of blood for guiding VCM dosing regimens. This will also aid in obtaining accurate AUC values, which may be useful for designing more precise dosing regimens. The advantages of using urine as a sample over blood are (1) self-collection by the patient; (2) collection in large quantities (1.5 L/day); (3) urine is usually discarded and there is almost no additional burden on the patient; (4) using a urinary catheter, it is possible to collect all urine excreted in a certain period of time; and (5) there is less chance of contamination because the substance filtered by the glomerulus and not reabsorbed by the renal tubules is excreted.

Various reports on the measurement of urinary VCM have shown a good correlation between blood and urine concentrations (Shokouhi et al. 2017), and urine may serve as an alternative sample for guiding VCM dosing regimens. Additionally, VCM concentration in 24-h urine samples has been reported to be much higher than the blood VCM concentration (several hundred μg/mL to 1 mg/mL) (Javorska et al. 2017). For measuring the concentration of VCM in blood, immunoassay is frequently used clinically (Sattur et al. 2000; Vila et al. 2007), and recently, a method using high performance liquid chromatography (HPLC) has also been developed which is used for short-time analysis in clinical use (Farin et al. 1998; Trujillo et al. 1999; Javorska et al. 2016). However, these analytical methods require expensive equipment, and it is difficult to measure high concentrations of VCM (several 100 mg/mL or more) accurately using common competitive immunoassays. Therefore, in this study, we developed a new method for measuring urinary VCM that can be easily used in a clinical setup and can measure a wide range of VCM concentrations.

Methods and materials

Chemicals and reagents

Ammonium formate, citric acid anhydrous, *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethanol, formic acid, methanol, trisodium citrate dihydrate, and VCM were purchased from Fujifilm Wako Pure Chemical Corporation, Ltd. (Osaka, Japan). Glycerol was purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Sulbactam sodium/ampicillin sodium and piperacillin/tazobactam were obtained from Meiji Seika Pharma Co., Ltd. (Tokyo, Japan). Meropenem and ceftriaxone were obtained from NIPRO Corporation (Osaka, Japan). Cefepime was obtained from Sandoz K.K. (Tokyo, Japan).

Urine sample analysis

Urine was obtained from healthy five male volunteers with ages from 20 to 50 s (median age, 41). Approximately 50 mL voluntary urine was collected and centrifuged by centrifugate (MX-300, Tomy Seiko Co., Ltd., Tokyo, Japan) at 600 × *g* for 10 min to remove the cells (Kato et al. 2020). The supernatant of the urine was stocked in a refrigerator. A concentration of 10 mg/mL VCM was prepared in water. The VCM solution was added to the stocked urine just before the measurement. MonoSpin® Ph (GL Sciences Inc., Tokyo, Japan) was preconditioned by centrifugate (7780II, KUBOTA Corporation, Tokyo, Japan) at 10,000 × *g* for 1 min with methanol and water as per the manufacturer's protocol. Then, 600 μL of urine sample was added to the preconditioned MonoSpin® Ph and washed four times with 550 μL phosphate-buffered saline (PBS). The captured VCM was eluted in 50 μL eluent (citrate buffer (pH 2): methanol; 90:10). To the eluted solution, 270 μL DMSO was added, followed by 300 μL of the mixture solution was moved to a 96-well plate for fluorescence analysis.

HPLC measurement

HPLC analyses were performed using a Hitachi LaChrom Ultra series (Hitachi High-Tech Science Corporation, Tokyo, Japan) consisting of two L-2160 U LaChrom Ultra pumps, an L-2200U LaChrom auto sampler, an L-2455U LaChrom diode array detector, and an HPLC system organizer. A Resolve of 5-μm Spherical C18 column (3.9 mm × 150 mm, Waters, Milford, MA, USA) was used. Mobile phase A had 20 mM formic acid/ammonium formate and mobile phase B had 100% methanol. The gradient elution program of the mobile phases was as follows: 5–10% (B) from 0 to 5 min. Flow rate was 1 mL/min. The injection volume was 10 μL, and a fluorescence detector with an excitation wavelength (ex) at 290 nm and emission wavelength (em) of 330 nm was used for detection. All samples were filtered using a Millex-LG syringe filter (pore size, 0.2 μm, Millipore) before analysis.

Measurement of three-dimensional (3D) fluorescence spectrum

The 3D fluorescence spectra were measured using a fluorescence spectrometer (F7100, Hitachi High Technologies Corporation, Tokyo, Japan). Excitation spectra were recorded in the 200–500 nm range with emission measurements from 200 to 500 nm. The slit width was 5 nm. The 3D spectra were shown using SpectAlyze software package (Dynacom Co., Ltd., Chiba, Japan).

Measurement of fluorescence spectrum and intensity

The fluorescence of VCM was measured using a multiplate reader (SH-9000, Corona Electric Co., Ibaraki, Japan). Fluorescence spectrum was obtained in the emission wavelength from 300 to 400 nm when excited at 290 nm. Fluorescence intensity was obtained in the emission wavelength of 340 nm when excited at 290 nm.

Measurement of VCM in a clinical laboratory

The clinical laboratory used Emit®2000 Vancomycin Assay kit (Siemens Healthineers, Erlangen, Germany) and BioMajesty JCA-BM8000 series (JEOL Ltd., Tokyo, Japan) for the analysis. The measurements were performed as described in the manufacturer's protocol.

Results and discussion

Fluorescence spectroscopy is a very sensitive and selective technique. Therefore, it is an ideal method for the detection of trace substances in biological fluids. In addition, simple and inexpensive fluorometers are now available in the market. Supporting Fig. 1 shows the 3D fluorescence spectrum of VCM at the excitation (ex.) wavelength range of 200–500 nm and emission (em.) wavelength range of 200–500 nm. Warm colors (Ex: red) indicate a strong fluorescence intensity, whereas cold colors (Ex: blue) indicate a weak fluorescence intensity. VCM has fluorescence intensity in the ultraviolet region at an excitation of 280–300 nm and emission of 290–340 nm. Next, when the 3D-fluorescence spectrum of the urine of a healthy volunteer was measured, there were two fluorescence peaks, the first with an excitation of 250–290 nm and emission of 325–400 nm, and the second with an excitation of 310–360 nm and emission of 360–400 nm (Supporting Fig. 1). For accurate measurements of VCM concentration in the urine for clinical use, it is necessary to remove fluorescent substances (amino acids, flavins, NADH, and others) present in urine (Kušnír et al. 2005) because the first fluorescence peak in the urine sample partially overlaps with the fluorescence of VCM.

Hence, we first determined the purification conditions for VCM from urine using a solid phase extraction (SPE) cartridge. A phenyl group-modified SPE cartridge was selected because VCM has five aromatic rings. VCM was applied to the cartridge, and each fraction was eluted in PBS solution and citrate buffer (pH 2) containing 10, 15, 20, and 60% methanol. The eluted samples were analyzed by HPLC. VCM was not detected in the flow-through fractions, indicating that VCM was efficiently captured in the SPE cartridge. Also, in the eluted fractions, VCM was detected at 9 min only in the eluted fraction of 10% methanol solution, and not in the other fractions (Fig. 1). Specifically, urinary VCM was purified by passing the

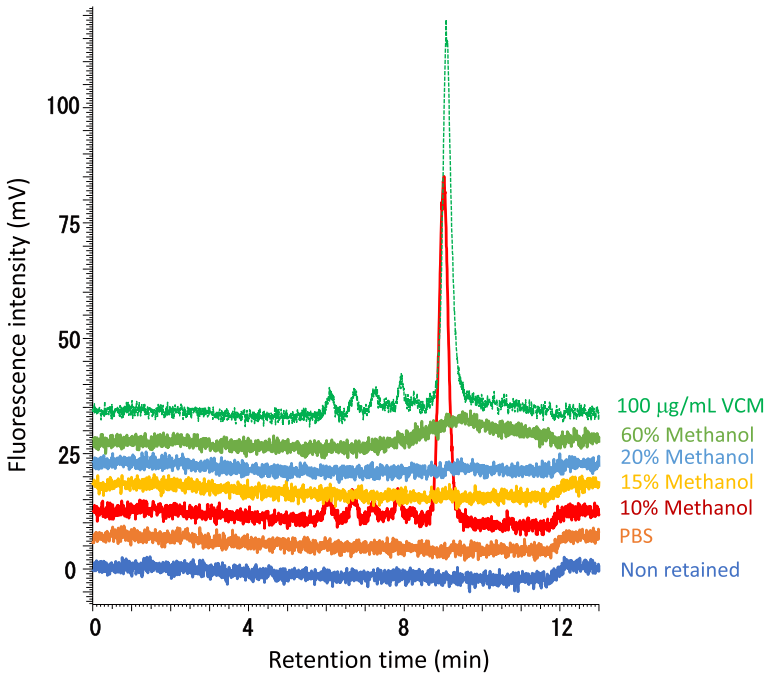

Fig. 1 Chromatograms of fractionates and 100 µg/mL VCM solutions. Column: Resolve 5-µm spherical C18 column (3.9 mm × 150 mm), mobile phase A: 20-mM formic acid/ammonium formate, B: 100% methanol, gradient program: 5–10% (B) from 0 to 5 min, flow rate: 1 mL/min, detection: fluorometry (ex/em. 290/330 nm)

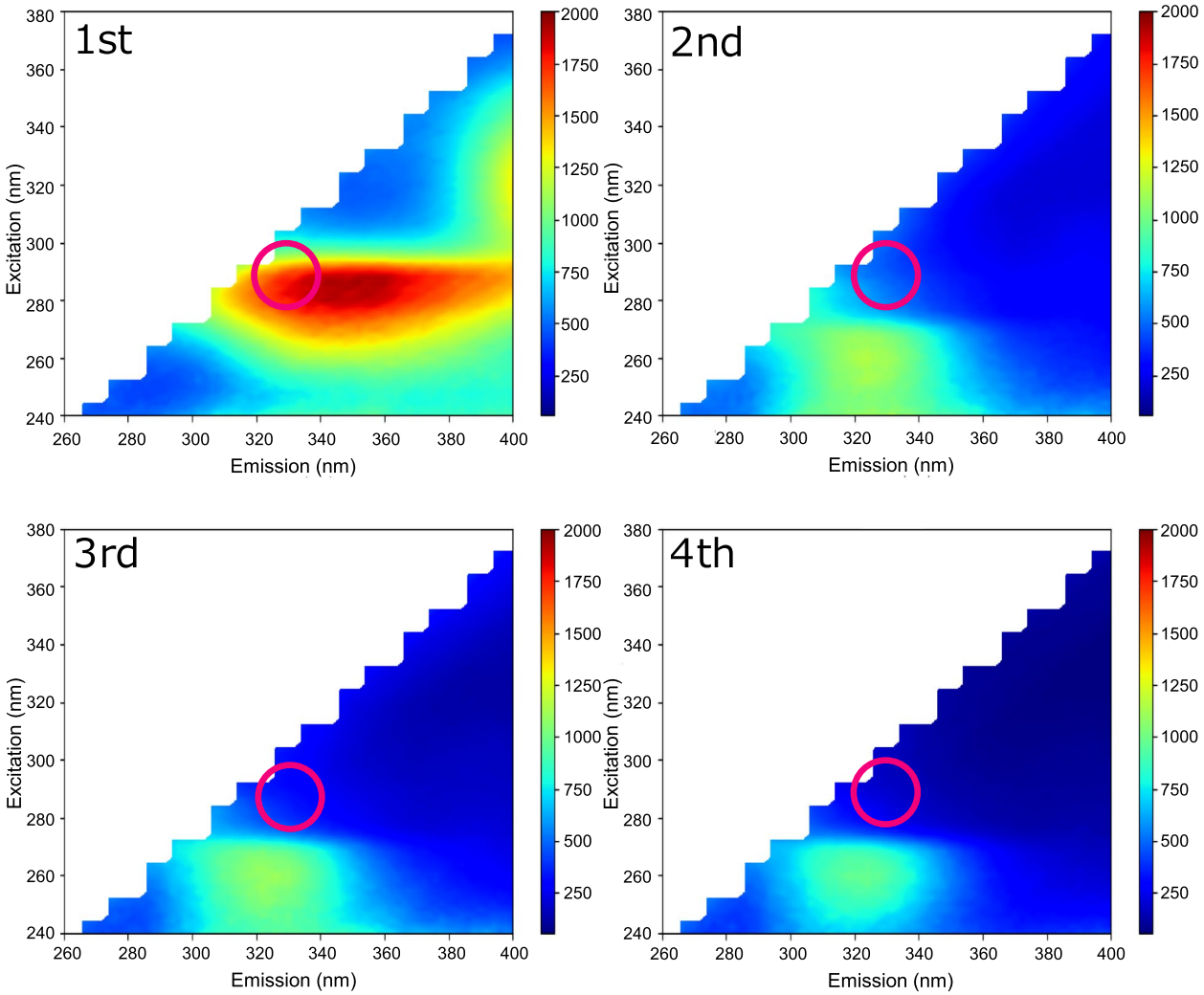

Fig. 2 3D fluorescence spectra of washed solution. Excitation: 240–380 nm, emission 260–400 nm; the red circle indicates region of VCM fluorescence signal

urine sample through an SPE cartridge, washing the cartridge repeatedly with PBS, and performing final elution in a 10% methanol solution.

Next, the number of washings with PBS required for purification of the urine sample was examined. A urine sample was placed on a cartridge, washed repeatedly with PBS, and the 3D fluorescence spectrum of the eluted fractions were measured (Fig. 2). In the first washed fraction, strong fluorescence was detected near excitation of 290 nm and emission of 330 nm (red circle). This indicates the elution of endogenous substances that exhibit similar fluorescence properties to those of VCM in this fraction. The fluorescence in the region decreased with repeated washing, and no significant change was observed even after 4 or more washes. However, fluorescence signal around 300–340 nm was observed and the intensity remained constant regardless of the number of washings (Fig. 2). This signal was derived from solvent-derived Raman scattered light.

Then, we examined solvents that reduced the influence of the Raman scattering of the solvent itself. Fluorescence spectra of five solvents (DMF, DMSO, methanol, glycerin, and ethanol) that were excited at 290 nm are shown in Supporting Fig. 2. The scattered light of DMSO was the smallest among them.

In order to completely eliminate the scattered light of the eluent, the eluent must be completely evaporated and redissolved in DMSO before fluorescence analysis. However, drying of 300 µL of 10% methanol aqueous solution is unsuitable for clinical use due to the extra time and equipment required. Furthermore, there is a possibility that the decomposition of VCM, which is unstable in the solution, may occur in the drying process (White et al. 1988; Serri et al. 2017; Cao et al. 2018). Therefore,

we thought that if the volume of the eluent from the cartridge was reduced as much as possible, and DMSO was added without drying, it would be easier to use in the clinical setup. The volume of the cartridge of SPE is approximately 20.8 µL ($2.1 \times 2.1 \times \pi \times 1.5$ mm^3) and its porosity is 80%; therefore, the void volume of the cartridge is 16.6 µL. In other words, it was expected that most of the VCM captured on the cartridge would be eluted using an eluent several times as large as 16.6 µL.

Hence, we loaded the cartridge with the same amount (90 µg) of VCM and measured the fluorescence of VCM in each fraction that was eluted in different volumes (10–300 µL) of the eluent (Fig. 3a). As a result, it was found that some VCM was eluted even in 10 µL of eluent, and the amount of eluted VCM increased as the volume of eluent increased. Approximately 95% of the VCM was eluted when 300 µL eluent was used and only 36.1% VCM was eluted by 50 µL eluent. However, their variability was 3.10 and 1.51%, respectively, indicating quantitative elution even with a small amount of eluent.

Then, the effect of the mixing ratio of 10% methanol solution, which is the eluent, and DMSO on the fluorescence intensity of VCM was investigated. The fluorescence spectra of VCM were measured when the proportion of DMSO in the measurement solvent was changed in the range of 0–97% (Fig. 3b). Even without the DMSO solution, the fluorescence intensity increased slightly by the addition of VCM. The intensity was increased by increasing the proportion of DMSO and it reached the maximum when the DMSO proportion was 97%. However, when the proportion of DMSO was approximately 80%, the fluorescence intensity was 10 times stronger than that of the sample without DMSO, and even if the DMSO proportion was increased further, the increase in the fluorescence intensity was not very high. Based on the above results, we determined the procedure of the analysis of urinary VCM as follows: urine sample was centrifuged for removing cells and debris. Then, 600 µL supernatant was applied to Ph-modified SPE cartridge and washed four times with 550 µL PBS. The captured VCM was eluted in 50 µL of 10% methanol, and then, 270 µL of DMSO was added. The fluorescence intensity (excitation at 290 nm, emission at 340 nm) of 300 µL of the mixture solution was measured by a fluorometer.

First, we made a calibration curve in the range of 0–50 µg/mL, which is necessary for measuring the therapeutic concentration range of VCM in the blood (Fig. 4). The samples were used where VCM was added to PBS or urine from healthy volunteers. As a result, the calibration curves for urine and PBS were similar, suggesting that contaminants in urine did not interfere with the measurement of VCM. The correlation coefficient of the calibration curve of urine and PBS was 0.94 and 0.94, respectively. The validation data (intra-day and inter-day reproducibility at three different concentrations (10, 20, and 30 µg/mL) are shown in Table 1. The accuracy of 10, 20, and 30 µg/mL VCM solutions were between 93.18 and 109.76%. The RSD of intra-day and inter-day analysis were less than 6.25% and 6.28%, respectively. Therefore, it was concluded that this assay was applicable for quantitative analysis. To examine

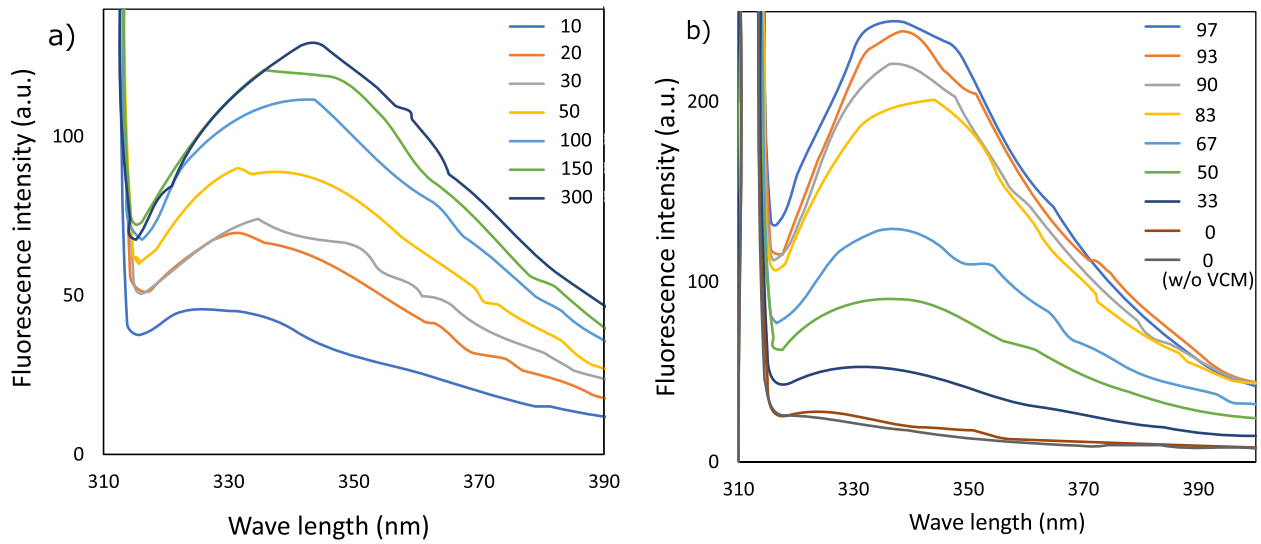

Fig. 3 **a** The relationship between elution volume and quantity of VCM, **b** relationship between ratio of DMSO to 10% methanol solution and quantity of VCM. Fluorescence spectra were obtained when excited at 290 nm. The sample volume was adjusted to 300 µL by adding 10% methanol solution before the fluorescence analysis

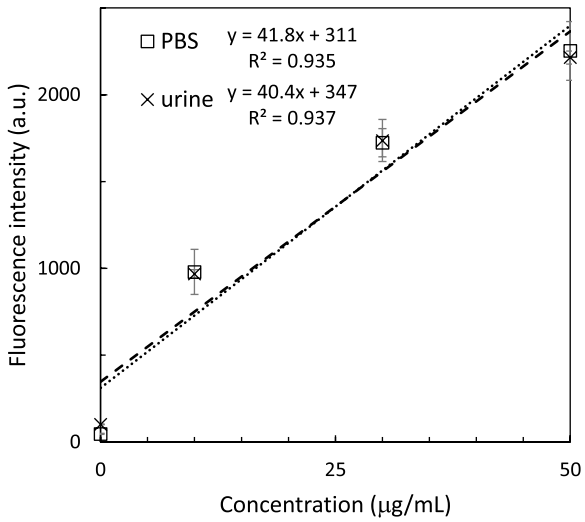

Fig. 4 Calibration curve for VCM in PBS and urine solution with VCM concentrations from 0 to 50 μg/mL. Square and cross indicates PBS and urine, respectively. Error bars represent CV of three measurements

the effect of co-administrated drugs for the analysis, fluorescence of 5 frequently administrated drugs (sulbactam sodium/ampicillin sodium, piperacillin/tazobactam, meropenem, ceftriaxone, and cefepime) was examined (Raverdy et al. 2013). Supporting Fig. 3 shows the 3D fluorescence spectra of the 200 mg/mL co-administrated drug solutions. Strong fluorescence signal was observed from sulbactam sodium/ampicillin sodium, and weak signal was observed from meropenem. Other co-administered drugs did not show fluorescence signals in the range of 200 to 600 nm when excited from 200 to 600 nm. Although sulbactam sodium/ampicillin sodium and meropenem showed fluorescence signals, the wavelength of fluorescence signals were different from that of VCM. Hence, these co-administered drugs did not interfere with the VCM measurement. The degradation of VCM was evaluated during the measurement, because it was reported that VCM is unstable in aqueous solutions (White et al. 1988; Serri et al. 2017; Cao et al. 2018). Supporting Fig. 4 shows chromatograms of VCM samples immediately after preparation and samples left at 37 °C for 1 h that was more severe than the measurement conditions of 20 °C for 30 min. The peak intensity of VCM did not change and no new peak derived from degradants appeared due to the storage. Hence, the VCM degradation was neglectable during the measurement.

Furthermore, since it has been reported that more than 100 μg/mL of VCM exists in urine, a calibration curve was also made using urine samples adjusted to VCM concentrations of 100, 300, 500, and 1000 μg/mL (Vila et al. 2007). A good calibration curve (correlation coefficient 0.97) was obtained even in the high-concentration region (Supporting Fig. 5). To confirm the reliability of the developed method, we compared the measured values of the same samples with that by the method currently used in clinical practice. Figure 5 shows the measurements of six different urine samples using the developed method and EMIT method by a clinical laboratory (Chen et al. 2020). All samples showed similar results, indicating reliability of the developed method for the analysis of urinary VCM.

Although urine from healthy subjects were used in this study, in order to use this method in clinical practice, it is necessary to verify its effectiveness using patient urine. The composition of patient specimens may differ significantly from those of healthy individuals. One advantage of the developed method is that it is a non-destructive method. In other words, if the measured value by the developed method is abnormal, it can be re-measured by other existing methods to confirm the accuracy of the value. Therefore, we will measure patient specimens using this method and obtain the AUC/MIC necessary for VCM administration design in our next study.

Table 1. Inter-day and intra-day accuracy and validation at three different concentrations

	Spiked concentration	Measured concentration	Accuracy	SD	RSD
	(μg/mL)	(μg/mL)	(%)		(%)
inter-day	10	10.29	102.90	46.29	6.25
(n=3)	20	21.95	109.76	62.55	5.40
	30	27.95	93.18	19.01	1.53
intra-day	10	10.10	101.00	50.05	6.28
(n=3)	20	19.80	99.00	44.90	4.27
	30	30.00	100.00	43.06	3.85

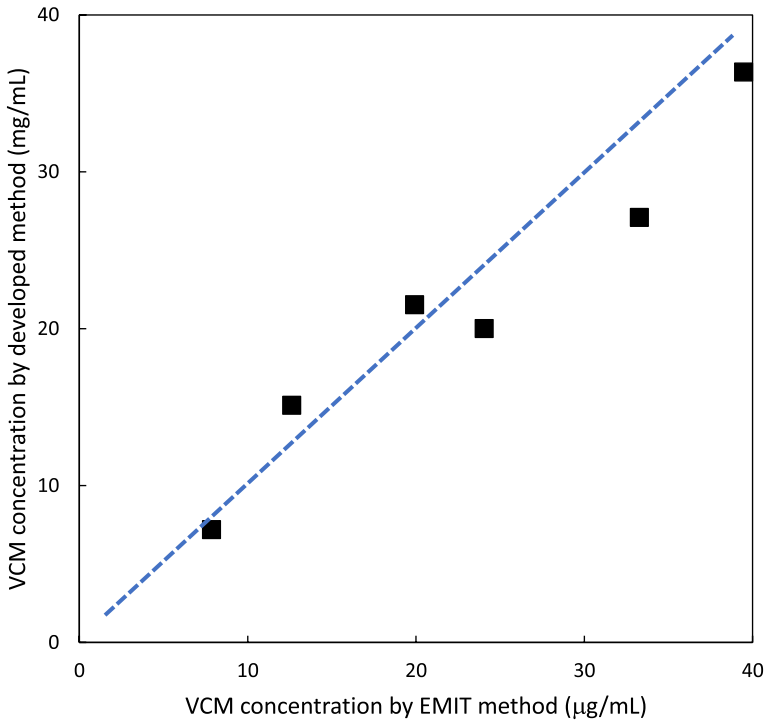

Fig. 5 Comparison of measurement values by the developed method and a clinical laboratory using EMIT method. EMIT method used Emit®2000 Vancomycin Assay kit and BioMajesty JCA-BM8000 series

Conclusions

In this study, we developed a simple and rapid method for the analysis of urinary VCM. Since the method uses a centrifuge and fluorometer as equipment, it is cost-effective compared to the other existing methods and is suitable for clinical use. The developed method was able to measure up to 1000 μg/mL VCM, which is the assumed amount in urine samples, in contrast to the one currently used in clinical laboratories (100 μg/mL). In the future, the use of this method to measure VCM in urine samples could help us clarify the relationship between urinary VCM concentration and AUC/MIC and also guide VCM dosing regimens.

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Authors' contributions
Y.O. contributed conceptualization, methodology, formal analysis, investigation, resources, writing original draft, writing-review & editing, visualization, supervision, and project administration. M. H. & M. M. contributed methodology, formal analysis, investigation, resources, writing original draft, writing-review & editing, and visualization. M.K. contributed conceptualization, methodology, formal analysis, investigation, resources, writing-review & editing, visualization, supervision, project administration, and funding acquisition. The authors read and approved the final manuscript.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
All clinical studies involving human urine samples were conducted in adherence to the procedure approved by the Human Ethics Committee of the Showa University (approval no. 315), and informed consent was received from the volunteers.

Competing interests
The authors declare that they have no competing interests.

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