

# Urine Vancomycin Level as a Method for Drug Monitoring in Patients With Normal and Decreased Kidney Function

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**Introduction.** Therapeutic drug monitoring of vancomycin is an important issue in clinical decision-making and dosage modifying, particularly among patients in critical conditions and decreased kidney function. Urine is typically readily available in hospitalized patients and therapeutic drug monitoring in urine may be a reliable and noninvasive procedure compared to frequent blood sampling. We aimed to determine and validate the diagnostic yield of vancomycin trough level in urine.

**Materials and Methods.** In a prospective study, 95 patients who were treated with vancomycin for any clinical condition were enrolled in this study. Patients were divided into 2 groups according to their glomerular filtration rate (greater than 80 mL/min/1.73 m<sup>2</sup> versus 15 mL/min/1.73 m<sup>2</sup> to 80 mL/min/1.73 m<sup>2</sup>). Vancomycin serum trough levels and simultaneous urine trough levels were detected by high-pressure liquid chromatography.

**Results.** The mean serum and urine trough levels of vancomycin were 13.13 ± 1.34 mg/L and 7.79 ± 1.23 mg/L, respectively. The serum and urine trough levels had a positive linear correlation ( $r = 0.38$ ,  $P < .001$ ), which was also significant in patients with normal kidney function ( $r = 0.43$ ,  $P = .001$ ). The estimated serum concentration was equal to urine vancomycin concentration plus 5.3 mg/L.

**Conclusions.** Urine levels of vancomycin correlate with simultaneous serum levels and may consistently predict serum levels in patients with normal kidney function. Therefore, urine vancomycin monitoring might be used as a noninvasive alternative to blood sampling, particularly in patients with normal kidney function.

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## INTRODUCTION

Vancomycin is an antibiotic that is used to treat gram-positive bacterial infections. Its therapeutic effect becomes evident when the serum drug concentration level is at an adequate level, which depends on the specific infection being treated. Likewise, an adequate drug concentration is also needed to prevent antibiotic resistance.

Vancomycin is a large glycopeptide with a high

molecular weight.<sup>1</sup> It does not have appreciable oral bioavailability and its main route of clearance is through the kidneys.<sup>2</sup> Vancomycin pharmacokinetic profile is complicated and there are still some unresolved issues surrounding it. In patients with normal kidney function, its peak occurs in 1.0 hours, with a half-life of 6 to 12 hours with a distribution width of 0.4 L/kg to 1.0 L/kg.<sup>3</sup> On the one hand, vancomycin is an antibiotic that its

time above minimum inhibitory concentration and action are dependent on its distribution, purity, and protein binding. Vancomycin has good tissue penetration into most body sites, although this depends on the specific site and somewhat on the amount of surrounding inflammation.<sup>3</sup>

For adequate dosing, measuring the drug concentration in the body is necessary. Currently, serum concentrations are measured. The importance of this is underscored in cases of poor clinical outcomes being associated with low serum levels of vancomycin.<sup>4</sup> We sought to test whether urine levels of vancomycin could be used as a substitute for serum levels, given its potential benefits compared to drawing blood samples (easier to administer, less costly, less time consuming, and no contribution to iatrogenic anemia).

## MATERIALS AND METHODS

Over a 12-month period, patients over the age of 14 years who were being treated with intravenous vancomycin were enrolled into this study. Patients with acute kidney injury were excluded. Patients' age, sex, body weight, indication for treatment, serum creatinine level, glomerular filtration rate (GFR), and vancomycin dosing were recorded. Patients were divided into 2 groups based on their GFR level. Group A consisted of those with a GFR greater than 80 mL/min/1.73 m<sup>2</sup> treated with a vancomycin loading dose of 30 mg/kg, followed by a dose of 15 mg/kg every 12 hours. Group B consisted of patients with a GFR from 15 mL/min/1.73 m<sup>2</sup> to 80 mL/min/1.73 m<sup>2</sup>, treated with a vancomycin loading dose of 30 mg/kg, followed by a daily dose of  $(\text{GFR} \times 15.4) \pm 150$  mg.

Prior to the 4th dose, 2 concurrent urine and plasma samples were obtained for measurement of vancomycin trough level. Vancomycin levels were immediately measured with high-performance liquid chromatography (Agilent Technologies, Santa Clara, California, USA). This study was done in a prospective fashion over 12 months, and the health care providers and patients were blinded to the actual group assignment and dose of vancomycin used. Associations between the serum and urine trough levels were assessed using the paired *t* test and the Pearson correlation test. A *P* value less than .05 was considered significant.

This study was registered at the Infectious Diseases and Tropical Medicine Research Centre

of Shahid Beheshti University of Medical Sciences (identification number: 1391-1-132-1023) and was approved by ethics committee of Shahid Beheshti University of Medical Sciences (official approval number: 1391-1-132-1023-11722).

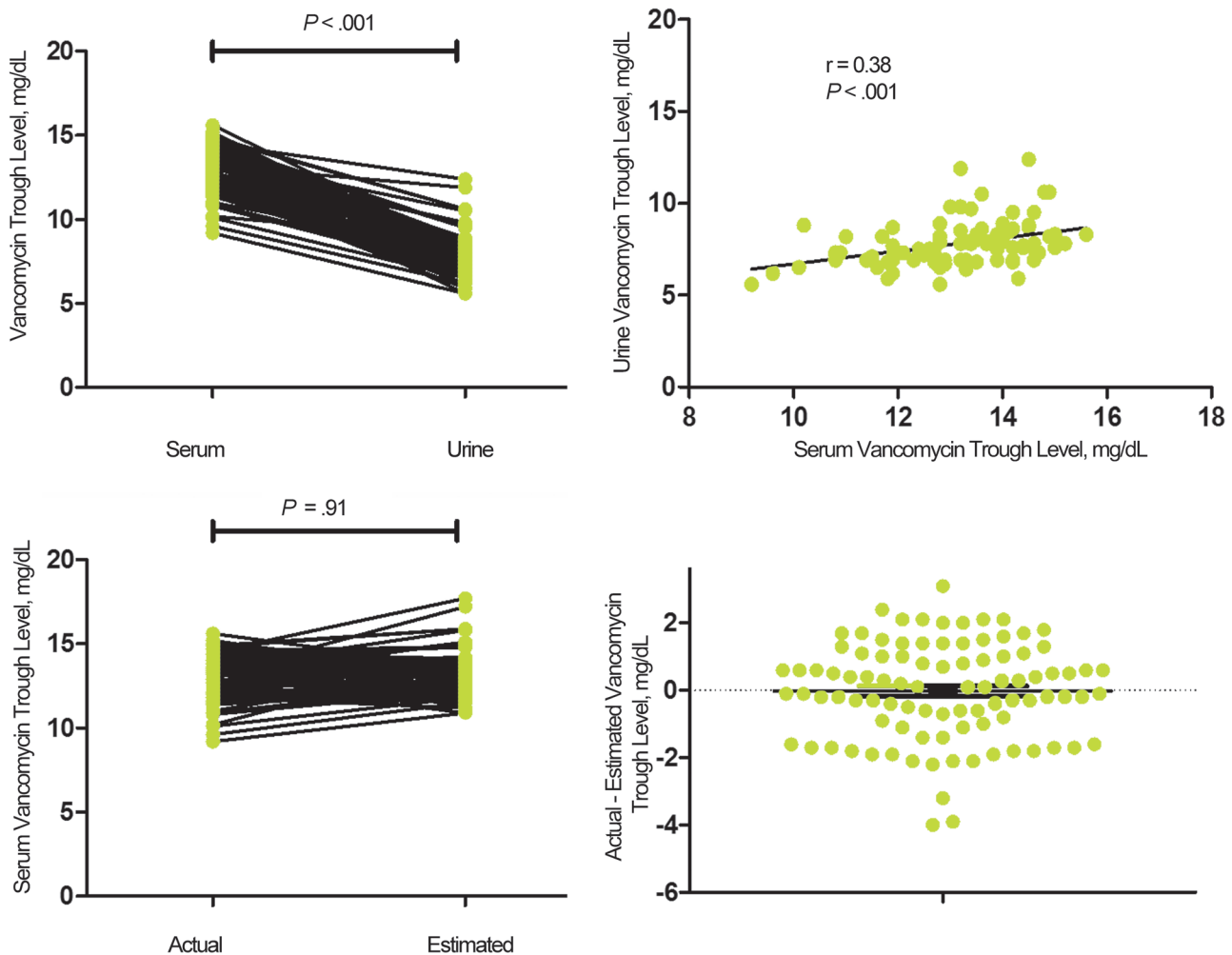
## RESULTS

A total of 95 patients were enrolled. These included 75 men and 20 women. Fifty-eight patients with normal kidney function were assigned to group A, and the remaining 37 patients with low GFRs were assigned to group B. Group A patients had a mean age of 36.4 years and group B had a mean age of 61.7 years, which was a significant greater (*P* < .001). Serum creatinine levels were also different between the two groups (*P* < .001). Clinical indication for vancomycin treatment were meningitis (30.5%), cellulitis and soft-tissue infections (25.3%), hospital-associated pneumonia (20.0%), and sepsis (0.3%).

The mean serum vancomycin trough level was  $13.44 \pm 1.23$  mg/L in group A, and  $12.64 \pm 1.39$  mg/L in group B. The concurrent mean urine trough level was  $7.86 \pm 1.29$  mg/L and  $7.69 \pm 1.14$  mg/L, respectively. Overall, the samples in the urine and their corresponding serum samples correlated well with each other (*P* < .001; Figure A). The serum and urine samples also demonstrated linear correlation (*r* = .38, *P* < .001; Figure A). The serum and urine samples in group A were correlated with each other (*r* = 0.43, *P* = .001; Figure B), while those for group B only showed a trend towards correlation (*r* = 0.30, *P* = .07; Figure C). Overall, the Pearson coefficients were significant.

We calculated a conversion factor between urine and serum vancomycin based on the mean differences (5.3 mg/L). Thus, the estimated serum concentration was equal to urine vancomycin concentration plus 5.3 mg/L. The actual and estimated serum concentrations of vancomycin were comparable (*P* < .91; Figure D). There was only a 1-mg/L variance in the 25th to 75th percentiles, with 92% of the samples within a 2-mg/L difference between the actual and estimated levels (maximum variance of 4 mg/L; Figure D).

There was no correlation between serum vancomycin levels and GFR in group A or group B (*P* = .08 and *P* = .88, respectively); however, the overall analysis of the two groups showed that serum vancomycin level was weakly correlated



Relationship between urine and serum vancomycin trough levels in 95 patients. A, Comparison between urine and serum trough levels as measured by the paired  $t$  test ( $P < .001$ ). B, Linear correlation between urine and serum trough vancomycin levels ( $r = .14$ ;  $P < .001$ ). C, Comparison between actual and estimated serum vancomycin trough levels by the paired  $t$  test ( $P < .91$ ). Estimated serum vancomycin level was equal to urine vancomycin + 5.3 mg/L. D, Variance between actual and estimated serum vancomycin trough levels. There was a 1-mg/L variance in the 25th to 75th percentiles, with 95% of the samples within a 2.1-mg/L difference.

with GFR ( $r = 0.256$ ,  $P = .01$ ). The correlation between urine vancomycin levels and GFR was not significant ( $P = .77$ ).

## DISCUSSION

In this study, we found a direct correlation between the vancomycin trough levels measured in the serum and urine. Even though the two studied groups had vastly different kidney function and vancomycin dosing schedules, we observed an overall correlation, though this was significant only in those with a higher GFR. Lack of a stronger correlation in the patients with lower GFR levels might be due to the low number of patients in this group or alternatively because of changes in

urine volume.

To our knowledge, there has been no studies to address the question of the relationship between serum and urine vancomycin levels. Initial studies showed that renal clearance of vancomycin is the primary route of clearance, and no other ways have been described. It appears that 80% of vancomycin is cleared unchanged through the urinary system. In the 1980's, there were safety studies evaluating the deposition of vancomycin in the kidneys in animal models.<sup>5</sup> The results showed that on the 4th day of administration of vancomycin in rats with normal kidneys, 50.5% of the drug was cleared in the urine, while in rats with a kidney injury, only 36.5% of vancomycin was cleared.

Thus, it was learned that the pharmacokinetics of vancomycin were dependent on kidney function. Studies on vancomycin clearance and creatinine have showed a linear relationship between these.<sup>6</sup> However, with elevated serum creatinine level, the linear relationship begins to break down, likely from not taking into account other factors affecting the creatinine clearance; another study has shown a linear relationship between serum levels of vancomycin in those with creatinine clearance less than 85 mL/min.<sup>7</sup>

Although there have been many studies on the relationship between kidney function and vancomycin levels, we are unaware of any studies that have sought to correlate serum and urine trough levels of vancomycin in humans. In 2001, in a study to determine the accuracy of liquid chromatography tandem mass spectrometry in measuring serum and urine vancomycin levels, showed that this new method could be employed to measure vancomycin levels (with an error of 1 ng/mL).<sup>8</sup> However, in that study, the authors did not specifically look at the relationship between serum and urine levels of vancomycin. We have previously shown that high-performance liquid chromatography is accurate in measuring vancomycin levels.<sup>9</sup>

## CONCLUSIONS

Serum vancomycin levels have a direct correlation with urine vancomycin levels in persons with normal GFR levels. The urine vancomycin level can thus be used to accurately estimate the serum vancomycin level. This may hold true for lower GFR levels also, but our data did not support this. Additional studies will be necessary to more accurately determine the conversion factor between urine and serum levels, as well as the ideal time to measure a urine vancomycin trough level.

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## CONFLICT OF INTEREST

None declared.

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