Editorial

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Overestimation of Vancomycin Clearance by the Linear Regression Formula in Rodvold's Report: Why?

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Vancomycin therapy has long been individualized through concentration monitoring. Because the therapeutic drug concentration monitoring (TDM) service is not available in all hospitals, ways to predict its area under the curve (AUC) using estimated creatinine clearance (CLcr) without drug concentration have been sought. More than 80% of vancomycin is eliminated via renal excretion and its clearance (CL) is known to be approximately 50-80% of measured glomerular filtration rate (GFR) [1]. Thus, an equation describing linear relationship between vancomycin clearance (CL) and CLcr may be used to predict vancomycin AUC without measuring its concentration.

Rodvold et al. [2] first reported a formula predicting the CL of vancomycin with CLcr calculated by Cockroft-Gault (C-G) equation. The formula was applied in the report by Jin et al. [3] to calculate the AUC, however it was much smaller than the AUC estimated by the CAPCIL software (Simkin Inc., Gainesville, FL, USA) that gives maximum a posteriori (MAP) Bayesian estimates of vancomycin CL with trough concentration data. In other words, the vancomycin CL appeared to be overestimated by the Rodvold's formula.

Why did this happen? One possibility we may suspect is the difference in patient demographics. It is reported that C-G equation gives overestimated CLcr values in obese patients [4]. This is accordant with results summarized in Table 2 in Jin's report. However, it is not clear whether the difference in body mass indices (BMIs) is related with the vancomycin CL overestimation because the BMIs in Rodvold's patients are not clarified in the report. When compared with measured GFR values, CLcr estimation formulae such as C-G, Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) showed reduced precision and greater bias at low and high extremes of GFR, although the direction of biases were not consistent [4-6].

Thirty-seven patients with varying renal function and age participated in Rodvold's study to develop the formula. About 1/3 of the patients were classified into a renal failure group (serum creatinine 2.1 ± 1.0 mg/dL, mean ± SD). In Jin's study, as many as 596 patients' data were used, but few renal failure patients were included. The patients' serum creatinine level ranged from 0.4 to 1.2 mg/dL (0.78 ± 0.19 mg/dL, mean ± SD). If the C-G equation had given overestimated CLcr for those in the lower extreme of GFR distribution (*i.e.*, renal failure patients) in

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Rodvold's report, the correlation slope may also have been biased. When such a biased regression formula is applied to non-renal impairment patients to predict vancomycin CL, it would also result in biased vancomycin CL, and thus, biased AUC.

With the Rodvold's formula found inappropriate for the prediction of vancomycin CL or AUC, aren't we allowed to predict individualized vancomycin doses without drug concentration at all? Now, we may switch ideas. Why don't we use our own data such as those used in Jin's report to develop a new correlation formula? Given the estimated CLcr values (C-G method) in Jin's data, we may exclude extreme values by using cut-off margins for non-extreme GFR, *i.e.*, 60 ≤ CLcr ≤ 120 mL/min. Then, with the non-extreme CLcr values and their corresponding vancomycin CL values (estimated from CAPCIL), we may obtain another regression formula like in Rodvold's report. Limitation of the new formula would be that the serum creatinine values used came from patients within the non-extreme range of renal function only. Nevertheless, the limitation may rather strengthen its reliability to predict extreme GFR values because the CLcr values from most biased zones (low and high extremes of GFR) were excluded from the regression process. Reliability of the new formula for the estimation of the low extreme GFR zone may be clarified using vancomycin TDM data in patients with varying degrees of renal failure. This may be a crude idea, but it seems worth trying with varying cut-off ranges of CLcr because all physicians prescribing vancomycin are not being helped by TDM services, yet.

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