Case Report

Severely Prolonged Vancomycin Half-life in a Patient with Normal Serum Creatinine and Creatinine Clearance

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Abstract

Vancomycin remains the antibiotic of choice to treat resistant Gram-positive infections and is dosed utilizing weight-based protocols or pharmacokinetic calculations. Pharmacokinetic calculations are a more proactive approach to vancomycin dosing but are occasionally limited as certain patient-specific variables such as volume of distribution, renal function, and severity of illness do not allow all patients to follow population estimates. In these situations, if the above-mentioned variables are adjusted for an individual patient rather than the population estimates, the kinetic models reflect accurate vancomycin dosing. We present a patient with apparently normal renal function (Cockcroft–Gault) following a significant renal injury who had sustained supratherapeutic vancomycin serum concentrations and a calculated peak elimination half-life of 346 h. Importantly, this patient had adequate clearance of other highly renally eliminated medications (digoxin and meropenem), which suggests limited long-term deficit due to the previous sustained renal injury. In this patient case, vancomycin's chemical properties and pharmacokinetics are explored to best explain the patient's highly unusual response. In addition, an analysis of vancomycin's less well-described pharmacokinetics such as active secretion, tubular reabsorption, and nonrenal elimination pathways is explored. Ultimately, this patient represents a perplexing case which highlights the continued need for therapeutic drug monitoring with vancomycin.

Keywords: Creatinine clearance, pharmacokinetics, therapeutic drug monitoring, vancomycin

Introduction

Vancomycin remains the antibiotic of choice against potentially resistant Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus*. Population pharmacokinetics and weight-based dosing strategies are frequently used for vancomycin administration.[1] Utilization of population pharmacokinetics provides a proactive approach as estimated therapeutic steady state serum concentrations are targeted to minimize the risk of supratherapeutic serum concentrations. Once a serum concentration is obtained, patient-specific pharmacokinetic calculations are completed to predict the effect of subsequent doses. As vancomycin is extensively renally cleared, patient's estimated creatinine clearance (CrCl) (Cockcroft–Gault Equation) is utilized in initial, and most follow-up, pharmacokinetic calculations.[2] We present a patient with apparently normal renal function based on serum laboratory values, estimated CrCl, and therapeutic drug monitoring of renally cleared medications, whose vancomycin excretion was severely impaired without explanation.

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Case Report

A 56-year-old, weighing 71.1 kg, Caucasian male presented to an outside hospital following acute altered mental status changes at his long-term rehabilitation facility. The patient had a medical history significant for a triple-vessel coronary artery bypass graft procedure at a separate outside facility 10 weeks before the current presentation, which was complicated by biventricular failure and ultimately required extracorporeal membrane oxygenation for 3 days. In addition, due to hemodynamic instability, the patient developed anuric acute kidney injury and required continuous venovenous hemodialysis for 8 days, followed by intermittent hemodialysis for 6 weeks at which point, renal recovery was achieved.

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Eight days after the current presentation at the outside hospital, a magnetic resonance imaging (MRI) scan of the brain was completed and it revealed a 1.9 cm × 1.2 cm × 2.5 cm abscess in the right frontal lobe. Neurosurgery was consulted and recommended medical management without any need for surgical intervention. The patient was initiated on vancomycin 1 g every 12 h, and a reported serum trough concentration from the outside hospital after 5 doses was 51.8 μg/mL. Vancomycin was held and the patient was transferred to our facility for further management. The patient's serum creatinine (SCr) and the timing of the reported vancomycin trough at the outside hospital were not provided in the transfer summary at presentation to our hospital.

Upon arrival at our facility, the infectious diseases' service was consulted for the management of the patient's brain abscess and the elevated vancomycin serum concentration. As there was no surgical intervention planned, and no microbiological data available, meropenem 1 g every 8h was administered over a 30-min infusion in addition to the patient's empiric antibiotic regimen. A summary of the patient's laboratory and dosing information throughout hospitalization is provided in Table 1.

Vancomycin was withheld at our facility, and random serum values were obtained to calculate patient-specific pharmacokinetics. All vancomycin serum concentrations at our facility were measured using the commercially available MULTIGENT vancomycin homogeneous particle-enhanced turbidimetric inhibition immunoassay with the ARCHITECT *c*Systems (Microgenics Corporation; Freemont, CA, USA). On day 15, the patient's calculated elimination rate constant (k_e) was 0.003/h with a corresponding vancomycin half-life of 231 h. Given the extended vancomycin half-life and difficult pharmacokinetics, as well as the poor central nervous system penetration of daptomycin and ceftaroline, the patient was transitioned to linezolid therapy on day 17. Fourteen days later, the patient experienced thrombocytopenia [Table 1], potentially due to linezolid therapy, and was transitioned back to vancomycin. Utilizing the patient's prior pharmacokinetic values, it was estimated that the patient had a serum vancomycin concentration of around 6.0 μg/mL at this time (day 31). A single 250 mg dose was administered on day 31 with a corresponding trough of 18.5 μg/mL obtained 22 h after the dose. On day 36, when the serum vancomycin value was 13.0 μg/mL, the patient's calculated elimination rate constant (k_e) was 0.002/h which resulted in a calculated vancomycin half-life of 346.5 h. A single 150 mg dose was administered and provided a therapeutic serum concentration to complete the patient's planned course.

As the patient's vancomycin clearance (VCl) was impaired, there was concern for the accumulation of other renally cleared medications. First, the patient was receiving digoxin, which is largely renally cleared and has known toxicities including altered mental status when elevated. Both of the patient's digoxin serum concentrations were subtherapeutic and the patient did not complain or show symptoms concerning

Table 1: Summary of patient antimicrobial course, laboratory values, and therapeutic drug monitoring

	Day 1	Day 3	Day 7	Day 14	Day 15	Day 16	Day 17	Day 21	Day 28	Day 29	Day 31	Day 32	Day 33	Day 35	Day 36	Day 37	Day 43
Vancomycin serum concentration (μg/mL)	51.8*	39.6	30.1	17.2	-	-	-	-	-	-	-	18.5	15.3	13.6	13	20.9	10.2
Vancomycin dose				Held				Discontinued			250 mg		Held		150 mg	Held	EOT
Creatinine (mg/dL)	-	1.17	1.2	0.9	-	0.85	-	0.95	0.9	-	-	-	-	-	0.98	-	1.19
CrCl (mL/min)^		67.9		99.0				98.1							95.1		78.3
Platelets (10^3/μL)	-	267	249	163	173	156		202	104	98	-	-	-	-	164	-	260
Linezolid dose				-				600 mg Q12H						Discontinued			
Digoxin serum concentration (ng/mL)#	-	0.46	0.77	-	-	-	-	-	-	-		-	-	-	-	-	-
Meropenem serum concentration (μg/mL)†	-	-	-	-	-	-	-	-	-	-		-	-	-	-	24	-

*Vancomycin serum concentration obtained from outside hospital, ^CrCl calculated utilizing the Cockcroft–Gault calculation (CrCl=[140−age] × IBW/[SCr × 72]), #Digoxin reference range: 0.8-2.0 ng/mL, †Meropenem reference range: 55-62 μg/mL per ARUP laboratories bioassay. EOT=End of therapy, CrCl=Creatinine clearance, ARUP=Associated Regional and University Pathologist, Inc., IBW=Ideal Body Weight, SCr=Serum creatinine

for toxicity. Second, the patient received intravenous meropenem 1 g every 8 h administered over 30 min infusions based on his Cockcroft–Gault-calculated CrCl. To ensure adequate meropenem clearance, a meropenem peak serum concentration was obtained through ARUP Laboratories (Test Code-0060855; Salt Lake City, UT). The meropenem peak serum concentration was obtained 30 min after completion of infusion per reference laboratory instruction. Our patient's meropenem serum concentration was ultimately found to be subtherapeutic with the peak being about 50% of the expected value [Table 1].

The patient underwent a repeat MRI on day 41 which demonstrated that the abscess decreased in size to 1.9 cm × 1.2 cm × 0.5 cm and antibiotics were stopped. A repeat MRI obtained approximately 1 month later revealed that the abscess had not changed. The patient remains alive and asymptomatic 11 months after being discharged.

Discussion

In attempting to explain our patient's response to vancomycin, many factors must be evaluated. While an error in the vancomycin assay represents a possibility, this is highly unlikely for the following reasons. First, the same assay was utilized for all other patients receiving vancomycin at our institution during the described time frame without any suspiciously erroneous results. Second, the calculated vancomycin doses administered utilizing pharmacokinetic values identified from the patient's measured serum concentrations (i.e., 250 mg and 150 mg doses) resulted in serum concentration changes as predicted. Next, an allergic or autoimmune responses could be considered to explain the patient's response; however, the patient never portrayed any symptoms of an IgE or IgG allergic response, and the renal laboratory values did not support either acute interstitial nephritis or glomerulonephritis. Therefore, the pharmacokinetic principles of absorption, distribution, metabolism, and excretion must be evaluated to possibly explain the observed vancomycin response. As vancomycin was administered intravenously, inadequate absorption does not account for our patient's observed abnormalities. Further, the metabolism of vancomycin does not explicate our patient's response as it is generally accepted that vancomycin does not undergo metabolism.[3]

In evaluating the distribution of vancomycin in our patient, it is important to note his critical illness about 60 days before admission to our hospital. In noncritically ill patients, vancomycin is best described by a 2- or 3-compartment pharmacokinetic profile with a volume of distribution (Vd) of 0.4–1 L/kg and protein binding of 10%–50%.[4,5] However, in critically ill patients, the Vd has been shown to be increased (1.53 L/kg) compared to noncritically ill patients.[6] Our patient's estimated Vd at the start of therapy was about 1.31 L/kg, suggesting that his critical prior critical illness may have been clinically relevant at presentation despite his discharge more than 8 weeks prior and being without any renal replacement therapy for more than 4 weeks. Further, towards the latter part of the patient's treatment course, the patient's estimated Vd was significantly reduced at 0.345 L/kg. While the resolution of critical illness may explain part of the decrease, it is unlikely to account for the observed 74% drop in Vd. Importantly, the patient's Vd does not adequately explain the low VCl, and in fact makes this case more perplexing as the two variables are normally proportionally related. It would be expected that the patient's initial VCl would be significantly increased with his approximated Vd of 1.31 L/kg; however, the patient's calculated K_e was similar at all time points. Ultimately, the observed changes in the patient's Vd do not adequately explain this patient's response alone.

A second distributive factor that must be considered is the protein binding of vancomycin. As previously stated, vancomycin protein binding ranges from 10% to 50%.[4,5] As the patient had an extended half-life, a significant increase in the vancomycin protein binding in our patient would have been necessary to explain the observed serum concentrations and decreased clearance. While the level of protein binding was not confirmed in our patient, this explanation alone is also unlikely as the patient's hepatic function was normal and his albumin was slightly decreased throughout his hospitalization (2.5–3.5 g/dL).

The next pharmacokinetic parameter that must be assessed is vancomycin elimination. Given that vancomycin is a large molecule (molecular weight, 1448 g/mol), elimination is extensively renal through glomerular filtration.[2,4] In fact, as much as 80%–90% of an administered vancomycin dose can be recovered unchanged from the urine at 24 h.[2,4] Due to the above, VCl has been highly correlated with CrCl and it is generally believed that the drug does not undergo appreciable amounts of nonrenal metabolism or excretion.[3] However, some early vancomycin pharmacokinetic studies describe variance in the ratio of VCl to CrCl.[7,8] For example, Nielsen *et al*. evaluated 14 patients with infections and varying degrees of renal function who were treated with vancomycin.[7] VCl correlated well with CrCl (r = 0.90), but the VCl:CrCl ratio was lower than the VCl:^{125}iothalamate clearance ratio control (0.59 ± 0.11 vs. 0.79 ± 0.11).[7] This suggests that the estimated CrCl may underestimate VCl compared to VCl as measured by glomerular filtration. This was observed in our patient as the estimated CrCl significantly underestimated the VCl (VCL:CrCL ratio 0.024 on day 23) to an extent not previously described in the literature. A later, single-dose study conducted in four healthy males further demonstrated variance among the VCl:CrCl ratio (0.59–0.75).[8] The authors concluded that the variance could be explained by tubular reabsorption or protein binding.[8] In addition, another analysis identified tubular secretion as a potentially significant route of vancomycin elimination.[9] Both tubular reabsorption and inhibition of tubular secretion could help explain the higher than expected serum concentrations in our patient; however, given the patient's VCl:CrCl ratio, the etiology for either mechanism to result in such profound effects is unclear.

Further, while these represent a possible mechanism, there have been few additional studies to confirm that tubular reabsorption or tubular secretion represents a major elimination pathway for vancomycin.

Finally, it is necessary to assess if the patient's calculated CrCl was falsely elevated. During the patient's clinical course, both digoxin and meropenem serum concentrations were obtained for therapeutic drug monitoring and to help assess calculated CrCl. Digoxin is smaller than vancomycin (molecular weight 781 g/mol), and it undergoes significant renal elimination via glomerular filtration and active tubular secretion; about 75% of an administered dose can be recovered in the urine with the remainder undergoing hepatic metabolism and biliary elimination.[10] The patient presented received 0.125 mg of digoxin by mouth daily and had been receiving this dose for at least 14 days before transfer to our facility; the patient's digoxin serum concentration peaked at 0.77 ng/mL while his vancomycin serum concentration remained elevated at 30.1 mg/mL. Meropenem is even smaller than digoxin (molecular weight 383 g/mol) and undergoes both renal metabolism and excretion with up to 98% of a dose recovered in the urine (about 70% unchanged and 28% as inactive metabolite).[11] In addition to glomerular filtration, it is known that meropenem is actively secreted into the tubules of the kidney.[12] A meropenem serum concentration was obtained for our patient and was lower than expected. These results contradict the potential explanation of decreased glomerular filtration or tubular secretion explored above, unless the molecular size of vancomycin significantly altered one of its elimination parameters.

In this perplexing patient with normal measured SCr and CrCl values, it is difficult to determine a single explanation to best describe the observed therapeutic concentrations of vancomycin maintained for approximately 2 weeks after the last dose was administered. The observed 74% decrease in the patient's Vd only further adds complexity as unusually small doses resulted in therapeutic serum concentrations. These authors believe that the answer is multifactorial, involving many of the pharmacokinetic parameters discussed above, and ultimately may be related to some alteration in a less well-described, nonrenal elimination pathway of vancomycin. It is very possible that the size of the vancomycin molecule contributed as both meropenem and digoxin were appropriately cleared and are both smaller molecules than vancomycin. Ultimately, this is a cautionary tale of how different each patient's pharmacokinetics can be, and how crucial vancomycin serum concentration monitoring remains in clinical practice.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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