

CASE REPORT

Vancomycin and Gentamicin Pharmacokinetic Alterations in an Adolescent Amputee

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A 14-year-old male with bilateral above-the-knee amputations presented to our hospital for treatment of a skin and soft-tissue infection. We report the experience of vancomycin and gentamicin therapy in this patient. Because these medications require weight-based dosages and pharmacokinetic monitoring of serum levels, it was necessary to obtain peak and trough levels of the two drugs in order to determine the pharmacokinetic differences in this patient compared to those in an adolescent male without amputations. To our knowledge, this is the first report describing pharmacokinetic differences in an adolescent amputee.

INDEX TERMS adolescent, amputee, gentamicin, pharmacokinetics, vancomycin

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INTRODUCTION

Vancomycin and aminoglycoside dosages in children can be challenging because of developmental pharmacologic changes and pharmacokinetic differences observed in children compared to those in adults.¹ While generally uncommon, pediatric amputees represent a population for which, to our knowledge, no published reports describe pharmacokinetic alterations or provide specific dosing recommendations. We report pharmacokinetic alterations observed with vancomycin and gentamicin in an adolescent amputee and discuss considerations for pharmacists.

CASE REPORT

A 14-year-old (46.4 kg, 135 cm) Caucasian male presented to the hospital with redness, swelling, and serosanguinous drainage from the second digit on his left hand 3 days after sustaining an injury. It was reported that swelling and redness spread to the dorsal portion of the finger 2 days after the incident. The patient has a medical history significant for attention deficit hyperactivity disorder, bipolar disorder, congenital insensitiv-

ity to pain, and bilateral above-the-knee amputations (AKA; left lower extremity in 2006 and right lower extremity in 2008) because of recurrent lower extremity infections.

Upon hospital admission, vancomycin, 690 mg (15 mg/kg/dose) intravenous (IV) every 8 hours; clindamycin, 460 mg (10 mg/kg/dose) IV every 8 hours; and gentamicin, 140 mg (3 mg/kg/dose) IV every 24 hours were empirically initiated for activity against methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA, respectively) infection and group A *Streptococcus* spp infection. Blood and wound cultures were obtained on the day of admission and prior to antibacterial initiation. The wound culture subsequently grew MRSA and *Streptococcus pyogenes*, while the blood culture revealed *Streptococcus pyogenes* (susceptibility tests were not performed secondary to the rare occurrence of antimicrobial resistance in this organism). The vancomycin minimum inhibitory concentration for the MRSA was ≤ 0.5 mg/L. The patient's serum creatinine (SCr) concentration upon antibiotic initiation was within the institution's normal limits for the patient's age at 0.53 mg/dL.

Due to the amputation history and potential

Table. Calculated Pharmacokinetic Parameters and Monitoring

Parameter	Vancomycin	Gentamicin
Dosage	690 mg every 8 hr	140 mg every 24 hr
mg/kg/dose	15 mg/kg/dose	3 mg/kg/dose
Dose at which concentrations were obtained	Fifth	Second
Peak serum concentration (corrected)	43.2 (49.2) mg/L	10.8 mg/L
Time to peak obtained in relation to dose	30 min after 2-hr infusion	1 hr after 30-min infusion
Trough serum concentration (corrected)	8.4 (10.2) mg/L	< 0.5 mg/L
Time to trough obtained in relation to dose	8 hr and 45 min after last dose	23 hr and 40 min after last dose
Rate of elimination (K_e)	0.262 hr ⁻¹	*
V_d (L/kg)	0.27 L/kg	0.28 L/kg
Elimination half-life	2.6 hr	*

Ke, eliminate rate; Vd, volume of distribution

*Could not be accurately calculated as serum concentration values were below the lower limit of detectability.

for altered pharmacokinetic parameters, trough and peak concentrations of both vancomycin and gentamicin were obtained. It was suspected that the patient might have had an altered volume of distribution (V_d) for each drug and that his SCr concentration might not have adequately reflected drug clearance due to his limited mobility and lean adipose tissue. Concentrations and calculated parameters are described in the Table. Gentamicin pharmacokinetic parameters could not be completely calculated due to the reported trough concentration of less than 0.5 mg/L, which is the lower limit of detection at our institution's laboratory.

After final organism identification and susceptibility testing, gentamicin was discontinued. The vancomycin dose was increased to 750 mg every 8 hours to target a goal trough serum concentration of 10 to 15 mg/L. The patient received a total of 10 days of antibiotic therapy, including clindamycin monotherapy (450 mg IV every 6 hours) for the final 3.5 hospital days. Blood cultures were consistently negative after the original positive culture on the day of admission.

DISCUSSION

Limited pharmacokinetic data available for the amputee population makes drug dosages a significant challenge. Specifically, current literature on vancomycin or aminoglycoside dosages in pediatric amputees is not available. While there are a small number of resources available for determining body surface area and preamputa-

tion body weight in adults with lower limb amputations, there is currently no correlation to the pediatric population.^{2,3} The 14-year-old patient in this case report represented a unique dosage challenge because of general pharmacokinetic differences that can be observed in children and adolescents in addition to potential distribution volume alterations related to his amputations.

Actual body weight is used to calculate aminoglycoside doses for pediatric patients, unless the patient weighs more than 125% of their ideal body weight (IBW), in which case a dosing weight is recommended based on standard adult practice.⁴ Actual body weight is also used for vancomycin dosages.⁵ Our patient weighed 46.4 kg, reflecting a normal weight for a typical 14-year-old male. His amputation status made calculation of his true IBW and ultimately drug dosage difficult. Furthermore, a method for determining the adjusted or dosage weight for aminoglycosides in pediatric amputees is not available. As pharmacists, it is imperative to thoroughly review each patient's medical records for pertinent history and physical examination findings and even to visualize each patient in whom vancomycin or aminoglycosides is to be administered. Important insights can be gained by observing the patient.

Each of the drug serum concentrations were obtained to determine drug clearance and volume of distribution and to determine whether efficacy and safety concentration targets were met. The gentamicin peak serum concentration was higher than necessary for synergy (3 to 5

mg/L is our institution standard).⁶ We posit that the elevated concentration was caused by a slightly decreased V_d value resulting from the amputations, relative to those of normal pediatric levels.⁷ The true volume of distribution is likely slightly lower than the calculated value of 0.28 L/kg, as the serum concentration was obtained 1 full hour (compared to 30 minutes) following the end of a 30-minute infusion. The “peak” serum concentration may also be higher than expected because the patient was given a 3 mg/kg/dose based on his actual rather than an adjusted weight. While renal dysfunction would not be expected in an otherwise normal adolescent with bilateral AKA, SCr level may not be the most useful indication of renal function because of decreased muscle mass and mobility. The patient’s undetectable gentamicin trough serum concentration suggested adequate renal gentamicin clearance.

This patient’s therapy was initiated with 15 mg/kg of vancomycin every 8 hours, which is an appropriate empirical dose for a 14-year-old patient with normal renal function. The subsequent peak serum concentration was higher than anticipated given the dose administered and was most likely due to a calculated vancomycin V_d of 0.27 L/kg, which is lower than that expected for an adolescent. Typical “normal” values originate mostly from younger patients with a mean age of 7 years.⁸ Reported pediatric vancomycin V_d values range from 0.43 L/kg to 0.63 L/kg.^{8–10} It is difficult to determine whether the low V_d value in our patient was caused by normal variation or was secondary to the amputation, and unfortunately, no values for adult amputees could be found in the literature. Although the vancomycin trough serum concentration was not drawn at the correct time, the patient’s calculated true trough serum concentration of 10.2 mg/L was close to the recommended minimum value of 10 mg/L.¹¹ However, to ensure a trough concentration within a target range of 10 to 15 mg/L, the dose was increased. Further concentrations were not obtained as it could be reasonably expected that the change in dose would result in trough concentration within the target range.

The cost of serum concentrations should be a consideration when caring for unique patients. At our institution, patients are charged approximately \$150 for each serum concentration. While peak vancomycin concentrations are generally

not advocated because of the lack of correlation with efficacy, it was justified in this case in order to determine patient-specific pharmacokinetic parameters.¹¹ A peak gentamicin concentration was also obtained to determine pharmacokinetic parameters. In an otherwise healthy child, neither the vancomycin nor the gentamicin peak concentrations would have been obtained at our institution. It was believed that the benefit of using peak concentrations to calculate pharmacokinetic parameters in our adolescent amputee outweighed the additional charge.

CONCLUSIONS

This case report is the first to describe serum concentrations and pharmacokinetic alterations with vancomycin or aminoglycosides in an adolescent amputee and offers a reminder to pharmacists practicing with unique patient populations. While population pharmacokinetic data and medical guidelines aid in optimal vancomycin and gentamicin drug doses in a relatively robust group of patients, those cannot replace the evaluative process pharmacists must consistently perform to adequately ensure optimal doses in all populations. Pharmacists must work to find a balance between evidence-based guidelines or standards of care and the need to use serum drug monitoring to optimize drug efficacy and safety.

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ABBREVIATIONS AKA, above the knee amputation; IBW, ideal body weight; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SCr, serum creatinine; SD, standard deviation; V_d , volume of distribution

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REFERENCES

1. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology: drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349(12):1157-1167.

2. Colangelo PM, Welch DW, Rich DS, et al. Two methods for estimating body surface area in adult amputees. *Am J Hosp Pharm.* 1984;41(12):2650-2655.
3. Mozumdar A, Roy SK. Method for estimating body weight in persons with lower-limb amputation and its implication for their nutritional assessment. *Am J Clin Nutr.* 2004;80(4):868-875.
4. Kendrick JG, Carr RR, Ensom MHH. Pharmacokinetics and drug dosing in obese children. *J Pediatr Pharmacol Ther.* 2010; 15(2):94-109.
5. Moffett BS, Kim S, Edwards MS. Vancomycin dosing in obese pediatric patients. *Clin Pediatr.* 2011; 50(5):442-446.
6. Matsumoto JY, Wilson WR, Wright AJ, et al. Synergy of penicillin and decreasing concentrations of aminoglycosides against enterococci from patients with infective endocarditis. *Antimicrob Agents Chemother.* 1980;18(6):944-947.
7. Murphy JE, Matthias KR. Aminoglycosides. In: Murphy JE ed. *Clinical Pharmacokinetics.* 5th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2012:91-118.
8. Wrishko RE, Levine M, Khoo D, et al. Vancomycin pharmacokinetics and Bayesian estimation in pediatric patients. *Ther Drug Monit.* 2000;22(5):522-531.
9. Lamarre P, Lebel D, Ducharme MP. A population pharmacokinetic model for vancomycin in pediatric patients and its predictive value in a naïve population. *Antimicrob Agents Chemother.* 2000;44(2):278-282.
10. Rodvold KA, Everett JA, Pryka RD, Kraus DM. Pharmacokinetics and administration regimens of vancomycin in neonates, infants, and children. *Clin Pharmacokinet.* 1997;33(1):32-51.
11. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm.* 2009;66(10):82-98.