Comparison of Vancomycin Pharmacokinetics in Cystic Fibrosis Patients Pre and Post-lung Transplant

Shannon White[1] , Colleen Sakon[1], Linda Fitzgerald[2], Charissa Kam[3], Erin McDade[3] and Alanna Wong[4]

[1]Pharmacy Department, IU Health University Hospital, Indianapolis, IN, USA. [2]Pharmacy Department, Michigan Medicine, University of Michigan Health System, Ann Arbor, MI, USA. [3]Pharmacy Department, Texas Children's Hospital, Houston, TX, USA. [4]Pharmacy Department, Boston Children's Hospital, Boston, MA, USA.

ABSTRACT

BACKGROUND: Vancomycin is commonly used to treat acute cystic fibrosis (CF) exacerbations associated with methicillin-resistant *Staphylococcus aureus* (MRSA). Multiple studies have demonstrated pharmacokinetic differences of antimicrobials in the CF population. Very little data exist regarding pharmacokinetics postlung transplant, but 2 studies have noted changes in tobramycin pharmacokinetics. No such studies exist evaluating vancomycin in CF patients postlung transplant.

METHODS: A retrospective cohort review of CF patients who underwent lung transplantation and received vancomycin pre- and posttransplant was conducted. CF patients who underwent transplant between 2007 and 2016 at 4 medical centers throughout the United States were included. The primary endpoint was the change in elimination rate constant. The secondary endpoints were subgroup analyses of patients grouped by age, time posttransplant, and number of nephrotoxic medications.

RESULTS: A total of 25 patients were included, of which just under half were pediatric. Patients were significantly older and heavier posttransplant and had higher serum creatinine and number of nephrotoxic medications. The change in elimination rate constant from pre- to posttransplant was $-0.50\,hr^{-1}$ which was statistically significant ($P < .001$). This significant decrease was consistent among all subgroups of patients evaluated with the exception of pediatric patients.

CONCLUSION: Vancomycin pharmacokinetics are significantly altered in CF patients in the posttransplant setting as evidenced by a decrease in elimination rate constant. This decrease may be related to a decrease in renal clearance and higher numbers of nephrotoxic medications posttransplant. Regardless, pretransplant vancomycin regimens may not predict appropriate posttransplant regimens.

KEYWORDS: Cystic fibrosis, vancomycin, pharmacokinetics, transplant, drug monitoring

Background

Cystic fibrosis (CF) is a genetically inherited disease in which the activity of cystic fibrosis transmembrane conductance regulator (CFTR) is reduced or diminished, leading to mucus secretion and subsequent accumulation in the lungs. This buildup of mucus in the lungs eventually leads to bacterial infections due to colonization of the mucus. *Staphylococcus aureus* is one of the most common colonizing organisms of mucus; it is the most frequently cultured isolate from pediatric CF patients, and remains an important pathogen throughout adulthood, second only to *Pseudomonas aeruginosa*.[1-3] A previous report from the Cystic Fibrosis Foundation Patient registry estimated that just under one-quarter of all patients with CF are infected with methicillin-resistant *Staphylococcus aureus* (MRSA).[1-3] In general, systemic antimicrobials are required to treat acute CF exacerbations, and vancomycin is the intravenous (IV) agent most commonly used for the treatment of MRSA in both adult and pediatric patients.[2-5] Multiple organizations and clinical practice guidelines have emphasized the importance of appropriate vancomycin dosing and management, and an understanding of pharmacokinetics is vital for appropriate management of vancomycin.[6,7] Previous studies have investigated the differences in pharmacokinetics of vancomycin in CF patients compared with patients without CF, which have found conflicting evidence.[5-7]

In addition, several new treatments for pulmonary infections related to CF have been approved in the past few decades, and life expectancy has increased, likely related to these new treatments. There is still no cure for CF, and lung transplant remains a viable treatment for patients with end-stage lung disease and may be associated with prolonged survival.[3] Solid organ transplantation alone creates a complicated scenario for clinicians, but lung transplant in addition to CF creates several additional challenges. One of those challenges is understanding the pharmacokinetics of antimicrobial agents in these patients, which are not fully understood even prior to lung transplant.

Prior to this study, only 2 studies have investigated the pharmacokinetics of any antimicrobial agent in CF patients both pre- and postlung transplant, and both studies evaluated tobramycin. The first study, published in 1999 by Dupuis and colleagues, evaluated tobramycin pharmacokinetics in 29 patients

and ultimately found a lower elimination rate constant (Ke), a longer half-life ($t_{1/2}$), and a larger volume of distribution (Vd) posttransplant compared with pretransplant.[8] These results conflict with newer evidence from a study published in 2011 by Walsh and colleagues, which retrospectively evaluated 69 patient encounters (8 patients in total) and found a significantly lower tobramycin Ke but no difference in Vd posttransplant compared with pretransplant.[9] There were more nephrotoxic medications used concurrently in the posttransplant setting, but this did not result in a significant difference in renal function or estimated creatinine clearance. Thus, nephrotoxic medications alone could not explain the change in tobramycin Ke.

To date, no similar studies have been done evaluating vancomycin in the posttransplant setting. This remains an important clinical question due to the high infection risk in these patients related to persistent CF infections and also new-onset immunosuppression.

Methods

The objective of this study was to compare the pharmacokinetics of vancomycin in CF patients pre- and posttransplant. This was a retrospective, cohort review of patients with CF who received a lung transplant between January 1, 2007, and December 30, 2016, at Indiana University Health, University of Michigan Hospital, Texas Children's Hospital, and Boston Children's Hospital. This study was granted Institutional Review Board (IRB) exemption by the Indiana University Health IRB Committee (Protocol No. 171059723). To be included, patients must have received vancomycin within 2 years prior to transplant, received vancomycin within 1 year after transplant, have at least one vancomycin level both pre- and posttransplant, and have documented administration and collection times. Vancomycin levels must have been troughs, which was defined as being drawn within 1 hour of the next time of vancomycin administration, and must have been drawn at steady state, which was defined as having received at least 3 doses. Each patient's pretransplant data were assessed based on the most recent vancomycin course immediately prior to transplant, and each patient's posttransplant data were assessed based on the first vancomycin course after transplant that was 30 days to 1-year posttransplant. Patients were excluded if they did not have a documented serum creatinine prior to and within 48 hours after vancomycin initiation.

The primary endpoint for this study was vancomycin elimination rate constant (Ke), which was calculated using equation (1). Volume of distribution was included in the Ke calculation, and a value of 0.57 liters per kg of actual body weight was used based on previous pharmacokinetic studies in adult and pediatric CF patients.[3,10] Elimination rate constants were also used to calculate vancomycin $t_{1/2}$. Secondary endpoints were comparisons of subgroups of patients with potential factors that may affect vancomycin Ke. Patients were compared based on age at the time of transplant (⩽18 vs >18 years), number of months

posttransplant (<6 months vs ⩾6 months posttransplant), and change in number of nephrotoxic medications posttransplant (⩽1 additional nephrotoxic medication vs >1 additional nephrotoxic medication). Nephrotoxic medications evaluated were based on package inserts and reflected those used in similar, previous studies. These included IV aminoglycosides, IV colistin, piperacillin/tazobactam, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs), tacrolimus, trimethoprim/sulfamethoxazole, and valganciclovir or ganciclovir. Concurrent administration was defined as at least one overlapping dose with the course of vancomycin. Vancomycin was administered over at least 1 hour.

$$Ke = \frac{-\ln\left[\frac{(C_{tr})(Vd)}{Dose}\right] \div \left[\frac{1+(C_{tr})(Vd)}{Dose\ n}\right]}{Time}, \quad (1)$$

where trough concentration (C_{tr}) = drawn vancomycin blood concentration (mg/L); volume of distribution (Vd) = 0.57 × actual body weight (L); time = time from start of infusion to time of level drawn (hr); half-life ($t_{1/2}$) = ln(2)/Ke.

To achieve a power of 80% and an α of 0.05, at least 18 patients needed to be included based on an estimated Ke difference of 0.07 hr^{-1}. This estimate was used based on the Ke reported in adult CF patients in the study by Pleasants et al and reported Ke estimates of healthy adult patients. Continuous data were evaluated using Wilcoxon rank-sum test or paired t test, and categorical data were evaluated using Mann-Whitney *U* test.

Results

A total of 25 patients were included, and a summary of baseline characteristics is shown in Table 1. Of the 25 patients, 11 were younger than 18 years of age. The average age of pediatric patients included was 13 years which ranged from 8 to 18 years. Forty-four percent of patients included were male. In the posttransplant setting, patients were significantly older (18 vs 19 years; *P* < .001) and heavier (44 vs 48 kg; *P* = .021). Posttransplant patients also had a significantly higher serum creatinine (0.40 mg/dL vs 0.60 mg/dL; *P* < .001) and were on a higher number of concurrent nephrotoxic medications with vancomycin (1 vs 2; *P* < .001). A breakdown of nephrotoxic medications is shown in Table 2. In the pretransplant setting, 36% and 16% of patients concomitantly received an IV aminoglycoside and IV colistin while on vancomycin. In the posttransplant setting, 96% concurrently received tacrolimus, 68% received trimethoprim/sulfamethoxazole, and 56% received valganciclovir or ganciclovir.

The change in elimination rate constant from pre- to posttransplant was −0.05 hr^{-1} (*P* < .001). This decrease demonstrates a significantly slower rate of clearance in the posttransplant setting compared with pretransplant. With regard to secondary endpoints, the change in Ke in adult patients was −0.06 hr^{-1} (*P* = .002) compared with −0.03 hr^{-1} in

Table 1. Baseline characteristics of patients pre- and posttransplant.

	PRETRANSPLANT	POSTTRANSPLANT	*P* VALUE
Male gender	44%		–
Age, years[a]	18 (15-26)	19 (17-26)	<.001
Weight, kg[b]	44 (13)	48 (14)	.021
Serum creatinine, mg/dL[a]	0.40 (0.29-0.60)	0.60 (0.40-0.93)	<.001
Number of nephrotoxic medications[a]	1 (0-1)	2 (2-3)	<.001

[a]Median (interquartile range).
[b]Mean (SD).

Table 2. Summary of nephrotoxic medications pre- and posttransplant.

	PRETRANSPLANT N (%)	POSTTRANSPLANT N (%)
IV aminoglycoside	9 (36)	1 (4)
IV colistin	4 (16)	0 (0)
Piperacillin/ tazobactam	2 (8)	5 (20)
NSAID	2 (8)	0 (0)
Tacrolimus	0 (0)	24 (96)
Trimethoprim/ sulfamethoxazole	2 (8)	17 (68)
Valganciclovir or ganciclovir	0 (0)	14 (56)

Abbreviations: IV, intravenous; NSAID, nonsteroidal anti-inflammatory drugs.

Table 3. Summary of changes in elimination rate constant from pre- to posttransplant.

	CHANGE IN K_E (hr⁻¹)	*P* VALUE
All patients	−0.05	<.001
Secondary endpoints by age at the time of transplant		
≤18 years (n = 13)	−0.03	.06
>18 years (n = 12)	−0.06	.002
Secondary endpoints by number of months posttransplant		
<6 months posttransplant (n = 14)	−0.05	.003
≥6 months posttransplant (n = 11)	−0.06	.02
Secondary endpoints by change in number of concurrent nephrotoxic medications		
≤1 nephrotoxic change (n = 12)	−0.06	.004
>1 nephrotoxic change (n = 13)	−0.04	.02

Data reported as medians.

pediatric patients (*P* = .06). Although the change in pediatric patients was not statistically significant, it should be noted that subgroups were not powered to detect a difference. Furthermore, the decreases in elimination rate constant of pediatric and adult patients were not significantly different (*P* = .06). The change in eliminate rate constant in patients less than 6 months posttransplant was −0.05 hr⁻¹ (*P* = .003) compared with −0.06 hr⁻¹ in patients 6 months or more posttransplant (*P* = .02). Again, the decreases were not significantly different when compared (*P* = .40). Finally, the change in elimination rate constant of patients whose number of nephrotoxic medications increased by 0 or 1 posttransplant was −0.06 hr⁻¹ (*P* = .004) compared with −0.06 hr⁻¹ in patients whose number of nephrotoxic medications increased by more than one (*P* = .02). Again, the decreases were not significantly different (*P* = .43). These results are summarized in Table 3.

Vancomycin $t_{1/2}$ in pre- and posttransplant patients reflected the changes in elimination rate constants. Half-life in pretransplant patients was 3.7 hours compared with 5.5 hours posttransplant (*P* < .001). Similarly, half-life was significantly longer in the posttransplant setting in all adult subgroups of

patients, although subgroups were not powered to detect a difference. These results are summarized in Table 4.

Conclusion

Previous studies have found that CF patients have unique pharmacokinetic profiles of multiple antimicrobial agents that are unlike those of non-CF patients. Prior to this study, only tobramycin had been studied in CF patients comparing pre- and postlung transplant pharmacokinetics. The most recent of these studies from 2011 demonstrated a decreased rate of tobramycin clearance in posttransplant patients. Results from this study evaluating vancomycin also demonstrated a decreased rate of clearance in the posttransplant setting. Our study was also similar with regard to the number of nephrotoxic medications used concurrently with vancomycin; Compared with pretransplant patients, posttransplant patients were consistently on a higher number of nephrotoxic medications—most commonly

Table 4. Summary of vancomycin half-life in pre- and posttransplant patients.

	PRETRANSPLANT $T_{1/2}$ (H)	POSTTRANSPLANT $T_{1/2}$ (H)	P VALUE
All patients	3.7	5.5	<.001
Compared by age at the time of transplant			
≤18 years (n = 13)	3.0	4.0	.06
>18 years (n = 12)	4.3	6.3	.001
Compared by number of months posttransplant			
<6 months post-transplant (n = 14)	3.6	5.7	.001
≥6 months post-transplant (n = 11)	4.0	5.0	.01
Compared by change in number of concurrent nephrotoxic medications			
≤1 nephrotoxic change (n = 12)	3.9	5.8	.03
>1 nephrotoxic change (n = 13)	3.6	4.0	.02

Data reported as medians.

tacrolimus, trimethoprim/sulfamethoxazole, and valganciclovir. However, in the tobramycin study, the higher number of nephrotoxic medications posttransplant did not result in a slower estimated creatinine clearance. In this study, posttransplant serum creatinine was significantly higher, resulting in decreased estimated creatinine clearance. Therefore, the pharmacokinetic changes of vancomycin were likely due, at least in part, to changes in renal function.

Regardless, these results are important clinical findings. The decrease in Ke and thus the increase in half-life were consistent among all patient populations, with the exception of pediatric patients. This finding was likely incidental as there was no difference in the elimination rate constant changes between pediatric and adult patients, and this study was not powered to see statistically significant changes in these smaller subsets of patients. Time posttransplant did not have an effect on the decrease in Ke, although only patients who received vancomycin within 1 year posttransplant were eligible for inclusion, so these results may not be applicable to patients further out than 1 year from transplant. In addition, patients whose number of nephrotoxic medications increased by only 0 or 1 in the posttransplant setting still demonstrated a significant decrease in Ke, which was not significantly different from the decrease demonstrated by patients whose number increased by 2 or more. This may be due to the fact that nephrotoxic medications evaluated are not all associated with the same degree of nephrotoxicity. Furthermore, the number of concurrent nephrotoxic medication doses was not assessed.

Major strengths of this study include its multicenter study design, standardization of pharmacokinetic calculations, and the inclusion of both pediatric and adult CF patients. Major limitations also exist. Patients were included over a 10-year range to increase sample size. Several changes have been made with regard to pre- and posttransplant care over the past 10 years, most notably aminoglycoside dosing frequency and

posttransplant immunosuppressive agents. In addition, there are differences in pre- and posttransplant care from center to center; one of the most important differences in this study is vancomycin infusion time. There are also significant variations in pharmacokinetics of antimicrobial agents, including vancomycin, as a pediatric patient ages. This study did not include any pediatric patients below the age of 8, so these results cannot be generalized to all pediatric patients. Finally, single levels were used to assess vancomycin pharmacokinetics pre- and post-transplant, and while one-level pharmacokinetics are commonly used to evaluate vancomycin, it is not the most accurate way to determine pharmacokinetics as some population pharmacokinetic information is still used.

In summary, this study demonstrates a significantly lower rate of clearance of vancomycin in CF patients postlung transplant. Thus, vancomycin regimens that were deemed to be appropriate and therapeutic in the pretransplant setting may not predict appropriate posttransplant regimens. Therapy should be individualized, and pharmacokinetic parameters should be reassessed on each admission.

Author Contributions
Study conception and design: SW, CS; Acquisition of data: SW, LF, CK, EM, AW; Analysis and interpretation of data: SW, CS; Drafting of manuscript: SW; Critical revision: CS

ORCID iD
Shannon White https://orcid.org/0000-0003-0887-8750

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