CLINICAL INVESTIGATION

A Prospective Pilot Study on the Systemic Absorption of Oral Vancomycin in Children With Colitis

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BACKGROUND: Oral vancomycin is used to treat refractory colitis due to *Clostridium difficile* infection. Traditionally, oral vancomycin was thought to not be absorbed systemically, but recent adult studies have demonstrated detectable serum levels in over half of patients with severe colitis. This has not been studied in children.

OBJECTIVE: To determine the absorption of oral vancomycin and the renal safety profile of oral vancomycin in children hospitalized with colitis.

METHODS: We performed a prospective, observational, pilot proof of principle study at the North Carolina Children's Hospital in patients 2 years to 18 years of age receiving oral vancomycin for the treatment of *C difficile* colitis. Severity of disease was determined using a validated scoring system. Serial serum vancomycin levels and renal function tests were performed during the administration of oral vancomycin.

RESULTS: All patients enrolled (n = 8) had mild to moderate *C difficile* colitis and varying severity of underlying systemic diseases; 7 with inflammatory bowel disease and 1 with acute kidney injury following renal transplantation. No enrolled patients had detectable levels of serum vancomycin. Additionally, no adverse renal outcomes were attributed to oral vancomycin, and no cases of "Red Man" syndrome were observed.

CONCLUSIONS: Unlike studies in adult patients, oral vancomycin is likely not absorbed in children with mild to moderate colitis. Further study is needed to determine the pharmacokinetics in severe colitis and those with severe illness in a critical care setting.

INDEX TERMS: *C difficile* colitis, oral vancomycin, pediatric pharmacology, pharmacokinetics

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INTRODUCTION

Clostridium difficile colitis is a common condition in children, with over 17,000 pediatric cases per year in the United States.¹ The incidence of disease increased over time, and there has been a 75% and 53% increase in the incidence of community-acquired and hospital-acquired disease, respectively, in the pediatric population since the 1990s.^{2,4} The highest incidence of disease in children occurs in those 1 to 5 years old and in patients with chronic medical conditions.³ *C difficile* colitis is also a common hospital condition, and the incidence of severe and fatal infection has increased in recent years.

Unfortunately, almost 25% of patients have disease recurrence after initial treatment.⁵ The effectiveness of antibiotic therapy for a first recurrence remains approximately 60% and a second recurrence occurs in 35% of patients.^{5,6} Per the current Infectious Diseases Society of America (IDSA) and American Academy of Pediatrics (AAP) guidelines, oral vancomycin is the first-line treatment of refractory and severe infectious colitis.^{7,8} Intravenous vancomycin is known to cause proximal tubule damage in the kidneys; however, oral vancomycin is believed to be a safe treatment even for those with renal disease.⁹

Several studies suggest that oral vancomycin is not absorbed in healthy individuals and those

with mild colitis.¹⁰⁻¹² However, recent reports in adult¹³⁻²⁰ and pediatric^{15,21} patients have demonstrated absorption from the gastrointestinal tract in those with moderate or severe colitis. In some cases, vancomycin serum levels were sufficient to cause renal damage and even renal failure.^{19,21} One recent prospective study suggests that up to 68.3% of adult patients with severe *C difficile* colitis have detectable vancomycin blood levels.²² To date, there are no prospective trials studying enteral absorption of vancomycin in children with *C difficile* colitis. To fill this void, we initiated a study to prospectively evaluate the systemic absorption of oral vancomycin and better understand the pharmacology of enteral administration of vancomycin in children with colitis.

METHODS

Study Design and Data Collection

We performed a prospective, observational study at the North Carolina Children's Hospital in hospitalized patients 2 years to 18 years of age receiving oral vancomycin for the treatment of *C difficile* colitis from July 1, 2013, through March 1, 2015. Exclusion criteria included intravenous vancomycin administration during the preceding 7 days to enrollment and concurrent intravenous vancomycin administration. Severity of the colitis was determined using a modified risk stratification scoring system, criteria incorporating fever, leukocytosis, hypoalbuminemia, and imaging results on day of enrollment.^{8,23} This scoring system was validated utilizing 150 adult patients with *C difficile* colitis and cited as the primary study in the IDSA guidelines for recommending vancomycin for severe *C difficile* colitis.^{7,8} Patients with > 2 points will be considered to have severe disease. One point was given for temperature > 38.3°C, albumin level < 2.5 mg/dL, or peripheral white blood cell count 115,000 cells/mm³ within 48 hours of enrollment. Two points were given for endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit.

The choice of antibiotic therapy and dose and frequency of vancomycin were determined by the clinical team. Serum vancomycin, blood urea nitrogen, and creatinine levels were performed with every clinically indicated blood draw while the patient was hospitalized and receiving oral vancomycin.

Table. Patient Demographics (n = 8)

Age, mean (range)	13 (8-17)
Sex, female	6 (75%)
Race/ethnicity	
Caucasian	5 (63%)
African American	2 (25%)
Hispanic	1 (13%)
Days on study, mean (range)	4 (1-5)
Disease characteristics	
Previously treated	2 (25%)
Concurrent metronidazole	3 (38%)
Antibiotic-induced	None
Positive <i>C difficile</i>	7 (88%)
Severe <i>C difficile</i> colitis	None
Fever on enrollment	4 (50%)
Mean days of illness (range)	10.3 (0-40)
Previous GI surgery	1 (13%)
Underlying diagnoses	
Ulcerative colitis	3
CMV colitis	1
Renal transplant	1
Wilm's tumor	1
Central line infection	1
None	1
Dosing frequency	
Three times a day	2
Four times a day	6

CMV, cytomegalovirus; GI, gastrointestinal

The study was approved by the University of North Carolina Institutional Review Board.

RESULTS

Study Subjects and Demographics

A total of 8 patients were consented and enrolled in the study. Mean age was 13 years (range, 8-17 years) on admission, and there was a female and Caucasian predominance (75% and 63% of patients, respectively; Table). All but 1 patient had an underlying condition predisposing them to *C difficile* infection, with the most common underlying condition being ulcerative colitis.²⁴

There was a wide variation in disease characteristics and presentation. All but 1 patient had a new positive *C difficile* toxin identification dur-

Figure 1. Laboratory value on day of enrollment.

ing that admission, while the remaining patient was treated for disease recurrence. Mean days of symptoms at diagnosis was 10.3 (range, 0-40 days), and 50% of patients had fever on admission. Two cases were previously treated with metronidazole (1 for disease for recurrence and the other for progression of symptoms on metronidazole), while 6 cases used oral vancomycin as their initial treatment of choice. The reasons for initially treating with vancomycin included history of *C difficile* infection and provider preference of oral vancomycin over metronidazole. Two patients were treated concurrently with both oral vancomycin and metronidazole.

Baseline laboratory values on admission are shown in Figure 1. No patient had endoscopic or radiographs performed that demonstrated evidence of pseudomembranous colitis. Based on the predetermined modified severity scoring system, no enrolled patients met criteria for severe *C difficile* colitis.

Oral Vancomycin Dosing and Scheduling

There was a wide variation in dosing used for treatment of *C difficile* colitis in the study. The mean weight based dosage was 6.36 mg/kg per administration, ranging from 2.01 mg/kg to 14.80 mg/kg per dose (Figure 2). Frequency of administration and absolute dose were also variable (Table) and did not correlate with disease severity, age, weight, or previous treatment.

Absorption and Adverse Effects

All patients received creatinine and vancomycin levels on study enrollment and then with each subsequent blood draw performed by the primary team. Overall, patients received between

Figure 2. Variation of vancomycin treatment dose. Patient weight listed above corresponding bar.

2 and 5 creatinine determinations while on study. Patients had serum levels of vancomycin for an average of 4 days and ranged from 1 to 5 days. One patient had a mildly increased creatinine level compared to baseline (this patient had a history of renal transplantation and renal disease) during oral vancomycin administration, while 7 patients had no change or decreased levels (Figure 3). There were no cases of renal failure or sustained decreased renal function attributed to oral vancomycin.

Overall, study patients received between 1 and 4 serum-vancomycin levels. The study was designed to coordinate intravenous sampling at the time of primary provider blood draws. Therefore, the timing of serum vancomycin levels compared to drug administration was variable and ranged from 1 to 6 hours postdrug administration. The levels associated with the longest drug treatment duration were drawn on day 5 of treatment in 3 patients. No patient had detectable levels of oral vancomycin while enrolled in the study. There were no cases of "Red Man" syndrome or other adverse effects attributed to drug absorption during the study.

DISCUSSION

C difficile associated colitis remains an increasingly common pediatric condition, with an incidence of 24.1 per 100,000 persons in the United States.¹ In the pediatric population, the peak incidence is at 1 year of age (66.3 per 100,000), decreasing to 35.6 per 100,000 by 2 to 3 years of age.³ Similar to adults, approximately 75% of pediatric *C difficile* infections are community

Figure 3. Patient serum creatinine levels on day of oral vancomycin administrations.

● Patient 1; ■ Patient 2; ▲ Patient 3; ▼ Patient 4; ◆ Patient 5;
○ Patient 6; □ Patient 7; △ Patient 8

acquired with a roughly 20% rate of recurrence.²⁵ Severe disease is relatively common and includes 10% to 12% of pediatric *C difficile* infections.^{3,25} Per the AAP and IDSA guidelines, oral vancomycin should be considered as a first-line treatment in these cases. To our knowledge, this is the first prospective study in children on the absorption of oral vancomycin in children with colitis. No enrolled patients had detectable levels of serum vancomycin.

Studies in adults concerning the overall absorption of oral vancomycin are conflicting. Our findings contrast with recent reports in adult patients where up to 68% of adults on oral vancomycin had detectable serum levels of the drug.²² There are several factors that may explain this discrepancy. First, while our study design incorporated those with severe colitis by predefined criteria, no patients with severe disease were captured. This is most likely due to the low incidence of severe *C difficile* colitis in children and coadministration of empiric serum vancomycin in severely ill children, which excluded them from the study. Severe inflammation diminishes the integrity of gastrointestinal mucosa allowing for absorption of larger molecules like vancomycin that otherwise remain in the gastrointestinal tract. It is possible that the mild to moderate inflammation in our patients was not sufficient to compromise the integrity of intestinal mucosa to the degree required for vancomycin absorption. Furthermore, our study was designed to detect serum vancomycin early in the treatment course, and no patients were tested after 5 days of drug admin-

istration due to patients being discharged from the hospital prior to the end of the fifth day. In contrast, Pettit et al²² found that the median time of detection of serum vancomycin was 6 days of therapy (ranging 5-52 days) and we would not have been able to detect absorption late in the course of treatment.

Our study did not find any adverse renal outcomes attributed to oral vancomycin and no cases of “Red Man” syndrome were observed, which correlates with the lack of detectable serum vancomycin. While additional larger trials are needed for confirmation, these findings suggest that oral vancomycin has minimal adverse effects in children with mild to moderate colitis.

While studies in mild to moderate colitis have failed to demonstrate improved outcomes with initial dual therapy, recent evidence in adults suggests dual therapy may improve outcomes in severely ill patients with *C difficile* infections.¹ These findings highlight the need for further studies determining the safety and efficacy of oral vancomycin in the treatment of pediatric infectious colitis.

CONCLUSIONS

In this pilot prospective, observational study, oral vancomycin was not absorbed in children with mild to moderate colitis and there were no systemic adverse events attributed to oral vancomycin. In addition, there is a significant degree of variation in the use of oral vancomycin and its dosing as well as in the use of dual therapy in children with colitis. Further study is needed to determine vancomycin pharmacokinetics in severe colitis and in those with severe illness in a critical care setting.

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Abbreviations AAP, American Academy of Pediatrics; IDSA, Infectious Diseases Society of America

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