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Effect of vancomycin dose on treatment outcomes in severe *Clostridium difficile* infection

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ABSTRACT

Current guidelines recommend vancomycin 125 mg four times daily for the treatment of severe *Clostridium difficile* infection (CDI). However, the optimal dose of vancomycin has not been elucidated. This study was conducted to evaluate outcome differences in patients with severe CDI treated with either low-dose (≤500 mg daily) or high-dose (>500 mg daily) oral vancomycin. The medical records of 78 patients with severe CDI were evaluated retrospectively. The primary outcome was time to clinical cure of CDI, defined as the first day of resolution of diarrhoea for ≥48 h without development of a complication. Other endpoints included cure rates, complication rates and recurrence rates. Overall, 48 patients (61.5%) achieved clinical cure at Day 10 after treatment initiation. The cure rates in the high-dose and low-dose vancomycin groups were 60% and 64%, respectively ($P = 0.76$). Using a multivariate Cox proportional hazards model adjusting for baseline discrepancies, vancomycin dose was not independently associated with clinical cure. No difference in time to cure, complication rates or mortality was observed between the groups. There was a trend towards lower rates of recurrence associated with higher doses of oral vancomycin (12% vs. 1.9%; $P = 0.09$). In conclusion, these data suggest that there is no difference in treatment outcomes between high-dose and low-dose vancomycin for the treatment of severe CDI. The potential difference in recurrence rates between the groups warrants further investigation.

1. Introduction

Clostridium difficile infection (CDI) is a large epidemiological problem for hospitalised patients across the world, with incidences ranging from 3.4 to 8.4 cases per 1000 admissions [1]; however, the incidence is rising, with rates of hospital discharges for CDI doubling from 1996 to 2003 [2,3]. Furthermore, the severity of CDI-related illness is increasing [4], with mortality rates in the USA increasing four-fold between 2000 and 2004 [5]. The increase in severity of CDI may partially be explained by the emergence of hyper-toxin-producing *C. difficile* strains [6,7]. Metronidazole has traditionally been the preferred treatment of CDI given its low cost and lack of association with the emergence of vancomycin-resistant enterococci [8]. However, increased rates of treatment failure and recurrence with metronidazole have been observed in patients with more severe CDI [9,10]. As such, recent guidelines have recommended vancomycin as the initial therapy in severe CDI [11,12].

However, the optimal dosage of vancomycin has not been elucidated. Currently, the Infectious Diseases Society of America (IDSA)/Society of Healthcare Epidemiology of America (SHEA) guidelines recommend oral vancomycin 125 mg four times daily (500 mg/day) for severe cases of CDI and 500 mg four times daily (2000 mg/day) with intravenous (i.v.) metronidazole in severe-complicated CDI involving shock, ileus or toxic megacolon [12]. In addition, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends giving vancomycin 125 mg four times daily orally for severe CDI if oral therapy is possible. If oral therapy is not possible, then severe CDI should be treated with the combination of i.v. metronidazole, intracolonic vancomycin and/or 500 mg vancomycin four times daily by nasogastric tube [11].

A study by Fekety et al. compared the use of 125 mg or 500 mg of oral vancomycin four times daily for the treatment of CDI and found no significant differences in response rate, time to response or recurrence [13]. However, as the authors of this study pointed out, the study may have been underpowered to evaluate small but clinically significant differences between the two treatment regimens. Furthermore, the study did not stratify patients based on severity of illness and was performed over 20 years ago, preceding recent reports of increasing CDI virulence [6].

A recent pharmacokinetic study evaluated faecal concentrations of different doses of oral vancomycin and discovered that levels in the stool rose correspondingly with increasing doses [14]. There was large interpatient variability, and stool concentrations were inversely correlated with the number of stools per day [14]. In

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one patient who was prescribed 125 mg four times daily, the vancomycin level on Day 1 was as low as 15 mg/L [14].

A composite evaluation of earlier studies demonstrated that vancomycin at a dosage of 500 mg four times daily for 10 days achieved a 100% resolution rate, whereas response rates dropped to 75–86% when the regimen was decreased to 125 mg four times daily [8]. In addition, in an evaluation of recurrent CDI, there was a trend for a lower recurrence rate when vancomycin was used at doses ≥2000 mg/day [15]. As such, several CDI treatment reviews recommend utilising doses higher than those recommended in the IDSA/SHEA guidelines for the treatment of initial episodes of CDI [8,16].

Given the pharmacokinetic variability of oral vancomycin [14,17], the increase in incidence and virulence of *C. difficile* [6], the lack of comparison in dosing of oral vancomycin since the emergence of hyper-toxin-producing strains and the considerable variability in dosing reported in the literature [18], the optimal dose of vancomycin for severe CDI warrants further investigation. As such, the purpose of this study was to evaluate for differences in time to clinical cure as well as rate of overall cure, complications and recurrence for patients with severe CDI treated with high-dose (>500 mg/day) compared with low-dose (≤500 mg/day) vancomycin.

2. Materials and methods

2.1. Study design

This was a retrospective cohort study evaluating low-dose (≤500 mg daily) compared with high-dose (>500 mg daily) oral vancomycin for the treatment of severe CDI. The study was performed at a large, tertiary care, academic medical centre and was approved by the Cleveland Clinic Institutional Review Board (Cleveland, OH) with a waiver of informed consent. This study was designed in conjunction with a separate study evaluating the role of combination therapy for the treatment of severe CDI, and patients were eligible for inclusion in both studies [19].

Adult patients were eligible if they were ≥18 years of age, admitted between July 2006 and July 2011 with a diagnosis of severe CDI, and were treated with oral vancomycin. CDI was defined as the presence of diarrhoea and laboratory confirmation of *C. difficile* toxin. Toxin testing was performed with either enzyme immunoassay detection of toxins A and B (Wampole, Blacksburg, VA) or PCR (BD GeneOhm™; BD, Franklin Lakes, NJ). Diarrhoea was defined as either three unformed stools, 200 mL of watery rectal bag output or 1 L of colostomy output in 24 h [20]. Severe CDI was defined according to IDSA/SHEA guideline definitions, which included a white blood cell (WBC) count of $\geq 15 \times 10^3$ cells/μL, a serum creatinine (SCr) of ≥1.5 times the pre-morbid level or inpatient documentation of acute kidney injury [12].

Patients were excluded if they met criteria for mild-moderate, severe complicated or recurrent CDI. Patients were also excluded if they had baseline conditions that could influence the assessment of the primary outcome variable. These disease states included irritable bowel disease, graft-versus-host disease, neutropenia or cirrhosis. Criteria for mild-moderate CDI were defined as a WBC count $<15 \times 10^3$ cells/μL and SCr <1.5 times the pre-morbid level. Severe complicated CDI was defined as the presence of ileus, shock with the use of a vasopressor, or evidence of toxic megacolon (including colectomy, colonic perforation or radiographic evidence) within 48 h of CDI onset [12].

Patients were screened for inclusion from a list of patients with positive detection of *C. difficile* toxin from stool samples. After screening for eligibility, the patient's vancomycin regimen was evaluated and each patient was classified into high-dose and low-dose groups. Patient demographic data, co-morbidities and baseline severity of illness were recorded through retrospective chart review at the time all inclusion and exclusion criteria were met. Patients with incomplete medical chart data were excluded. Data collection included components of the Charlson co-morbidity index (CCI) [21], Sequential Organ Failure Assessment (SOFA) score [22] and baseline laboratory markers (e.g. WBC count, SCr, lactate). Daily medication use and stool frequency were evaluated based on inpatient documentation of bowel movements and medication administration records for the first 10 days after satisfying inclusion and exclusion criteria. Medications of interest included all antibiotics with in vitro activity against *C. difficile*. In addition, other therapies that may affect CDI course were also detailed, including adjunctive probiotics, i.v. immunoglobulins and other systemic antibiotics. Physician and radiographic notes were assessed for evidence of complications.

2.2. Outcomes

The primary outcome measure was time to clinical cure of CDI, which was defined as resolution of diarrhoea for ≥48 h without the development of a complication. CDI-associated complications included colectomy, colonic perforation, ileus and toxic megacolon. Secondary outcomes included Day 10 clinical cure and complication rates, and Day 30 mortality and CDI recurrence rates. Recurrence was defined as satisfying the definition of CDI within 30 days after initial cure.

2.3. Statistics

Assuming a 70% cure rate [23], it was determined that 78 patients would be needed to detect at least a 25% difference in cure rate between treatment groups with a two-sided α level of 0.05 and power of 80%.

Nominal data were evaluated using χ^2 test or Fisher's exact test as appropriate. Continuous and interval data were evaluated using the Mann–Whitney *U*-test. Kaplan–Meier curves were constructed to show the time to clinical cure and were compared using the log-rank test. A Cox proportional hazards model with adjustments for baseline differences between groups was also developed for time to clinical cure. The variables entered into the multivariate model using the best subset method included the patient group and any other baseline factors with biological plausibility for affecting the primary outcome and that met the a priori determined statistical criteria of $P < 0.20$ on baseline univariate comparisons. The proportional hazards assumption was assessed by inspection of the log (−log survival function) versus time plot. All analyses were two-sided and were considered statistically significant at the $P < 0.05$ level. All statistics were computed using SPSS v.11.5 software (SPSS Inc., Chicago, IL).

3. Results

In total, 651 patients with positive *C. difficile* toxin testing from a laboratory report were screened; 78 patients met the inclusion criteria but did not meet exclusion criteria and were enrolled in the study, including 25 patients (32%) in the low-dose group and 53 patients (68%) in the high-dose group (Fig. 1). Baseline characteristics are summarised in Table 1. Overall, patients who received high-dose vancomycin appeared more severely ill compared with the low-dose group; both median CCI and SOFA scores were numerically higher in patients who received higher vancomycin doses. However, only the difference in SOFA score reached statistical significance, with patients who received high-dose vancomycin having a higher likelihood of having neurological and renal dysfunction. Furthermore, a higher proportion

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