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Short Communication

Impact of vancomycin faecal concentrations on clinical and microbiological outcomes in *Clostridium difficile* infection

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ABSTRACT

To assess the impact of faecal vancomycin concentrations on clinical and microbiological outcomes in patients with *Clostridium difficile* infection (CDI) and whether these concentrations vary with stool consistency and frequency, faecal concentrations of vancomycin were measured in stools collected at various times from patients initiated on 125 mg every 6 h (q6h) for 10 days. Stool consistency and frequency were determined over the course of therapy. Clinical and microbiological outcomes were assessed during therapy, at the end of therapy (EOT) and during a 19–38-day follow-up visit. Faecal vancomycin concentrations in 55 stool samples from 15 patients ranged from 175–6299 μg/g at Days 3–5 of therapy (midpoint), 17–5277 μg/g at EOT and 0–70 μg/g at follow-up. Clinical cure or failure at EOT and at follow-up was not dependent on vancomycin concentrations measured at the midpoint ($P = 0.72$) or at EOT ($P = 0.76$). Likewise, concentrations at EOT and at follow-up did not predict colonisation at follow-up ($P = 0.85$ and 0.71, respectively). Faecal vancomycin concentrations during the course of therapy (Days 3–5) did not differ with either stool consistency or frequency ($P = 0.94$ and 0.16, respectively). However, after completion of therapy, patients with more frequent stools showed higher concentrations than patients with less frequent stools ($P = 0.04$). Oral vancomycin 125 mg q6h led to faecal concentrations that did not predict clinical outcomes of CDI in terms of cure or gut colonisation and did not vary with stool consistency and frequency.

1. Introduction

Clostridium difficile infection (CDI) is the major cause of antibiotic-associated diarrhoea both in the hospital and the community, accounting for 15–25% of cases of nosocomial antibiotic-associated diarrhoea [1]. Vancomycin is a frequently utilised therapy and is recommended for moderate-to-severe CDI cases, including hospitalised patients, in the current guidelines published by the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [1,2].

Unlike metronidazole, which is systemically absorbed and thus has lower faecal concentrations, the potential for extraintestinal adverse events and drug interactions, vancomycin is poorly absorbed from the gastrointestinal tract, has limited systemic exposure and achieves high concentrations in stool [3,4]. Despite the widespread use of vancomycin, there remains considerable debate over the optimal dosage for CDI treatment since no difference in cure rates was found between patients who received 125 mg four times daily versus those who received 500 mg four times daily [5]. Both of these doses, as well as the 250 mg dose, appear capable of achieving faecal concentrations that are 100–1000-fold higher than the MIC_{90} (minimum inhibitory concentration that inhibits 90% of isolates) of vancomycin against *C. difficile* of 1–2 mg/L [1,3]. Therefore, both guidelines recommend the 125 mg dose as the standard dose of oral vancomycin for severe CDI [1,2].

Studies assessing faecal vancomycin concentrations are sparse [3,6,7]. Only one of these studies looked at the correlation between concentrations and stool frequency [3], and none studied the relationship with stool consistency or clinical outcomes. Therefore, the aim of this study was to describe the correlation of faecal concentrations of vancomycin with treatment success and gut colonisation with *C. difficile* as well as with stool consistency and frequency from a pharmacokinetic perspective in patients with CDI.

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2. Materials and methods

Stool samples were collected from patients enrolled in the vancomycin arm of a randomised, open-label study of vancomycin versus fidaxomicin for CDI, defined as a positive PCR test for *C. difficile* using GeneXpert® (Cepheid, Inc., Sunnyvale, CA) [8]. The study protocol was approved by the Institutional Review Board of Hartford Hospital (Hartford, CT), and all patients provided written informed consent prior to entry into the study. Patients received 125 mg of oral vancomycin formulated from the generic intravenous formulation for 10 days. Samples were collected at four time intervals: baseline (before initiation of therapy, Day 0); midpoint (Days 3–5); end of therapy (EOT) (Days 10–13); and follow-up (Days 19–38).

Vancomycin concentrations were determined using a previously validated high-performance liquid chromatography (HPLC) assay at the Center for Anti-infective Research and Development (Hartford, CT) [9]. Samples were initially diluted at a 1:40 ratio with HPLC-grade water in order to obtain detectable concentrations and to reduce the effect of faecal matter on the assay. Samples with concentrations above the maximum detection limit were further diluted to 1:100 and were re-analysed. On the other hand, samples with concentrations below the lower detection limit were concentrated to a 1:20 ratio, then to a 1:10 ratio if they remained undetectable. The lower and upper limits of detection of the assay were 1 μg and 8000 μg of vancomycin per gram of stool, respectively.

Clinical cure was defined as resolution of clinical signs and symptoms of CDI, including normalisation of stool consistency and frequency, without the need for further treatment. Deterioration of the disease during the course of therapy and the subsequent need for modification of treatment was considered a failure. CDI recurrence during follow-up (i.e. Days 19–38 of therapy initiation) was deemed therapeutic failure for that time period. Colonisation, defined as the presence of *C. difficile* without clinical diseases, was assessed during the 19–38-day follow-up period. Stool consistency was determined based on the Bristol stool scale [10]. Stool frequency was determined based on the number of bowel movements over the last 24 h prior to sample collection.

For analysis of clinical outcomes, Student's *t* test was used for normally distributed data, and thus the mean and standard deviation (S.D.) are presented. Mann–Whitney *U*-test was used for data that were not normally distributed, for which the median and interquartile ranges are presented. Normal distribution was determined by the Shapiro–Wilk test for normality. Linear regression was used to evaluate the correlation between faecal vancomycin concentration and stool consistency and frequency. A *P*-value of $\leq$0.05 was considered significant. Data were analysed using SigmaPlot v.12.5 (Systat Software, Inc., San Jose, CA).

3. Results

Fifteen patients with CDI received vancomycin 125 mg orally every 6 h (q6h). Patients had a mean ± S.D. age of 65.5 ± 15.4 years and 10 (67%) were female. More than one-half of the patients (60%) had community-associated CDI, defined as CDI diagnosis in patients who had not been discharged from a healthcare facility in the previous 12 weeks [1]. Five patients (33%) received at least one dose (but <24 h worth of treatment) of oral vancomycin as part of their standard of care and prior to study enrolment.

Fig. 1 displays the flow and outcomes of the enrolled patients. Twelve patients (80%) were clinically cured by the end of the 10-day course and three were failures. Fig. 2 shows the faecal vancomycin concentrations measured before, during and after therapy. During therapy (i.e. Days 3–5), all patients had concentrations that

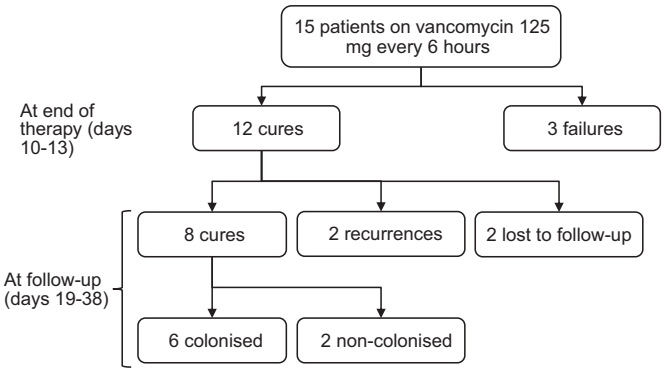

Fig. 1. Flow chart from enrolment to clinical outcomes for patients receiving oral vancomycin for *Clostridium difficile* infection.

were 100–1000-fold higher than the expected *C. difficile* MIC_{90} of vancomycin. During the follow-up period (Days 19–38), two patients (20%) had CDI recurrence versus eight patients (80%) who remained in remission (two patients were lost to follow-up). Despite a post hoc power analysis based on the primary endpoint of faecal vancomycin concentration and clinical outcome at the EOT that revealed a power of 87%, faecal vancomycin concentrations at EOT and at follow-up were indeterminate of clinical outcomes as no significant differences in concentrations were found between patients who were cured and those who failed therapy (Table 1).

In terms of *C. difficile* colonisation during follow-up, six (75%) of the eight patients who remained cured at that time period became colonised, whilst two patients did not develop gut colonisation. Four of the six patients who became colonised had undetectable concentrations of the drug in their stools collected during this time frame. Interestingly, and somewhat surprisingly, several patients had detectable vancomycin concentrations in stool 20 days after EOT. When colonised and non-colonised patients were compared in terms of vancomycin concentrations determined at EOT and at follow-up, no differences were found between the two groups at either time point (Table 1). Therefore, vancomycin concentrations were not predictive of colonisation status, whilst colonisation with *C. difficile* was documented in two patients despite their having detectable vancomycin concentrations in stool.

When faecal vancomycin concentrations in stools collected during the course of therapy (i.e. Days 3–5) were analysed against stool consistency in terms of Bristol stool scores and frequency of bowel movements over the last 24 h prior to each sample collection, no significant correlation was found between the drug concentrations and either parameter ($P = 0.94$ and 0.16, respectively). Likewise, no association was found between concentrations in stools collected after completion of therapy and Bristol stool score ($P = 0.45$); however, an unexpected positive correlation existed with increased stool frequency at that time point (i.e. higher stool frequency resulted in higher concentrations of vancomycin; $P = 0.04$).

4. Discussion

The purpose of this observational study was to describe whether faecal vancomycin concentrations may predict clinical and microbiological outcomes of CDI patients treated with a 125 mg q6h regimen, as well as whether a relationship exists between these concentrations and stool consistency and frequency. Studies that have assessed vancomycin concentrations in stools are scant. A study by Abujamel et al. [6] looked at the period of vulnerability for colonisation with *C. difficile* after finishing a 10-day course of CDI therapy. They compared patients who received vancomycin (of different dosages) with patients who received metronidazole 500 mg every 8 h. When they tracked the change in vancomycin concentrations