Original Article

THAI J GASTROENTEROL 2006
Vol. 7 No. 2
May - Aug. 2006

Early Clinical Improvement in Low-albumin Patients with-*Clostridium difficile*-associated-colitis after Oral Vancomycin vs Oral Metronidazole

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ABSTRACT

Objective: To determine the early clinical improvement in low albumin patients with *Clostridium difficile* associated diarrhea (CDAD) after treatment with oral vancomycin compared to oral metronidazole.

Patients and Methods: Tewenty-six low albumin CDAD patients were randomized to received oral vancomycin or oral metronidazole for at least 5 days. Clinical data were recorded at the day of diagnosis and at day 5 after to compare early clinical improvement (at day 5) between both groups.

Results: All low albumin CDAD patients, ten were randomized to receive oral vancomycin and sixteen to receive oral metronidazole. There was no significant difference in clinical data at the day of diagnosis (day 0) and day 5 after treatment between both groups except the decreasing of bowel movement. Bowel movement < 2 times per day was found in vancomycin group more common than in metronidazole group. All clinical signs and symptoms (body temperature <38 ˚C, absence of abdominal pain, bowel movement ≤2 times per day) of early clinical improvement were shown at day 5 in vancomycin groups. However, there was no statistical difference between both groups. One patient from metronidazole group died from pneumonia with sepsis before finished 5 days of treatment.

Conclusion: Oral vancomycin treatment seems to have a better effect for low albumin CDAD than oral metronidazole treatment but it was not significant by statistic analysis.

Key words : *Clostidium difficile*, Low albumin, Vancomycin, Metronidazole

[Thai J Gastroenterol 2006; 7(2): 61-65]

BACKGROUND

Clostridium difficile associated diarrhea (CDAD) is responsible for 15-20% of antibiotic associated diarrhea and clostridium difficile also colonized the colon in 5% of healthy adults[1,2]. The frequency and incidence of CDAD varies widely not only geographically but within different institutions in the same area[3].

C. difficile is highly susceptible in vitro to many antibiotics including vancomycin, metronidazole, bacitracin, rifampin[4], teicoplanin[5]. Both vancomycin and metronidazole have been used successfully to treat *C. difficile* colitis, with clinical response usually observed in 3-4 days in most patients[6], except patient with hypoalbuminemia. In addition, patients who failed metronidazole therapy had a much longer hospital stay[7].

The primary objective of the present study was to

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compare early response of metronidazole versus vancomycin for the treatment of low albumin (<2.5 g/dL) CDAD.

Patients and Methods

All patients admitted at the Rajavithi Hospital between June 2004 and January 2006, with the diagnosis of CDAD and low serum albumin were recruited. Outpatients were excluded. All patients included in the study had *C. difficile* infection confirmed by toxin assay (ELISA) or pseudomembranous detected during flexible sigmoidoscopy or colonoscopy. They all had serum albumin ≤2.5 g/dL. All of them did not receive metronidazole or vancomycin prior to the diagnosis of CDAD. They were divided into 2 groups (vancomycin treatment group and metronidazole treatment group) by box randomization.

All patients received either vancomycin or metronidazole for 5 consecutive days and their clinical data were recorded to assess early improvement (day 5 after oral treatment). Exceptions were those patients with documented improvement and discharged prior to day 5. These were considered to have a successful response to the treatment. Patients were excluded from evaluation if: 1) did not complete 5 days of vancomycin or metronidazole; 2) were transferred or discharged prior to day 5 without documentation of improvement; 3) died before completion of therapy not directly related to CDAD; 4) had a coexistent gastrointestinal disease (e.g. ulcerative colitis); 5) had previous or simultaneous use of vancomycin or metronidazole; 6) were switched to vancomycin prior to day 5 due to documented intolerance of metronidazole side effects (e.g.,nausea,metallic taste); and 7) clinical patients data were not recorded completely. Response to treatment was defined as the absence of fever (T <38˚C) and abdominal pain, and ≤2 bowel movements per day by the fifth day of the treatment. Failure of treatment was defined as the persistence of fever or abdominal pain or ≥3 loose bowel movements per day after 5 full days of treatment. Additional variables recorded for each patient were age, gender, continuation of antibiotics during CDAD therapy, albumin level, duration of admission before diagnosis, diabetes mellitus, hypertension, cerebrovascular disease, chronic respiratory disease, hepatic disease, infection, and hemodialysis.

Treatment regimens Vancomycin was administered at a dosage of 125 mg qid for 10 days[8] and metronidazole 400 mg tid for 10 days.

Assessment of adverse reactions Adverse reaction was assessed by monitoring both clinical and laboratory parameters. Complete blood counts and test for renal function and hepatic function were performed at the beginning of therapy and at the end of treatment (5 day).

Statistical analysis

Difference were assessed with use of the Student' t-test and the χ^2 test. All analysis were two-tailed, and a P value of <0.05 was considered to indicate statistic significance. Statistics analysis was performed using Epi Info 3.

Results

There were 26 patients who diagnosed with low albumin CDAD. Ten patients (3 male 7 female) were randomized to receive oral vancomycin treatment and 16 (9 male 7 female) were randomized to receive oral metronidazole treatment. One was excluded due to death of patient for a reason unrelated to CDAD (pneumonia with sepsis) in the metronidazole treatment groups. There was no difference in gender between the two treatment groups. Mean age of patients was 64.1 ± 18.9 years for vancomycin treatment group and 54.4 ± 21.6 years for metronidazole treatment group. Severity of CDAD as judged by frequency of fever, abdominal pain, and duration of diarrhea was similar in two groups, and there were no significant differences in age, underlying diseases, albumin level, number of bowel movement (Table 1). All patients had a history of prior antimicrobial treatment, 17 of them used antibiotics within 14 days of the onset of diarrhea. The remaining 9 patients had antimicrobial at 18, 21, 24, 26, 29, 30, 34, 38, and 43 days before diarrhea. The types of prior antimicrobial treatment in each group were also similar. Third generation cephalosporins was the common antibiotics used (n = 18, or 72% of those receiving antibiotics). The second and third common most frequently used antibiotics were quinolone (n = 4) and clindamycin (n = 2) respectively. The rest were trimethoprim sulfamethoxazole (n = 1) and macrolides (n = 1).

Diagnostic criteria and clinical signs and symptoms were shown in Table 2. Diarrhea was the most common symptom in both groups (100% in both vancomycin and metronidazole treatment groups). Both

Table 1 Clinical characteristics of patients randomized to receive vancomycin or metronidazole.

	Vancomycin	Metronidazole	p-value
Numbers of patients	10	16	
Age (years)	64.1 ± 18.9	54.4 ± 21.6	0.256
Male (%), Female (%)	3 (30.0), 7 (70.0)	9 (56.2), 7 (43.7)	0.367
Duration of admission before diagnosis	42.2 ± 20.5	39.5 ± 17.7	0.724
Antibiotics usage prior diagnosis	3.8 ± 1.03	3.1 ± 1.1	0.102
Fever ≥38 ˚C (%)	8 (80.0)	13 (81.2)	0.665
Abdominal pain (%)	7 (70.0)	10 (62.2)	0.974
Frequency of diarrhea per day	6.9 ± 1.9	6.9 ± 1.9	0.959
Serum albumin (g/dL)	2.2 ± 0.3	2.1 ± 0.3	0.671
Dialysis (%)	4 (40.0)	4 (25.0)	0.712
Dm (%)	8 (80.0)	10 (62.2)	0.614
HT/CVA (%)	6 (60.0)	10 (62.2)	0.774
Chronic respiratory disease	5 (50.0)	4 (25.0)	1.000
Hepatic disease (%)	3 (30.0)	6 (37.5)	0.974
Infection (%)	9 (90.0)	14 (87.5)	0.662

Table 2 Diagnostic criteria and clinical sign and symptoms of Clostridium difficile associated diarrhea with low albumin

	Vancomycin	Metronidazole	p-value
Fever ≥38 ˚C	8 (80.0)	13 (81.25)	0.665
Abdominal pain (%)	3 (30.0)	10 (62.25)	0.107
Diarrhea (%)	10 (100.0)	16 (100.0)	-
Positive by endoscopy*	5 (50.0)	9 (56.25)	0.926
Positive C.difficile toxin	7 (70.0)	12 (75.0)	0.861
Duration of diarrhea before treatment (days)	4.3 ± 1.7	4.4 ± 2.3	0.869

**flexible sigmoidoscopy or colonoscopy showed pseudo membrane*

Table 3 Clinical data at the fifth day after treatment with vancomycin or metronidazole

	Vancomycin	Metronidazole	p-value
Number of patients	10	15*	
Male (%), Female (%)	3 (30.0), 7 (70.0)	9 (60.0), 6 (40.0)	0.288
Fever <38 ˚C (%)	5 (62.50)	5 (38.46)	0.534
Absence of abdominal pain (%)	3 (100.0)	9 (90.0)	1.000
Bowel movement ≤2 times/day	7 (70.0)	3 (20.0)	0.037

**1 death before day 5 of treatment was excluded*

groups had similar positive results of flexible sigmoidoscopy or colonoscopy (50% vs 56.2%, p = 0.926). There was no difference in the results difficile toxin in both treatment groups (70% vs 75%, p = 0.861). Duration of diarrhea before treatment was 4.3 ± 1.7 days for vancomycin group and 4.4 ± 2.3 days for metronidazole group which was not statistically significant.

Clinical data at the fifth day after treatment with vancomycin or metronidazole were shown in Table 3. There was no difference in fever and absence of abdominal pain in both treatment groups (62.5% vs 38.46, p = 0.534 and 100% vs 90%, p = 1). The vancomycin group had more "bowel movement ≤2 times/day" than metronidazole group (70% vs 20%, p = 0.037) but

Table 4 Early clinical improvement in low albumin CDAD patients

	Vancomycin	Metronidazole	p-value
Number of improved patients(%)	5 (50.0)	3 (20.0)	0.151

total outcome (early response) was not statistically significant (50% vs 20%, p = 0.151) as in Table 4.

After 5 consecutive days of treatment regimen, complete blood counts and test for renal function and hepatic function were performed to find out adverse effects. We found that all patients had no serious adverse effects from these regimens.

DISCUSSION

Metronidazole is the drug of choice for the treatment of *Clostridium difficile* associated diarrhea. Patients who failed metronidazole are usually switched to vancomycin, and many improved. Hypoalbuminemia is one of predictive factors for the failure of therapy. We chose a cutoff of 5 days as the time period of interest because, in study of Fernandez,A *et al.* found a response to metronidazole would typically occur by this time and because most physicians would consider a switch at this period if the patient was not improving.[7] It was not surprising that a low albumin has been associated with early treatment failure. A low albumin has been linked to increased morbidity and mortality in many clinical situations.[3,9,10] Hypoalbuminemia is probably the result of protein loss in the stool from the inflammatory exudates or depressed the hepatic synthesis in response to sepsis.[11,12] Nair *et al*. found that patients failed vancomycin was 8/31 and metronidazole was failed in about 1/5.[6]

Our study showed no significant difference in demographic data, early response [absence of fever (T <38˚C) and abdominal pain by the fifth day of treatment] to oral vancomycin and metronidazole treatment in low albumin CDAD. However, bowel movement was the only significantly difference observed in this study (70% vs 20%, p = 0.037). Bowel movement ≥4 per days was found in all patients, so decreasing in bowel movement after the treatment may be the early sign for clinical improvement and it was not disturbed by other current illness and infection. It is possible that the patients with significant improvement of bowel movement, may improve from CDAD. Because of the high efficacy of oral vancomycin, all strains of *C. difficile* are highly sensitive to it in both vitro and vivo.[13-17] Drug levels in colon after oral doses of 125 mg (given 4 times daily) are up to 500 μg/g stool, while most strains have an minimal inhibitory concentration (MIC) of 1 μg/mL or less and none have an MIC greater than 16 μg/mL.[8] In contrast, metronidazole is well absorbed when administered orally that colonic levels and in vitro activity are less predictable. Metronidazole relies on secretion into the inflammed colon, and lower levels are probably happened when the inflammation has subsided.

Results from our study included various the classes of antibiotics that likely facilitated the development of CDAD. Low albumin *Clostridium difficile* associated diarrhea was found less often than classical CDAD cases, so there were small number of patients in our study. Data retrieved concerning stool frequency and consistency as well as patients symptoms might have been inaccurate. Our study was not designed to evaluate further need for the offending antibiotic, nor did we interfere by removing the antibiotic as a part of the therapeutic management of the colitis. Therefore, the significance for statistics was improper to analyse and interpret.

In conclusion, those patients with CDAD with an albumin ≤2.5 mg/dL have a higher rate of early treatment failure for vancomycin than metronidazole but not statistically significant. The potential consequences of this include prolonged hospitalization and potentially increased morbidity. Close observation and early awareness will shorten duration of stay and decrease patients' suffering.

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