Continuous Administration of Vancomycin through a Long Intestinal Tube for *Clostridium difficile* Infection

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Abstract

A 76-year-old previously healthy Japanese man experienced severe diarrhea (8,000 mL per day) after undergoing laparotomy for small bowel obstruction and was diagnosed with *Clostridium difficile* infection. Although he developed a maculopapular rash secondary to the systemic absorption of enteral vancomycin (VCM), the patient was successfully treated with the continuous administration of VCM through a long intestinal tube placed in the terminal ileum. This method ensured the reliable delivery of VCM to the colon, while the continuous administration maintained high fecal levels of the drug. This treatment approach is an effective minimally invasive option for patients with severe diarrhea.

Key words: continuous administration, *Clostridium difficile*, vancomycin, long intestinal tube, maculopapular rash, systemic absorption

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Introduction

Clostridium difficile infection (CDI) is the most frequent cause of hospital-acquired diarrhea. The clinical manifestations of CDI range from asymptomatic carriage, to mild diarrhea and fulminant colitis (1). Patients with severe complicated CDI are treated with oral vancomycin (VCM) and intravenous metronidazole (MNZ). If their condition does not improve with medical therapy, subtotal colectomy may be considered (1-3). In Japan, intravenous MNZ was not licensed for use until May 2014, and subtotal colectomy for CDI is not common. In contrast, oral VCM is the most widely used treatment for CDI in Japan. To our knowledge, there have been no previous reports of treatment with the continuous infusion of enteral VCM. We herein report a case of CDI with large-volume diarrhea successfully treated with the continuous administration of VCM via a transnasal ileus tube.

Case Report

In December 2013, a 76-year-old Japanese man with no

significant past medical history was admitted to our hospital with a diagnosis of small bowel obstruction. On a physical examination, his temperature was 37.3°C, his heart rate was 98 beats/min, his blood pressure was 138/78 mmHg and his oxygen saturation was 98% on ambient air. He presented with diffuse abdominal distension and tenderness, although no signs of peritoneal irritation were noted. Laboratory tests revealed a white blood cell count of 5,400 cells/mm³, C-reactive protein level of 0.43 mg/dL and normal hepatic and renal functions. A contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis showed dilatation of the small bowel with a caliber change in the terminal ileum. A long transnasal intestinal tube was inserted for bowel decompression, and the administration of cefmetazole was started at a dose of 1 g twice a day. However, decompression was not achieved successfully, and laparotomy was subsequently performed on hospital day 3. After exploring the peritoneal cavity, stenosis and adhesion were identified in the terminal ileum, and adhesiolysis was performed without bowel resection. The tip of the long intestinal tube was placed in the terminal ileum during the operation (Fig. 1). Postoperatively, the patient exhibited a persistently high fever, and cefmetazole was changed to ceftriaxone at a dose

Figure 1. Abdominal radiograph showing the tip of the long intestinal tube placed in the terminal ileum.

of 1 g twice a day on hospital day 6.

On day 9, the patient developed watery diarrhea 12 times a day and was diagnosed with CDI based on an enzyme immunoassay for *C. difficile* glutamate dehydrogenase and toxins A and B (C. DIFF QUIK CHEK COMPLETE; Alere). The administration of ceftriaxone was immediately stopped, and treatment for CDI with VCM (500 mg) was initiated four times a day through the long intestinal tube. On day 10, he was admitted to the intensive care unit due to hypovolemic shock (Acute Physiology and Chronic Health Evaluation II score: 14; Sequential Organ Failure Assessment score: 2). His temperature was 38.0°C, his heart rate was 114 beats/min and his blood pressure was 82/59 mmHg. Laboratory tests showed a white blood cell count of 8,600 cells/mm³, C-reactive protein level of 13.75 mg/dL, serum albumin level of 2.7 g/dL, serum creatinine level of 1.72 mg/dL and serum lactate level of 2 mmol/L. A non-contrast CT scan showed the large bowel to be filled with fluid in addition to thickening of the wall of the sigmoid colon (Fig. 2). A rectal catheter (Flexi-Seal; ConvaTec Japan, Tokyo, Japan) was inserted to measure the volume of diarrhea. The patient subsequently passed 8,000 mL of diarrhea and was given 10,000 mL of lactated Ringer's solution the same day. Although he became hemodynamically stable and the drainage volume through the long intestinal tube was ≤200 mL/day, the reduction in stool output achieved after five days of VCM therapy was insufficient (Fig. 3). On day 14, the treatment was changed to the continuous administration of VCM (saline 100 mL + VCM 500 mg; for six hours four times a day) through the intestinal tube, and the stool output decreased over the next few days.

On day 18, the patient's temperature rose to 39.1°C. A contrast-enhanced CT scan showed multiple wedge-shaped and low-density lesions in the right kidney. He was therefore diagnosed with right pyelonephritis, and *Pseudomonas aeruginosa* was subsequently identified in urine cultures. Cefepime (1 g) and tobramycin (240 mg) were administered, after which a faint maculopapular rash developed on

Figure 2. Non-contrast CT scan of the abdomen and pelvis. White arrows show the thickening of the wall of the sigmoid colon.

the limbs. The antibiotic therapy was immediately changed to tazobactam/piperacillin (4.5 g three times a day); however, the rash gradually spread to the face and trunk (Fig. 4). On day 22, after 13 days of VCM therapy, the serum VCM concentration was 3.9 µg/mL; the administration of VCM was thus stopped immediately. The patient was then administered a topical corticosteroid and oral antihistamine, and the rash resolved over the next few days. He thereafter exhibited a good recovery and was discharged on day 31.

Discussion

The diagnosis of CDI is made based on a combination of particular signs and symptoms confirmed according to microbiological evidence of *C. difficile* toxin and toxin-producing *C. difficile* in the stool (1-3). In the current case, although methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from a stool culture, the patient was diagnosed with CDI based on the results of an enzyme immunoassay for *C. difficile* glutamate dehydrogenase and toxins A and B (4).

Classifying the severity of colitis is important for determining the appropriate treatment regimen for CDI. The present patient met the criteria for severe complicated CDI (1, 2). The treatment of severe complicated CDI involves VCM delivered orally or via an enteric feeding tube (125 mg or 500 mg four times per day) and MNZ administered intravenously (500 mg three times a day) (1, 2). Because diarrhea results in significant volume depletion, providing supportive care with intravenous fluid resuscitation and electrolyte replacement is also important. In the current case, a rectal catheter was useful for determining the quantity of fluid loss.

Treatment for CDI with VCM was initiated at a dose of 500 mg four times a day through the long intestinal tube; however, the patient failed to improve after five days of VCM therapy (Fig. 3). The time to resolution of diarrhea in patients treated with VCM using a regimen of 500 mg four times a day is 2.8 days (5), and most VCM-treated patients

Figure 3. Clinical course of the patient. CMZ: cefmetazole (1 g twice a day), CTRX: ceftriaxone (1 g twice a day), VCM: vancomycin (2 g a day), CFPM: cefepime (a single dose of 1 g), TOB: tobramycin (a single dose of 240 mg), TAZ/PIPC: tazobactam/piperacillin (4.5 g thrice a day), CPFX: ciprofloxacin (300 mg twice a day)

Figure 4. Image of the maculopapular rash on the patient's back.

exhibit resolution of diarrhea within five days (6, 7). Therefore, if the patient fails to improve within five days, surgical intervention may be considered (1). Recently, diverting loop ileostomy and colonic lavage have been shown to reduce mortality compared with that observed in historical controls treated with colectomy (19% versus 50%). This surgical approach involves loop ileostomy, intraoperative colonic lavage and postoperative antegrade instillation of VCM flushes via the ileostomy (8). The success of this technique highlights the importance of reliably administering VCM to the colon. In our patient, VCM was reliably delivered into the colon via the tube placed in the terminal ileum, as can be achieved via ileostomy; however, this treatment resulted in only a slight decrease in stool output. Therefore, subtotal colectomy was considered. Nevertheless, the 30-day postoperative mortality rate is high (41.3%) in patients with severe CDI treated with emergency surgery (9). Furthermore, subtotal

colectomy is rarely performed for CDI in Japan, and our search of the Japan Medical Abstracts Society (1974-2013) identified only four cases.

We suspected that the VCM was being expelled just after administration in the 300 mL of diarrhea passed by the patient each hour. In other words, the residence time of VCM on the surface of the colon was extremely short. With the patient's consent, the intermittent VCM therapy was changed to continuous administration via the intestinal tube. Consequently, he displayed no symptoms of abdominal distension or vomiting during the continuous treatment, and his stool output decreased over the next few days (Fig. 3).

The fecal level of VCM is affected by the stool frequency (10). In the present case, the fecal VCM concentration following continuous administration reached very high levels (due to the presence of the watery component, the fecal samples were centrifuged and the concentration of the supernatant was measured by SRL Inc. using an enzyme immunoassay), as follows: 554 µg/mL on day 14 (4,000 mL of diarrhea per day) and 1,127 µg/mL on day 15 (2,000 mL of diarrhea per day). Indeed, the total daily level of fecal excretion of VCM was almost equal to the daily dose of 2,000 mg. The minimum inhibitory concentration (MIC) of VCM for *C. difficile* is 0.5-4.0 µg/mL (11). Although the effective fecal concentration of VCM is unclear, the fecal VCM level in this case was maintained at several hundred times the MIC for *C. difficile*.

Unfortunately, a maculopapular rash appeared after 11 days of VCM therapy. Oral VCM is poorly absorbed; however, bowel inflammation may enhance the absorption of oral VCM (12). The accumulation of oral VCM is most often reported in patients with renal insufficiency, although it can also occur in patients with a normal renal function (12-14). On day 22, our patient had a normal renal function (serum creatinine: 0.68 mg/dL). Nevertheless, the

high dose of VCM induced a high serum VCM concentration (3.9 µg/mL). The systemic absorption of oral VCM is known to cause adverse effects, including maculopapular rashes (15, 16), red man syndrome (13, 17, 18), anaphylaxis (19), leukopenia (14) and encephalopathy (20). Based on these findings and the patient's clinical course, we suspected that he developed the maculopapular rash secondary to VCM (21). Tests for identifying the causative drug were subsequently conducted; the drug-induced lymphocyte stimulation test was positive for VCM but negative for cefepime and tobramycin, and patch testing was negative for VCM. Although the continuous administration of VCM may have contributed to increased drug absorption in this case, it is important to monitor the serum VCM concentration regardless of the renal function, particularly in patients exhibiting such adverse effects.

The current patient was successfully treated with the continuous administration of VCM through a long intestinal tube, thus avoiding the need for subtotal colectomy. The VCM was reliably delivered into the colon via the tube placed in the terminal ileum, and the continuous administration maintained high fecal levels of the drug. Although further research is needed to confirm the safety and efficacy of this treatment, this technique may be an effective minimally invasive treatment option for patients with severe diarrhea.

The authors state that they have no Conflict of Interest (COI).

Written informed consent was obtained from the patient for the publication of this case report.

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References

1. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol* **108**: 478-498, 2013.
2. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* **31**: 431-455, 2010.
3. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect* **20**(Suppl 2): 1-26, 2014.
4. Iwata K, Doi A, Fukuchi T, et al. A systematic review for pursuing the presence of antibiotic associated enterocolitis caused by methicillin resistant *Staphylococcus aureus*. *BMC Infect Dis* **14**: 247, 2014.
5. Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium difficile*-associated diarrhoea and colitis. *Lancet* **2**: 1043-1046, 1983.
6. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis* **45**: 302-307, 2007.
7. Al-nassir WN, Sethi AK, Nerandzic MM, Bobulsky GS, Jump RL, Donskey CJ. Comparison of clinical and microbiological response to treatment of *Clostridium difficile*-associated disease with metronidazole and vancomycin. *Clin Infect Dis* **47**: 56-62, 2008.
8. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated *Clostridium difficile* associated disease. *Ann Surg* **254**: 423-427, 2011.
9. Bhangu A, Nepogodiev D, Gupta A, Torrance A, Singh P. Systematic review and meta-analysis of outcomes following emergency surgery for *Clostridium difficile* colitis. *Br J Surg* **99**: 1501-1513, 2012.
10. Gonzales M, Pepin J, Frost EH, et al. Faecal pharmacokinetics of orally administered vancomycin in patients with suspected *Clostridium difficile* infection. *BMC Infect Dis* **10**: 363, 2010.
11. Drummond LJ, McCoubrey J, Smith DG, Starr JM, Poxton IR. Changes in sensitivity patterns to selected antibiotics in *Clostridium difficile* in geriatric in-patients over an 18-month period. *J Med Microbiol* **52**: 259-263, 2003.
12. Armstrong CJ, Wilson TS. Systemic absorption of vancomycin. *J Clin Pathol* **48**: 689, 1995.
13. Bergeron L, Boucher FD. Possible red-man syndrome associated with systemic absorption of oral vancomycin in a child with normal renal function. *Ann Pharmacother* **28**: 581-584, 1994.
14. Aradhyula S, Manian FA, Hafidh SA, Bhutto SS, Alpert MA. Significant absorption of oral vancomycin in a patient with *Clostridium difficile* colitis and normal renal function. *South Med J* **99**: 518-520, 2006.
15. McCullough JM, Dielman DG, Peery D. Oral vancomycin-induced rash: case report and review of the literature. *DICP* **25**: 1326-1328, 1991.
16. Osawa R, Kaka AS. Maculopapular rash induced by oral vancomycin. *Clin Infect Dis* **47**: 860-861, 2008.
17. Rao S, Kupfer Y, Pagala M, Chapnick E, Tessler S. Systemic absorption of oral vancomycin in patients with *Clostridium difficile* infection. *Scand J Infect Dis* **43**: 386-388, 2011.
18. Nallasivan M, Maher F, Murthy K. Rare case of "red man" syndrome in a female patient treated with oral vancomycin for *Clostridium difficile* diarrhoea. *BMJ Case Rep*, 2009.
19. Bossé D, Lemire C, Ruel J, Cantin AM, Ménard F, Valiquette L. Severe anaphylaxis caused by orally administered vancomycin to a patient with *Clostridium difficile* infection. *Infection* **41**: 579-582, 2013.
20. Thompson CM, Long SS, Gilligan PH, Prebis JW. Absorption of oral vancomycin: possible associated toxicity. *Int J Pediatr Nephrol* **4**: 1-4, 1983.
21. Stern RS. Clinical practice. Exanthematous drug eruptions. *N Engl J Med* **366**: 2492-2501, 2012.