Elevated Serum Vancomycin Concentrations After Oral Administration in a Hemodialysis Patient with Pseudomembranous Colitis

Sumio HIRATA*1 Mami MATOBA*1 Satoshi IZUMI *1 Taku FURUKUBO*1 Miyuki OTA*1 Minori FUJITA*1 Senji OKUNO *2 and Tomoyuki YAMAKAWA*2

(Received on August 28, 2002)

*1 Department of Pharmacy Service, Shirasagi Hospital
7-11-23 Kumata, Higashisumiyoshi-ku, Osaka 546-0002, Japan
*2 Department of Medicine, Shirasagi Hospital

We present a 68-year-old male case, hemodialysis patient (body weight 56.8 kg) with Clostridium difficile (C. difficile)-induced pseudomembranous colitis. The colitis was treated with orally administered vancomycin (VCM), 2.0 g/day, for 14 days leading to high serum levels. At this time, the VCM treatment was discontinued following negative stool cultures for C. difficile, and the serum VCM concentration was 58.7 µg/mL, the highest level in oral VCM case reports up to the present. Mean bioavailability was estimated as 16.8% during the VCM administration period in this patient, and it was assumed that the intestinal absorption of VCM was increased with severe colitis. As the serum VCM levels continued to decrease gradually, the symptoms of colitis improved. Nevertheless, the patient's colitis relapsed after oral levofloxacin treatment for bronchitis and high fever, although the serum VCM levels were still far greater than the minimum inhibitory concentration of C. difficile infection.

This finding suggests that VCM concentrations may remain insufficient in the colon despite the high serum levels. The high and persistent serum VCM concentrations in this patient may be due to the following: 1. increased absorption of VCM with severe colitis, 2. decreased excretion with renal impairment leading to VCM serum accumulation, and 3. too high a VCM dosage. We conclude that patients with both renal failure and severe intestinal disease may absorb and accumulate significant amounts of orally administered VCM. Therefore, a high dose oral VCM should be avoided in hemodialysis patients with severe pseudomembranous colitis.

Key words: vancomycin, pharmacokinetics, Clostridium difficile, pseudomembranous colitis

Introduction

Oral vancomycin (VCM) has been reported to be effective against toxin-producing Clostridium difficile (C. difficile) superinfections. Generally, it had no significant absorption problems or other side effects. However, in end-stage renal disease, patients treated with multiple-dose oral VCM therapy for C. difficile-induced colitis were reported to have substantial serum VCM levels. In the present report, we introduce a case of a hemodialysis patient who accumulated significant concentrations of serum VCM after oral therapy for C. difficile-induced pseudomembranous colitis, and whose colitis relapsed after oral levofloxacin treatment, although the serum VCM levels were far greater than the minimum inhibitory concentration of C. difficile.

We also report our experiences with another five hemodialysis cases administered with oral VCM for C. difficile.

Case Report

A 68-year-old male hemodialysis patient with noninsulin-dependent diabetes mellitus was admitted to Shirasagi hospital for periproctal abscess with high fever. He was initially treated with intravenous cefotiam (CTM) therapy at 1.0 g per day. After 6 days of CTM treatment, ceftazidime (CAZ) at 1.0 g per day was started because his C reactive protein (CRP) levels had not improved (Fig 1). Intravenous clindamycin (CLDM) at 600 mg per day was begun 2 days...
Fig. 1 Clinical course
CRP : C reactive protein, P : protoscopy, CTM : cefotiam, CAZ : ceftazidime,
CLDM : clindamycin, VCM : vancomycin, LVFX : levofloxacin

after the beginning of CAZ therapy. The patient was treated with CAZ and CLDM for 16 and 14 days, respectively. His high fever continued throughout this time. Eleven days after being admitted to the hospital, the patient complained of abdominal pain and diarrhea. On day 22, a proctoscopy examination showed pseudomembranous colitis in the rectum. His stool cultures were positive for C. difficile and an assay for C. difficile toxin was also positive. At this time, the patient’s CRP level rose to 20.0 mg/dL and his white blood cell count increased to 29,190/μL. Both CAZ and CLDM therapies were then discontinued and oral VCM at 0.5 g four times daily was initiated. On day 24, metronidazole at 250 mg twice/day was also begun. The patient was also receiving insulin and famotidine treatment with 10 mg tablets, at this time. Calcium carbonate at 1,500 mg/day was discontinued after the diagnosis of colitis.

His vital signs before admission were normal and without a high fever. He produced 300-400 mL/day of urine and was dialyzed for 4 hours using an AMBC-80F dialyser (polyethylene glycol grafted cellulose membrane, membrane surface area 0.8 m²; Asahi Medical Co., Japan) with a blood flow rate of 150 mL/min and dialysate flow rate of 500 mL/min. After VCM and metronidazole therapy, the patient’s high fever and diarrhea gradually improved.

Stool cultures were negative for C. difficile on day 31 and the WBC count was normalized on day 35. The VCM serum concentration measured 52.0 μg/mL on day 36 of therapy. Since this concentration was higher than the appropriate peak therapeutic range of systemic intravenous therapy, oral VCM was discontinued. Since the duration of administration of VCM was 14 days, although the half-life after discontinuing VCM was 158 hr, a slightly prolonged, the serum level of 58.7 μg/mL was assumed to have reached almost steady state. Clearance of VCM was calculated from the half-life, then, mean bioavailability was calculated by the formula as follows. Apparent volume of distribution (Vd) was adapted from mean values, 0.956 L/kg, calculated from the peak levels of VCM by observation of 24 patients undergoing hemodialysis in our hospital5).

\[
\text{Clearance} = \frac{(\ln 2 \times Vd)}{t_{1/2}} = \frac{(0.693 \times 0.956 \times 56.8 \times 1,000)}{(158 \times 60)} = 3.97 \text{mL/min}
\]

Estimated bioavailability
\[
= \text{Clearance} \times \text{steady state serum VCM level/VCM dose}
= \frac{(3.97 \times 58.7)}{(2.0 \times 1,000,000 / (24 \times 60))} = 0.1678
\]

Mean bioavailability was estimated as 16.8%.

On day 48, a proctoscopy examination showed that the pseudomembrane colitis had disappeared. On day 58, bronchitis with coughing and a high fever were treated with levofloxacin at 100 mg twice/day for 7 days. However, on day 69, the patient’s WBC count rose to 23,560/μL. He had a watery stool and abdominal pain,
and his stool was again found to contain both C. difficile and cytotoxin. On the same day, oral VCM, 0.5 g q.i.d, was restarted. Stool cultures were negative for C. difficile on day 75, and oral VCM was discontinued again on day 80. Multiple VCM serum concentrations were obtained after the 36th day of therapy and are shown in Fig. 1, which shows his clinical course.

There were no adverse effects from VCM therapy throughout the study. The serum VCM concentrations were determined by fluorescence polarization immunoassay (FPIA)6).

Discussion

VCM is the first choice antibiotic for pseudomembranous colitis, because metronidazole has no indication for pseudomembranous colitis in Japan. It is believed that VCM is not absorbed by the intestine because it is watersoluble and a structurally large glycopeptide polymer. Although there are a few reports on VCM was absorption6), the serum levels of VCM were very low6). Dudley et al7) reported that serum VCM was undetectable in 8 of 12 patients with C. difficile-induced pseudomembranous colitis. In the other 4 patients, the levels were low (1.2-5.1 µg/mL)7). Therefore, we used a high oral VCM dose of 2.0 g/day for the C. difficile infection, without considering the risk of high serum levels of VCM in patients undergoing hemodialysis, because the highest level, within therapeutic range after oral VCM (2.0 g/1.73/m²/day) has been reported8), to be 34 µg/mL so far.

In the present case, serum VCM concentrations were not determined during the initial oral treatment, but levels of up to 58.7 µg/mL, the highest level in oral VCM case reports up to the present, were found soon after discontinuing the VCM therapy. He produced 300-400 mL/day of urine, and the elimination half-life of VCM was 158 hr including both the inter- and intra-dialysis periods. This prolonged half-life might be caused by a low blood flow rate of 150 mL/min during hemodialysis and the small surface area of the dialyser. Mean bioavailability was estimated as 16.8% during the VCM administration period in this patient, and it was assumed that the intestinal absorption of VCM was increased with severe colitis. As drugs are generally absorbed in upper intestine, they are not effected by inflammation of the colon, but for drugs with high water solubility like VCM, a large amount of the drug reaches the colon. Therefore, VCM may be absorbed significantly with wide-ranging colitis.

On day 65, the serum VCM concentrations decreased to less than 10 µg/mL. Although the serum VCM level (6.57 µg/mL) was far greater than the mean inhibitory concentration of C. difficile (0.78 µg/mL)9), the patient relapsed into colitis after oral administration of levofloxacin. About 20% to 25% of patients experience reinfection or relapse after initial therapy, because C. difficile is a spore-producing toxigenic bacterium9). On day 69, his stools were found to contain both C. difficile and cytotoxin, despite the serum levels remaining above the MIC of C. difficile. This finding suggested that VCM was insufficiently distributed in the colon. Hecht et al10) reported a case of C. difficile colitis resulting from monotherapy with intravenous VCM. Therefore, systemic therapeutic levels of VCM may not be associated with a clinical response for colitis.

We examined the serum VCM levels after oral administration in 5 additional patients undergoing. All of the patients were administered cephalosporins intravenously before suffering colitis. The dose of VCM was 0.5 g q.i.d in 4 patients and 0.5 g twice/day in one patient. Their serum albumin levels ranged from 2.1 to 3.5 g/dL and revealed malnutrition. The relationships between the highest serum VCM levels and the frequency of diarrhea, the highest CRP, or the highest WBC were unclear in these patients. Only one case, presented here as the case report (as shown in case 1 in Fig. 1 and Fig. 2), showed evidence of relapse. All the other patients were treated with VCM and all improved clinically without relapse. The VCM serum concentrations were quantifiable in 4 of the 6 patients and were found to be less than 5 µg/mL, and they were not detected in the other 2 patients. The VCM serum concentrations were greater than 5 µg/mL in the one case presented here (Fig. 2). None of the 6 patients receiving oral VCM experienced any adverse effects that could be attributed to the VCM therapy.

Cunney et al11) reported that C. difficile-induced diarrhea was potentially life-threatening and was more common and severe in patients with chronic renal failure than in other groups. Bárány et al12) reported that uremia is a risk factor for C. difficile infection and that mortality was significantly greater among patients with chronic renal failure. Only the one case presented here as the case report in the six cases showed pseudomembr-
branous colitis in the rectum by proctoscopic examination. Therefore, the severity of colitis may also affect the serum VCM levels. Mean bioavailability was estimated as 16.8% in this patient, but higher bioavailability in the early state of more severe colitis would have been estimated in this patient. According to Drug Information for the Health Care Professional (USPDI), the concentration of VCM in the stool would be approximately 350 µg/g following doses of 500 mg daily, and 3,100 µg/g following doses of 2.0 g/day\(^{13}\)). Therefore, in our case, a dose of 2.0 g/day of VCM seemed to be too high from the above data. It was reported that the usual recommended course of oral VCM treatment is 0.5-1.0 g per 24 hr over 7-10 days\(^{13}\)). Keighley et al\(^{14}\)) reported that 125 mg four times daily gave adequate concentrations of VCM in the feces, and this dose was continued for 5 days only.

We propose that these patients in this study may have responded to lower oral doses of VCM, even if the bioavailability was high. A lower dosage of VCM may be advantageous, since a high dose of VCM can disrupt the bowel flora and allow \textit{C. difficile} infection to become established soon after the antibiotic has been stopped\(^{13}\)). VCM is primarily excreted by the kidney (greater than 80% is recovered in the urine\(^{13}\)). High serum VCM levels in hemodialysis patients probably reflect both increased intestinal absorption due to inflammation and inadequate elimination.

In conclusion, patients with end-stage renal failure and intestinal disease may absorb and accumulate significant amounts of orally administered VCM. Therefore, a high oral dose VCM should be avoided in hemodialysis patients with severe pseudomembranous colitis.

References


