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Case Report

An extremely high bioavailability of orally administered vancomycin in a patient with severe colitis and renal insufficiency

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ABSTRACT

Because there is little absorption of orally administered vancomycin hydrochloride (VCM) through the normal intestinal microvillus membrane, the pharmacokinetics of VCM absorbed from the digestive tract are mostly unknown. Here we report a case of severe colitis and renal insufficiency in which the serum concentration of VCM reached the supratherapeutic range after oral administration. A 54-year-old man receiving outpatient chemotherapy for rectal cancer was admitted to our hospital for severe sepsis and acute renal failure. Multimodal therapy including continuous renal replacement therapy (CRRT) and mechanical ventilation was initiated, and oral VCM administration (0.5 g every 6 h) was begun for suspected severe pseudomembranous colitis with large amounts of watery stool. Despite continued CRRT, the serum VCM concentration increased to 30.6 μg/mL after 4 days. Based on pharmacokinetic analysis, the bioavailability of VCM was estimated to be over 54.5%. Colonoscopy showed that the mucosa was severely damaged throughout the large intestine, resulting in considerable exudation of plasma and blood. This case indicates the need for careful and early monitoring during high-dose oral VCM administration to patients with severe mucosal injury and renal insufficiency.

1. Introduction

Oral vancomycin hydrochloride (VCM) is widely used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) colitis and *Clostridium difficile* (*C. difficile*) colitis [1]. When VCM is administered intravenously, therapeutic drug monitoring is required to ensure safety and effectiveness [1–3]. However, routine monitoring of serum concentration is not necessary for oral VCM because many reports indicate that the serum VCM concentration after oral administration is within or less than the therapeutic range [4–8]. Additionally, increases in the serum concentrations of orally administered VCM have been reported in patients with severe intestinal mucosal injury and renal insufficiency [9–13]. Thus, these two factors are thought to be risk factors for increased absorption of orally administered VCM.

As far as we know, only two studies, including a previous report of ours, have examined the bioavailability (F) of oral VCM [9,13]. Hirata et al. reported that the F of VCM was 16.8% in a hemodialysis (HD) patient with pseudomembranous enterocolitis and that the serum concentration increased to 58.7 μg/mL after 14 days of oral administration [9]. They did not mention the severity of the patient's intestinal damage. The estimated F value of VCM was over 33% in our patient, who also had severe colitis and renal insufficiency [13].

Here, we report a patient with severe pseudomembranous colitis and renal insufficiency whose F value of VCM increased to a much higher level than in all of the previous reports. In addition, we evaluated the F of VCM in this patient by retrospective pharmacokinetic investigation.

2. Case report

The present case report concerns a 54-year-old Japanese male weighing 82 kg with a history of outpatient chemotherapy with

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FOLFIRI-3 (5FU, irinotecan hydrochloride, l-leucovorin) plus cetuximab for rectal cancer associated with brain and lung metastasis. On day 9 after 4 cycles of chemotherapy, he was transferred to the intensive care unit (ICU) of our hospital in shock. Findings on admission indicated hypovolemic and septic shock due to bowel obstruction by rectal cancer. Clinical laboratory data showed severe sepsis from severe colitis, and the sequential organ failure assessment (SOFA) score was estimated to be 11. Additionally, he had a blood coagulation abnormality, with an activated partial thromboplastin time (APTT) of 72.6 s (2.5 times the normal value) and a Japanese Association for Acute Medicine disseminated intravascular coagulation (DIC) score of 6. For the rectal obstruction, he underwent loop sigmoid colostomy, and respiratory support was introduced immediately. For the sepsis and acute renal failure, CRRT was started using a BK 2.1 polymethylmetacrylate membrane hemofilter (Filtryzer, Toray, Japan) with a blood flow rate of 120 mL/min, dialysate flow rate of 1000 mL/h, and a filtration volume of 500 mL/h; the supplementary flow rate was almost 500 mL/h [14,15]. The patient had neutropenia associated with the chemotherapy; his white blood cell count gradually decreased from 1200 cells/μL on admission to 200 cells/μL before granulocyte colony-stimulating factor was initiated. Massive watery stool was discharged, and the urine volume decreased accordingly.

On day 14 after admission, his watery colostomy output increased to 2000–3000 mL/day. CT showed severe edema of the total intestinal wall. Although the patient had a negative feces culture, we suspected pseudomembranous colitis and initiated oral VCM therapy (0.5 g every 6 h; 24.4 mg/kg/day). We did not measure the VCM serum level in the initial stage of the treatment. However, our experience shows that VCM may be absorbed from the intestinal tract if the mucosa of the intestine is extensively damaged and the blood vessels are exposed [13]. In this case, we monitored the serum VCM concentration 7 days after the initiation of oral VCM administration due to the considerable discharge of intestinal fluids and maximal doses of oral VCM. The serum concentration of VCM had elevated to 25.8 μg/mL and his watery colostomy output stool had not improved. Therefore, we immediately discontinued the oral administration of VCM.

The following serum VCM measurement method was used. The serum concentration of VCM was retrospectively measured using stock blood samples (stored at −20 °C until use). VCM was administered via a nasal tube at 6:00, 12:00, 18:00, and 24:00, and blood samples were collected just before the morning administration (6:00). Serum VCM concentrations were determined by a chemiluminescent immunoassay with an ARCHITECT® analyzer (Abbott Laboratories, Irving, TX).

Fig. 1 shows the concentration-time data for VCM during the oral administration period. The serum VCM concentration increased to 8.5 μg/mL in 24 h after the initiation of oral VCM therapy. The VCM concentrations ranged from about 15–20 μg/mL in the 48 h–72 h period. The VCM concentration increased very quickly, reaching 30.6 μg/mL in 96 h.

Endoscopic examination showed that the severe colitis had not improved after 36 days of oral VCM (Fig. 2A and B). A widespread mucosal defect, ulceration with a white coat, and considerable exudation of blood and plasma were observed throughout the large intestine. Hemodynamic instability was temporarily improved by the multimodal therapy and the patient left the ICU for a short period. However, his general status gradually worsened again, and he died of multi organ failure 3 months after admission.

3. Consent

Ethical approval was obtained from the medical research ethics committee at Chiba University (No. 1809).

4. Discussion

Some reports have indicated that oral VCM is highly absorbed [9,11–13]. Thompson et al. [12] reported a case in which a significant portion of the VCM administered in peritoneal dialysis solution entered the general circulation, suggesting that dissolved VCM can be absorbed from outside vessels by passive diffusion. VCM might enter the general circulation when blood vessels are dilated at the intestinal tract. Thus, factors that can cause high levels of

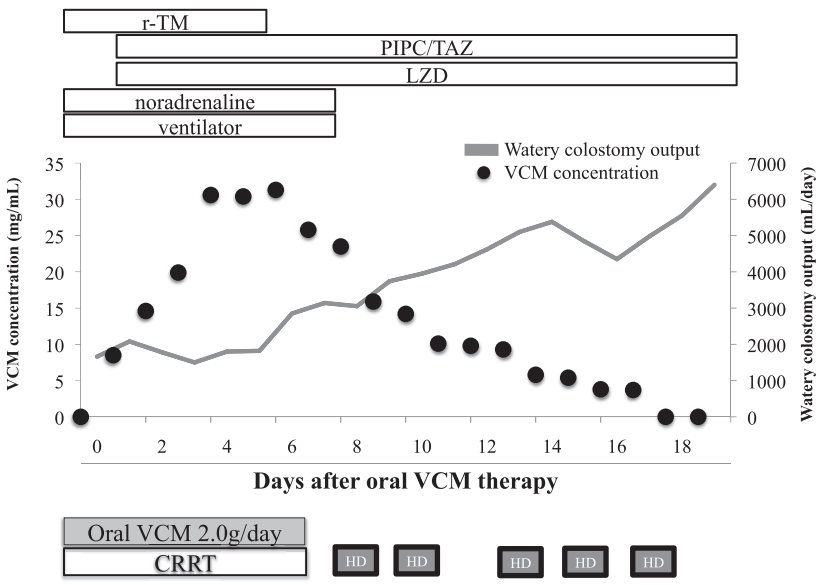

Fig. 1. Changes in the serum VCM concentration after the initiation of oral administration. The patient's serum VCM concentration increased to 25.8 μg/mL by day 7 and administration of oral VCM was discontinued. We changed the method of blood purification for sepsis improvement from CRRT to HD on the same day. Concomitant drugs and therapeutic measures are listed above.

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