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Heiman F.L. Wertheim
Medical Microbiology
L348
Erasmus MC
Dr Molewaterplein 40
3015 GD Rotterdam

Tel: 0104633510
Fax:
E-mail: h.wertheim@erasmusmc.nl
Budget: **2230**

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Heiman F.L. Wertheim Erasmus MC
Medical Microbiology
Dr Molewaterplein 40
3015 GD Rotterdam

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Oral Vancomycin Hydrochloride Therapy for Postoperative Methicillin-Cephem-Resistant *Staphylococcus aureus* Enteritis

TOSHIRO KONISHI[1], YASUO IDEZUKI[2], HIROYOSHI KOBAYASHI[3], KAORU SHIMADA[4], SHIGETOMI IWAI[5], KEIZO YAMAGUCHI[6], and NAGAO SHINAGAWA[7]

[1]Second Department of Surgery, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan
[2]Department of Surgery, Second Division, Saitama Medical Center, Saitama Medical School, 1981 Tsujido-machi, Komada, Kawagoe-shi, Saitama 350, Japan
[3]Infection Control and Prevention Service, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan
[4]Tokyo Senbai Hospital, 1-4-3 Mita, Minato-ku, Tokyo 108, Japan
[5]Third Department of Surgery, Nihon University School of Medicine, 30-1 Kami-machi, Oyaguchi, Itabashi-ku, Tokyo 173, Japan
[6]Department of Microbiology, Toho University School of Medicine, 5-21-16 Ohmori-nishi, Ohta-ku, Tokyo 143, Japan
[7]Department of Surgery, Nagoya-shi Koseiin Geriatric Hospital, 2-1501 Sekubo, Meito-ku, Nagoya 465, Japan

Abstract: The postoperative development of methicillin-cephem-resistant *Staphylococcus aureus* (MRSA) enteritis can be fatal unless it is detected at an early stage and treated with effective antibacterial agents. We report herein a Japanese multicenter collaborative clinical study on the efficacy and safety of oral vancomycin hydrochloride (VCM) in the treatment of MRSA enteritis. A total of 49 patients who had been diagnosed as having, or were strongly suspected of having, MRSA enteritis during the early postoperative period, were given oral VCM as four standard doses of 0.5 g per day. The VCM concentrations in the blood, urine, and feces were then measured. No side effects were observed and the clinical efficacy of oral VCM in the 31 evaluable patients was excellent. There was a 100% clinical response rate and a 95.8% bacterial elimination rate in the feces. The clinical complete response (CR) rate to oral VCM differed significantly between patients in whom MRSA was detected only in the feces (100%) and those in whom MRSA was isolated from an additional source (57%) ($P < 0.01$). Although VCM concentrations in the stools were extremely high, the levels in the blood and urine were very low. These results demonstrate that oral VCM should be the treatment of choice for postoperative MRSA enteritis due to its safety and efficacy.

Key Words: MRSA enteritis, vancomycin hydrochloride, postoperative infection, vancomycin concentration

Introduction

Methicillin-cephem-resistant *Staphylococcus aureus* (MRSA) infection was first reported in Europe in 1961.[1] In Japan, the first reports of MRSA isolation appeared in the early 1980s, since when the incidence has increased markedly.[2] MRSA has proven to be a serious clinical problem, since it shows resistance to the most commonly used chemotherapeutic agents and there are few drugs which are effective against it. In the field of surgery, the number of reports on postoperative infections in surgical wounds, respiratory infections, intra-abdominal abscesses, enteritis, and septicemia caused by MRSA has also been increasing. Among these infections, MRSA enteritis has shown the following characteristic clinical manifestations: the development of high fever, leukocytopenia, severe diarrhea, abdominal distention and other digestive dysfunctions,[3] and in some cases, toxic shock syndrome-like symptoms.[4] It has also resulted in multiple organ failure in the early postoperative period, particularly after surgery on the digestive tract such as gastrectomy.[5] Thus, the development of MRSA enteritis after surgery can be fatal unless it is detected at an early stage and treated with effective antibacterial agents.

Vancomycin hydrochloride (VCM, Vancocin, Eli Lilly, Indianapolis, IN, USA) is a glycopeptide antibiotic isolated from *Amycolatopsis orientalis* (formerly *Streptomyces orientalis*), and has a molecular mass of 1486 kDa.[6] By inhibiting the initial step of mucopeptide synthesis in the cell wall during cell division, VCM exerts a bactericidal action against aerobic and anaerobic Gram-positive organisms. In an in vitro subculture study, *Staphylococcus aureus* exhibited low tolerance to VCM and no cross resistance to other antibiotics.[7] As the minimum inhibitory concentration (MIC) of VCM against 106 strains of MRSA collected from 21 countries worldwide has been shown to be low, with a range of 0.25–2 mg/ml,[8] it has been the most frequently used drug for the treatment of MRSA infections.

Reprint requests to: T. Konishi, Department of Surgery, Showa General Hospital, 2-450 Tenjin-cho, Kodaira, Tokyo 187, Japan
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VCM is usually administered intravenously for MRSA infections such as septicemia, pneumonia, osteomyelitis, and postoperative wound infections. While intravenous VCM is largely excreted in the urine,[9] results from a pharmacokinetic study on patients with pseudomembranous colitis due to *Clostridium difficile* have shown that it is rarely absorbed into the blood through the alimentary tract when given orally, and is almost entirely excreted in the stool.[10] For this reason, oral VCM was predicted to be potentially the best treatment for MRSA enteritis. However, no large clinical studies have evaluated the use of oral VCM for MRSA enteritis, although several case reports have been published.[11–14] We report herein a multicenter collaborative clinical study on the efficacy and safety of oral VCM for MRSA enteritis developing in the early postoperative period. We also present the results of an investigation on VCM concentrations in the blood, urine, and feces after its oral administration.

Patients and Methods

A total of 49 patients from 27 centers in Japan (Table 1) were enrolled in this trial which was conducted over a 1-year period between April, 1992, and March, 1993. All the patients had either been diagnosed as having, or were strongly suspected of having, MRSA enteritis because of the development of watery diarrhea, high fever, abdominal pain and distention, and an increased volume of fluid draining from the nasogastric tube during the early postoperative period, defined as within 1 month after surgery. There were 20 patients enrolled after the isolation of MRSA from their feces or gastrointestinal fluid, and 29 enrolled before the isolation of MRSA. Informed consent was obtained from all patients prior to participation in the trial. VCM was either given orally or administered via a transnasal tube, generally at a dose of 0.5 g four times a day, for a period of 5 days or longer. No other oral antibacterial agents were given to any patient; however, intravenous VCM was also given to patients in whom MRSA was isolated from other sources such as the surgical wound, blood, urine, or sputum. When the intravenous administration of antibacterial agents other than VCM was indicated, these were limited to the proper agents for the flora isolated from each patient.

For the evaluation of VCM efficacy, daily changes in clinical symptoms such as fever, diarrhea, the nature of the stools, abdominal pain, and degree of meteorismus were recorded after the initiation of treatment. The clinical response to oral VCM for MRSA enteritis was evaluated using four categories, namely: complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). Thus, when the symptoms caused by the enteritis disappeared completely within 7

Table 1. The 27 collaborating Japanese clinics in the present study

First Department of Surgery, Sapporo Medical College
First Department of Surgery, School of Medicine, Akita University
First Department of Surgery, School of Medicine, Yamagata University
Second Department of Surgery, Chiba University School of Medicine
Second Department of Surgery, Faculty of Medicine, University of Tokyo
Third Department of Surgery, Nihon University, School of Medicine
Department of Surgery, Nihon University, Surugadai Hospital
First Department of Surgery, Teikyo University, School of Medicine
Third Department of Surgery, Toho University School of Medicine
Department of Gastroenterological Surgery, Tokyo Women's Medical College
Department of Surgery, Tokyo Metropolitan Geriatric Hospital
Department of Gastroenterological Surgery, Toranomon Hospital
Department of Surgery, Cancer Institute Hospital
Department of Surgery, Tokyo Kyosai Hospital
Department of Surgery, The Japanese Red Cross Medical Center
First Department of Surgery, National Defense Medical College
Department of Surgery, Showa University, Fujigaoka Hospital
Department of Critical Care and Emergency Medicine, Showa University, Fujigaoka Hospital
First Department of Surgery, Niigata University, School of Medicine
First Department of Surgery, Nagoya City University, Medical School
Department of Surgery, Chita Kosei Hospital
Department of Surgery, Kakegawa Municipal General Hospital
Department of Surgery, Kariya General Hospital
Department of Surgery, Toyama Prefectural Central Hospital
Department of Gastroenterological Surgery, Wakayama Medical College
Department of General Medicine, Hiroshima University Hospital
First Department of Surgery, Faculty of Medicine, Kagoshima University

days after the initiation of oral VCM, the patient was classified as having a CR; patients with some symptoms remaining 7 days after the initiation of oral VCM, but whose symptoms had almost disappeared by the end of treatment, were classified as having a PR; and patients who showed no improvement or the worsening of symptoms were classified as having NC or PD, respectively.

Feces or gastrointestinal fluid was collected for bacteriological investigation, and the number of bacteria contained in each sample was counted. Bacteriological efficacy was assessed by the decrease in the MRSA count in the feces or gastrointestinal fluid after treatment. Patients in whom MRSA completely disappeared after treatment were categorized as having a CR, those in whom the number of bacteria clearly diminished after treatment were categorized as having a PR, and those in whom the number did not change or increased were categorized as having NC or PD, respectively.

The VCM concentration in serum 1, 2, and 4 h after oral VCM administration between the 1st and 9th day was measured by fluorescence polarization immunoassay (FPIA),[15] while concentrations in feces and urine were measured by a bioassay method using *Bacillus subtilis* ATCC 6633 as the assay organism.[16]

The Wilcoxon rank-sum test was used for statistical analysis and P values of less than 0.05 were considered statistically significant.

Results

In this nationwide trial none of the 49 patients experienced any adverse effects caused by oral VCM. Of the total 49 patients, 18 were excluded from the evaluation of efficacy of oral VCM for MRSA enteritis. In 14 patients, this was because MRSA could not be isolated from their feces or gastrointestinal fluid despite their symptoms of enteritis, while in the other 4, although MRSA was isolated, the symptoms and clinical manifestations were too mild to classify their disease as MRSA enteritis.

The backgrounds of the 31 patients definitely diagnosed as having MRSA enteritis and included in the final analysis are summarized in Table 2. Their ages ranged from 33 to 84 years, with about two-thirds of the patients in their 60s and 70s. There were 19 patients who had undergone surgery for diseases of the upper digestive tract, namely, the esophagus or stomach; 9 who had undergone surgery for colorectal diseases; and 1 each who had undergone surgery for intestinal obstruction, pancreatitis, and urinary bladder carcinoma, respectively. Their symptoms of enteritis included watery diarrhea in 28 patients, high fever in 25, abdominal pain in 19, abdominal distention in 18, nausea and vomiting in 12, and an increased volume of fluid drained from the nasogastric tube in 8. The symptoms began between the 1st and 26th postoperative day, the average and standard deviation being 7.3 ± 5.8 days. The number of patients with moderate enteritis, as judged from the clinical manifestations, was 20 (64.5%). MRSA was isolated from the feces in 30 patients and from the gastrointestinal fluid in 1 patient. Bacteria other than MRSA isolated from the feces, such as *Clostridium difficile*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and others, are listed in Table 3. MRSA was also

Table 2. Characteristics of the 31 patients with MRSA enteritis given oral VCM

Total no. of patients	31	(%)
Sex		
Male	27	(87.1)
Female	4	(12.9)
Age		
Range	33–84	years
Mean ± SD	65.0 ± 11.2	years
Type of preceding operation		
Upper GI	19	(61.3)
Colon and rectum	9	(29.0)
Others	3	(9.7)
Severity of MRSA enteritis		
Mild	5	(16.1)
Moderate	20	(64.5)
Severe	6	(16.4)

VCM, vancomycin; MRSA, methicillin-cephem-resistant *Staphylococcus aureus*; SD, standard deviation; GI, gastrointestinal tract

Table 3. Bacteria isolated in the stools and gastrointestinal fluids

Bacteria	No. of patients
MRSA	31
Clostridium difficile	4
Enterococcus faecalis	3
Pseudomonas aeruginosa	3
Enterococcus sp.	2
Klebsiella pneumoniae	2
Staphylococcus epidermidis	1
Enterococcus faecium	1
Gram-negative rod	1
Candida sp.	1

Table 4. Sources of MRSA other than the stools and gastrointestinal fluids

Sources	No. of patients
Sputum	6
Wound	4
Sputum + blood	1
Urine	1
Blood	1
Ascites	1
Total	14

Table 5. Intravenous antibiotics given in addition to oral VCM to 19 patients

Antibiotics	No. of patients
Vancomycin	6
IMP/CS	5
Arbekacin	5
Latamoxef	4
Flomoxef	2
Cefmetazol	2
Piperacillin	2
Fosfomycin	2
Minocycline	1
Ceftazidime	1
Cefzonam	1

IMP/CS, imipenem/cilastatin

isolated from a source other than the feces, such as the sputum, wound discharge, or blood, in 14 patients (45.2%) (Table 4). There were 19 patients with infections other than MRSA enteritis who received additional intravenous antibiotics, including 6 who received intravenous VCM (Table 5).

A standard dose of 2 g VCM was given daily to 20 patients, 19 of whom received four daily doses of 0.5 g and 1 who received two daily doses of 1.0 g. In 11 patients the dose of VCM was reduced: to three doses of 0.5 g, being a total of 1.5 g/day in 5; to two doses of 0.5 g, being a total of 1.0 g/day in 4; and to four doses of 0.125 g, being a total of 0.5 g/day in 2 (Table 6). In most patients, the treatment period ranged from 5 to 10 days, although 2–4 days of oral VCM proved sufficient to cure MRSA enteritis in two patients (Table 7). The average treatment period was 7.68 ± 3.33 days.

Regarding the efficacy of oral VCM against MRSA enteritis, no mortality was observed in this study, and 25 of the 31 patients were judged clinically as having had a CR, 6 as having had a PR, and none as having had NC or PD (Table 6). The average period required to relieve the symptoms was 4 days or less. There were no significant differences in clinical efficacy attributable to sex, age, severity of enteritis, type of surgery, or the dose and duration of VCM administration. All 17 patients in whom MRSA was detected only in the feces were judged as having had a CR,

Table 6. Doses of oral VCM and clinical efficacy

Daily dose of VCM	(No. of patients)	CR	PR	NC	PD
0.5 g	(2)	1	1	0	0
1.0	(4)	3	1	0	0
1.5	(5)	3	2	0	0
2.0	(20)	18	2	0	0
Total	31	25 (80.6%)	6 (19.4%)	0	0

VCM, vancomycin; CR, complete response; PR, partial response; NC, no change; PD, progressive disease

Table 7. Duration of oral VCM and clinical efficacy

Duration of VCM	(No. of patients)	CR	PR	NC	PD
2–4 days	(2)	2	0	0	0
5–7	(15)	14	1	0	0
8–10	(10)	6	4	0	0
11–19	(4)	3	1	0	0
Total	31	25	6	0	0

Table 8. MRSA in nonfecal sources and the clinical efficacy of oral VCM in these patients

MRSA in nonfecal source	(No. of patients)	CR	PR
Absent	(17)	17 (100%)	0 (0%)
Present	(14)	8 (57%)	6 (43%)
Total	31	25	6

There was a significant difference in the efficacy of oral VCM between the patients in whom MRSA was detected only in the feces and those in whom MRSA was additionally isolated from another source ($P < 0.01$)

Table 9. PR patients

Sources of MRSA	Dose and duration of oral VCM	Duration of MRSA enteritis	Intravenous antibiotics
abdominal wound	1.5 g/day × 8 days	8 days	IPM/CS Piperacillin
sputum	0.5 × 9	9	Latamoxef Vancomycin
abdominal wound	2.0 × 8	8	IPM/CS Arbekacin
abdominal wound	1.0 × 5	8	IPM/CS Arbekacin
sputum	1.5 × 19	14	—
abdominal wound	2.0 × 10	9	Latamoxef Vancomycin

PR, partial response; IPM/CS, imipenem/cilastatin
In 6 patients with a PR, MRSA was also isolated from soruces other than the feces

while 6 of the 14 patients (43%) in whom MRSA was also isolated from a source other than the feces were judged as having had a PR (Table 8). There was a significant difference ($P < 0.01$) in efficacy between these two groups in terms of the CR rate at 100% *vs* 57%, respectively. In the six patients who showed a PR, MRSA was also isolated from the sputum or abdominal wounds, and their enteritis improved within 8 to 14 days with the concomitant use of intravenous antibiotics (Table 9).

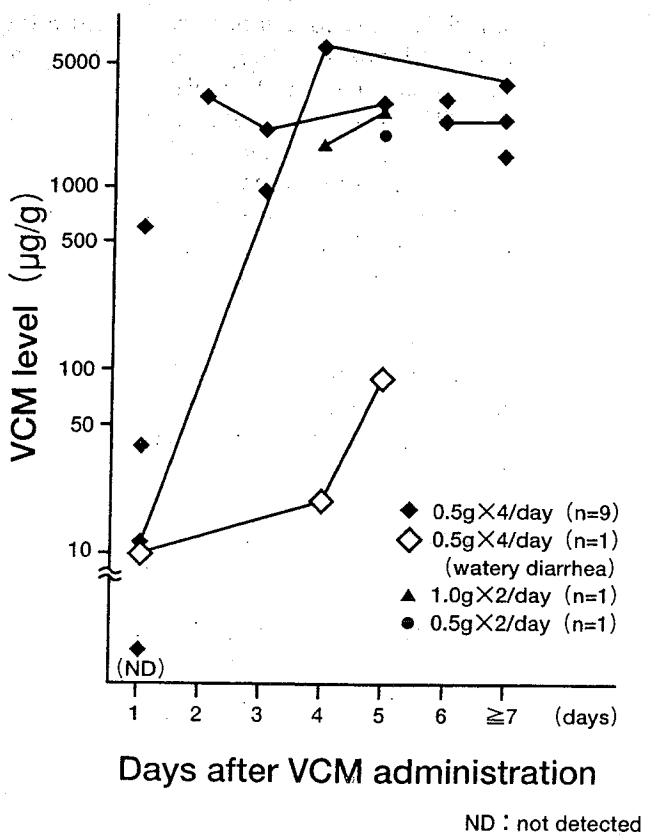

Fig. 1. Vancomycin (*VCM*) levels in the stools. VCM concentrations in the stools were generally extremely high, although they were low during the 1st day of treatment, and in patients with severe watery diarrhea

Excluding 7 patients on whom bacteriological examinations were not performed after the improvement of MRSA enteritis, the time course of changes in the MRSA counts in the feces or gastrointestinal fluids of the remaining 24 patients showed 23 to have had a CR, 1 to have had a PR, and none to have had NC/PD. The overall bacteriological CR rate was 95.8%.

VCM concentrations were measured in a total of 86 blood samples from 27 of the 49 patients. Serum VCM levels were undetectable, defined as below 1.0 mg/ml, in all samples including one from the patient given the highest dose of 1.0 g VCM.

Although the VCM concentrations in the stools were measured in 17 patients, data from 5 patients were excluded from the analysis because they had been given other intravenous antibacterial agents concomitantly with oral VCM, and it was therefore possible that the VCM levels analyzed by bioassay might be inaccurate. In the stool samples taken on the 1st day of enteral VCM administration and in those from patients with severe watery diarrhea, the VCM level was low at 10.5–92.5 mg/g. However, the VCM concentrations in all the other stool samples were extremely high, ranging from 500 to 5500 mg/g (Fig. 1). There was no correlation between the dose of oral VCM and the levels of VCM in the stools.

The urinary VCM level was also examined in 18 patients by the bioassay method, but was only able to be evaluated in 8 patients for the same reason as above. Very low levels of VCM were observed in the urine, ranging between unmeasurable and 23.40 mg/ml (Fig. 2).

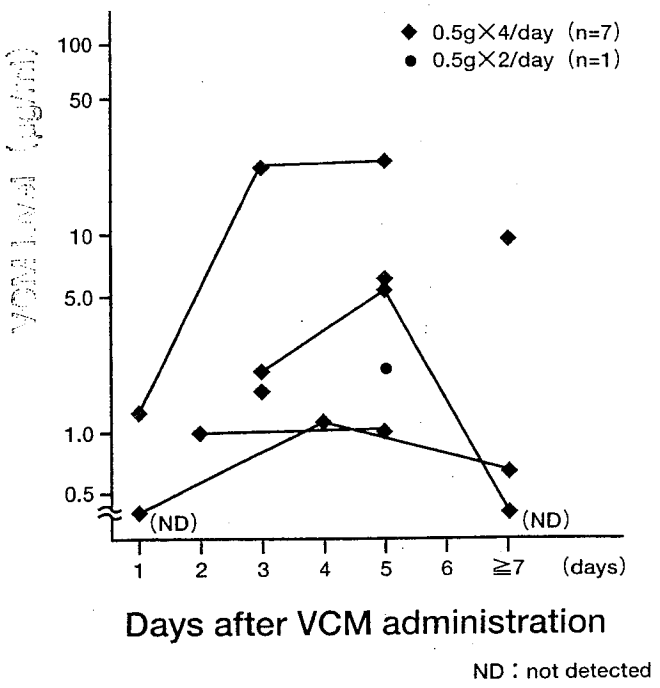

Fig. 2. VCM levels in the urine. Urinary VCM levels were very low, ranging between unmeasurable and 23.40 mg/ml

Discussion

In Japan, the number of patients who develop MRSA enteritis after surgery has been increasing[17] and oral VCM is recommended to reduce the risk of this infection during the perioperative period.[18] The purpose of this multicenter collaborative clinical study was to evaluate the efficacy and safety of oral VCM treatment for MRSA enteritis developing after surgery.

In the stools of 4 patients, 3 with a CR and 1 with a PR, *Clostridium difficile* was identified in addition to MRSA. We diagnosed these patients as having MRSA enteritis because the numbers of *Clostridium difficile* were relatively small compared with those of MRSA, and their enteritis symptoms improved in parallel with the elimination of MRSA from their stools.

The efficacy of oral VCM was demonstrated by the fact that none of the patients showed NC or PD, but 25 (80.6%) showed a CR and 6 (19.4%) showed a PR, judged according to the improvement in their symptoms. This 100% clinical response rate strongly indicates that oral VCM treatment is extremely effective for MRSA enteritis. In this study, there was no difference in efficacy between the CR and PR patients in terms of the clinical severity of enteritis, dose of VCM, or period of treatment. While patients with MRSA infection in multiple sites had less CRs, their enteritis improved within 2 weeks with concomitant intravenous antibiotics. Therefore, the systemic administration of VCM and/or other effective antibiotics in addition to oral VCM seems to be necessary if concomitant MRSA infections accompany enteritis.

According to the bacteriological examinations, the time course of changes in the MRSA counts in the stools of 24 patients indicated that none had NC or PD, while disappearance of the bacteria was observed in 23 (95.8%). Therefore, the use of enteral VCM led not only to a remarkable improvement in clinical symptoms, but also to a diminution in the numbers of MRSA in the stools. Unfortunately, it was difficult to analyze any correlation between clinical efficacy and the fecal bacteriological results because 5 of the 6 patients with a PR had been given other intravenous antibiotics, which could have interfered with the measurement of fecal VCM levels by the bioassay method.

According to an earlier nationwide questionnaire in Japan, MRSA enteritis had a mortality rate of 14.3%.[19] However, no patient died during this collaborative investigation of oral VCM treatment. In the present study, the oral VCM treatment was able to be started well before the disease had advanced to a state too severe to respond to treatment. In fact, 15 patients (48.3%) who showed distinct symptoms and signs strongly suggestive of MRSA enteritis started to receive oral VCM before the identification of MRSA in their feces or gastrointestinal fluids. If these patients had received oral VCM after MRSA had been isolated, the infection might have progressed too far to respond to treatment. Thus, when postoperative MRSA enteritis is suspected clinically, the immediate initiation of oral VCM is desirable.

From the viewpoint of safety, none of our 49 patients experienced any adverse effects attributable to oral VCM. According to a report based on results of the measurement of VCM levels in the blood after oral administration, VCM is not absorbed through the gastrointestinal tract and is mostly excreted in the stool.[10] Interestingly, a 14-year-old female receiving peritoneal dialysis after nephrectomy was reported to have developed a significant accumulation of serum VCM during oral VCM therapy for *Clostridium difficile* pseudomembranous colitis,[20] while a child with normal renal function was reported to have developed the red-man syndrome.[21] In adult patients with pseudomembranous colitis accompanying severe renal failure, oral VCM was observed to be absorbed into serum after doses of 2.0 gm/day;[22] however, the serum concentrations remained within the therapeutic range during the treatment of systemic infections. Therefore, it has been suggested that the routine monitoring of VCM concentrations in adult patients without renal insufficiency may not be necessary unless high-dose or prolonged therapy is required.[23] In the present study, the VCM blood concentrations were below the measurable range,

and it was barely detectable in the urine except in one patient with a low VCM level. Thus, it would appear that the systemic toxicity of VCM need not be considered when given orally to patients without severe renal insufficiency.

A VCM dose of 0.5 g four times daily to a total of 2.0 g per day, was employed in this study. Therapeutic efficacy would be expected with a lower daily dose, since the VCM level in the stools far exceeded the MIC after 0.5 g oral VCM, and the symptoms in two patients treated with 0.125 g four times daily subsided completely within 5 days. However, patients with severe watery diarrhea or frequent bowel movements occasionally had lower VCM levels in the stools; therefore, careful attention should be paid to the dose of oral VCM used, tailoring it to the severity of diarrhea in each patient.

The results of this analysis strongly indicate that oral VCM is the treatment of choice for MRSA enteritis developing after surgery, due to its safety and efficacy.

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