Combinatorial Vancomycin and Piperacillin/Tazobactam Results in Elevated Vancomycin Trough Concentration and Acute Kidney Injury: A Case Report

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In the hospital, antibiotics are widely used to treat infections. We report a case of acute kidney injury (AKI) caused by an antibiotic drug combination. A 30-year-old Japanese male presented with lung metastases, pneumothorax, empyema, and methicillin-resistant Staphylococcus aureus (MRSA) infection. The patient received a combination of vancomycin and piperacillin/tazobactam, which resulted in elevated vancomycin trough concentration and subsequently in AKI. Renal function was restored upon vancomycin and piperacillin/tazobactam cessation. Though this patient had AKI most likely due to the combined use of two agents as has been reported in many cases, vancomycin trough concentration showed an unexpected abnormal increase when halting vancomycin treatment. This is the first report indicating a drug-drug interaction between vancomycin and piperacillin/tazobactam with unexpected abnormal vancomycin trough concentration, leading to AKI, additionally we think that there was a situation that he stressed against the kidney by a history of medications caused renal dysfunction and co-administration. We suggest that when using vancomycin in combination with piperacillin/tazobactam, the trough concentration of vancomycin must be confirmed simultaneously with renal function and evaluation, and that the combination of these two drugs should be minimized.

Key words— acute kidney injury; vancomycin trough concentration; vancomycin; piperacillin/tazobactam

INTRODUCTION
Vancomycin, a glycopeptide antimicrobial agent, is widely used in clinical practice to treat acute, life-threatening infections caused by gram-positive bacteria that are resistant to many other antibiotics, including methicillin-resistant Staphylococcus aureus (MRSA).1 Piperacillin/tazobactam is a combination of the beta-lactamase inhibitor tazobactam and the penicillin antibiotic piperacillin at a ratio of 1:8. This potent drug combination is known to exhibit broad-spectrum activity against gram-positive, gram-negative, and anaerobic bacteria, and is sometimes administered simultaneously with other antibiotics.2 Owing to its broad-spectrum activity, it is frequently prescribed as an empirical therapy for patients with serious bacterial infections.2 Recently, it has been reported that combined use of vancomycin and piperacillin/tazobactam can cause acute kidney injury (AKI) compared to monotherapy or in combination with other beta-lactam drugs including meropenem and cefepim.3-7) The mechanism through which these agents cause AKI remains unknown, and warrants the investigation of this drug interaction to reduce the risk of AKI.8

Here, we report a case of AKI with unexpected abnormal vancomycin trough concentration caused by the combination of vancomycin and piperacillin/tazobactam.

CASE REPORT
A 30-year-old Japanese man was hospitalized for treatment with anti-cancer therapeutics. His medical history was as follows: he was diagnosed as having tongue cancer two years prior, and underwent partial tongue resection, followed by adjuvant chemotherapy including cisplatin after surgery. Nine months after surgery, metastasis was found in a lymph node located on the right side of the neck, followed by dissection of the right neck lymph node. Shortly after neck metastasis was observed, metastasis spread to the patient’s lungs, and cisplatin treatments were repeated. The patient was treated with 5 courses of treatment with anti-cancer drugs such as cisplatin, 5-fluorouracil, and cetuximab by this hospitalization. Cisplatin was administered at a dose of 80 mg/m²
every 4 weeks. He did not change the serum creatinine and body weight when administering cisplatin. His last administration of cisplatin was 18 d before the intrathoracic scraping. The patient was then hospitalized for central venous access port (CV port) insertion and anticancer drug treatment. Body weight at the time of hospitalization of patients was 62.3 kg. He presented with left pneumothorax, prompting clinicians to perform left chest drain insertion. Upon admission, the patient had a fever of 39°C, and the antibiotic levofloxacin (0.5 g) was administered once daily. The antibiotics and drainage treatment were not as effective and, so thoracoscopic tumour resection and intrathoracic scraping were performed on the left pneumothorax. The pleural effusion in operation revealed the presence of MRSA in the lung. Since the left pneumothorax, the pleural effusion in operation and intrathoracic scraping were performed on the left pneumothorax. The pleural effusion in operation revealed the presence of MRSA in the lung. Since he had postoperative pain, loxoprofen was started at 60 mg twice a day. He did not change the serum creatinine when taking loxoprofen.

Following this diagnosis, the treatment plan was changed to vancomycin 1 g every twelve hours for the treatment of empyema with MRSA. Prior to starting vancomycin, the patient did not have renal dysfunction, with a serum creatinine level of 0.46 mg/dL at the start of treatment. After three days of vancomycin treatment, dosage was increased to 1 g every eight hours since vancomycin trough concentration was 3.9 μg/mL, well below the target concentration range of 10–20 μg/mL. On the same time, he performed an examination using contrast agent. On the seventh day of vancomycin treatment, vancomycin trough concentration increased to 8.0 μg/mL, but was still below the target concentration. Dosage frequency was then increased to 1 g every six hours. On the same time, the patient experienced a fever of 38°C, and the combination of piperacillin/tazobactam (4.5 g every eight hours) was started for the treatment of infection caused by gram-negative and anaerobic bacteria. On the eleventh day of vancomycin treatment (third day of combination treatment with piperacillin/tazobactam), vancomycin trough concentration increased to 92.4 μg/mL, and serum creatinine levels were 4.67 mg/dL. Vancomycin and piperacillin/tazobactam were then discontinued and changed to the antibiotic linezolid 600 mg every twelve hours, in addition loxoprofen was discontinued at the same time. The trough concentration prior to the second dose of vancomycin was also measured and was found to be 97.2 μg/mL. On the second day of discontinuation of vancomycin, serum creatinine reached the highest value at 7.27 mg/dL, indicating AKI. On the fourth day of discontinuation of vancomycin, the blood concentration of vancomycin decreased to 69.2 μg/mL. On the seventh day of discontinuation of vancomycin, the blood level of vancomycin dropped to 12.1 μg/mL, which was the target level, and on the fourteenth day of discontinuation of vancomycin, the serum creatinine dropped to 0.65 mg/dL. Treatment with linezolid was continued for 21 d after discontinuation of vancomycin (Fig. 1).

This case was approved by the ethics review boards of Kurume University Hospital (2019-028).

### DISCUSSION

Because vancomycin and piperacillin/tazobactam play an important role in the treatment of healthcare-associated infections, they are often co-administered in the hospital. Though this patient had AKI most likely due to the combined use of two agents as has been reported in many cases, vancomycin trough concentration showed an unexpected abnormal increase when halting vancomycin treatment. The combination of vancomycin and piperacillin/tazobactam has been reported to increase the appearance of AKI compared to the combination of vancomycin alone, or with other beta-lactam drugs but a study showed that vancomycin trough concentration was unchanged when combined with piperacillin/tazobactam or when combined with cefepime before the onset of AKI. Patient was treated with cisplatin, the nonsteroidal anti-inflammatory drugs (NSAIDs) and contrast agent before two antibiotic treatments, these drugs have been reported to cause AKI. The patient had no change in the serum creatinine for this situation, but may have been stressed against the kidney. We considered that the administration of contrast agent did not match under the definition of contrast induced nephropathy, because it was administered 7 d before the onset of AKI. In addition, monotherapy of piperacillin/tazobactam and vancomycin of 4 g/d have been reported a risk factor for AKI, which may also have caused stress on the kidney. Although we could not deduce the reason for elevated trough concentration, we believe that AKI was caused by the combination of vancomycin and piperacillin/tazobactam, in addition, history of treatment with cisplatin, NSAIDs, and contrast agent, and delayed the excretion of
Fig. 1. Changes in Antimicrobial Therapy and Serum Creatinine

The combination starts date of vancomycin and piperacillin/tazobactam is set to day 0. The antibiotics used during the course of treatment included levofloxacin, vancomycin, vancomycin plus piperacillin/tazobactam, and linezolid. The status of administration of NSAIDs and contrast agent that may cause AKI is also added. The combination of vancomycin and piperacillin/tazobactam caused an increase in serum creatinine levels, and discontinuation of the two agents reduced serum creatinine. Vancomycin trough concentration showed an unexpected abnormal increase in combination with piperacillin/tazobactam and decreased after changing to linezolid.

[Graph showing changes in serum creatinine and vancomycin trough concentrations]

Vancomycin concentration (µg/mL) 3.9 8.0 97.2 69.2 12.1

LVFX: Levofloxacin, VCM: Vancomycin, PIPC/TAZ: Piperacillin/Tazobactam, LZD: Linezolid

In this extreme case, we observed a trough concentration of 97.2 µg/mL. Because we administered some drugs that cause AKI before using vancomycin and piperacillin/tazobactam, we report that in some patients, vancomycin trough concentrations may increase in combination with other agents like piperacillin/tazobactam, which can facilitate AKI. It has been reported that vancomycin trough concentrations show abnormally high and low values due to errors in measurement reagents and measurement methods. Although this case had an abnormally high value of vancomycin concentration, we suspected that the measurement reagent had no problem due to the clinical course and the decrease in blood concentration over time.

The strategies for preventing AKI include avoiding drug combinations, avoiding coadministration of nephrotoxic agents, adjusting doses, avoiding prolonged administration of two drugs, closely monitoring renal function, using daptomycin or linezolid in place of vancomycin, and using alternatives to piperacillin/tazobactam, such as cefepime or an anti-pseudomonal carbapenem. In this case, piperacillin/tazobactam was combined with vancomycin to treat empyema with MRSA. When starting piperacillin/tazobactam for anaerobic bacteria, we believe that meropenem but not piperacillin/tazobactam should be considered as an alternative therapeutic option, because the combination of meropenem and vancomycin is considered to have a lower risk of developing AKI compared to the combination of piperacillin/tazobactam and vancomycin. It has also been reported that AKI is more frequent as the number of nephrotoxic drugs and drug combinations increases. Because the patient in this case had a history of taking nephrotoxic drugs including contrast agent, cisplatin, and NSAIDs, this may have predisposed the patient to AKI prior to combinatorial vancomycin and piperacillin/tazobactam. Clinicians should investigate past medication use when determining appropriate drug regimens to reduce the risk of AKI, especially in cases that warrant using the combination of vancomycin and piper-
acillin/tazobactam.

This is the first case report that indicates a likely clinically important drug-drug interaction between vancomycin and piperacillin/tazobactam resulting in abnormal vancomycin trough concentration, leading to AKI. By halting vancomycin therapy and replacing it with a different antibiotic, renal function was eventually restored. These results suggest that concomitant therapy of vancomycin and piperacillin/tazobactam can lead to AKI and warrant close monitoring for serum creatinine and vancomycin trough concentration levels. This report also suggests that alternative drug combinations may provide better therapeutic outcomes in cases where AKI risk is increased.

Conflicts of Interest No conflicts of interest have been declared.

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