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Original Article

Comparative study on safety of linezolid and vancomycin in the treatment of infants and neonates for Gram-positive bacterial infections☆

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ABSTRACT

Background: Vancomycin has been the common antimicrobial treatment for Gram-positive infection even in neonates and infants, while it is difficult to adjust blood concentration. Linezolid is also effective for Gram-positive infection, and is not necessary to monitor drug blood concentration. Primary objective of this study was to compare the safety of linezolid and vancomycin in infants and neonates for resistant Gram-positive infections.

Methods: In total, 68 patients [linezolid group (32 patients); vancomycin group (36 patients)] treated with antimicrobials at Aichi Medical University Hospital between April 2014 and March 2017. Investigation items were as follows; sex, age, gestational age, birth weight, body weight, duration of treatment, Apgar score, laboratory data, rate of patients with blood transfusion, serum levels of vancomycin, disease type, concomitant medications, clinical isolates, adverse effects during antimicrobial treatment, antimicrobial susceptibility of isolated Gram-positive bacteria.

Results: Any substantially abnormal laboratory values were admitted in linezolid 40.6% (13/32) and vancomycin 41.7% (15/36) groups, respectively ($p = 0.93$). Platelet count was significantly decreased in only linezolid group ($p = 0.03$). Any adverse events during antimicrobial treatment were admitted in linezolid 46.9% (15/32) and vancomycin 58.3% (21/36) groups, respectively ($p = 0.34$).

Conclusion: There were no notable differences in safety of linezolid and vancomycin groups even in neonates and infants. However, platelet count was significantly decreased in only linezolid group. The careful monitoring of platelet count would be required for infants and neonates receiving linezolid treatment.

1. Introduction

Gram-positive pathogens, particularly coagulase-negative staphylococci (CoNS) and enterococci, have been identified as the most common cause of nosocomial infections in pediatric intensive care units as well as neonatal intensive care units (NICUs) [1–4]. Vancomycin, is a member of glycopeptides, containing antimicrobial regimens are the most frequently prescribed for sepsis in neonates and infants, but there are clearly very limited therapeutic options available for these patients, especially for infections caused by multidrug-resistant Gram-positive bacteria.

In previous studies, linezolid, a member of oxazolidinones, has shown antimicrobial activity against drug-resistant Gram-positive bacteria such as methicillin-resistant staphylococci, penicillin-and/or cephalosporin-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci [5–14]. In phase III study, linezolid showed the effectiveness for hospital-acquired pneumonia, bacteremia and complicated skin and skin structure infections caused by Gram-positive bacteria [15]. Additionally, one of the major side effects of linezolid is myelosuppression, especially for

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thrombocytopenia, while linezolid revealed higher tolerability, compared with vancomycin [16,17].

Of note, optimizing vancomycin dosing to rapidly achieve adequate drug exposure is imperative in treating infants and neonatal sepsis. However, this has been challenging in them as pharmacokinetics of vancomycin are highly variable among infants and neonates due to developmental and pathophysiological changes [18,19]. The ratio of the 24 h area under the concentration-time curve ($AUC_{0\text{-}24}$) to the MIC is the best predictor of successful outcomes when treating invasive MRSA infections with vancomycin. But it is not routinely utilized to assess the appropriateness of vancomycin dosing in neonates and infants, presumably due to practical limitations associated with calculating the $AUC_{0\text{-}24}$. Hence, we usually monitored blood trough concentration as alternative marker in clinical settings.

Then, previous clinical study have revealed that even after therapeutic drug monitoring (TDM) and dose adjustment of vancomycin, only 45% of neonates achieved the goal trough concentration of 10–20 μg/mL, is required for effective therapy and fewer side effects, including nephrotoxicity, at any point during their course of therapy [17]. Hence, vancomycin is the usual antimicrobial treatment for *staphylococcus* sepsis in neonates and infants but is difficult to adjust blood concentration. On the other hands, linezolid is not necessary to monitor blood concentration and also effective in infections caused by Gram-positive cocci, and devoid of renal side effects. Hence, linezolid seems like a more favorable antimicrobial treatment option than vancomycin.

However, there were few clinical reports to be compared the safety between linezolid and vancomycin treatments among infants and neonates with Gram-positive infections. Therefore, the primary objective of this study was to compare the safety between linezolid and vancomycin treatment for patients with known or suspected resistant Gram-positive infections.

2. Patients and methods

2.1. Patients

All patients were admitted to the NICU at Aichi Medical University Hospital (995 beds) and treated with linezolid or vancomycin from April 2014 to March 2017. The study was reviewed and approved by the ethics committee of the Aichi Medical University.

The patients who received two or more doses of linezolid or vancomycin were included in this study. But, the patients treated with more than 2 linezolid dosage regimen during the treatment period were excluded from this study. We collected demographic and laboratory test data on the patients such as gestational age at delivery, birth weight, gender, data and criteria for diagnosis was collected retrospectively. Additionally, we collected microbiological data if any Gram-positive bacteria were detected from any parts of the patients. All isolates were collected as part of standard patient care.

Vancomycin blood concentrations were always collected before next dose, corresponding to trough levels. Adequate serum levels of vancomycin were considered as those between 10 and 20 μg/mL. According to recent studies and considering that neonatal sepsis is a sever event, levels below 10 μg/mL were considered as decreased and inappropriate while those above 20 μg/mL were defined as increased and inappropriate.

2.2. Antimicrobial susceptibility testing

Antimicrobial susceptibility of Gram-positive isolates to linezolid and vancomycin were tested in accordance with Clinical and Laboratory Standards Institute (CLSI) guidance by broth microdilution in triplicate for each compound [20].

2.3. Safety assessments

Safety evaluations included periodic assessment of adverse events, laboratory (hematology and serum chemistry) assay results. Laboratory assay results were assessed with white blood cell count, neutrophil count, hemoglobin, hematocrit, platelet, total bilirubin, alanine aminotransferase and serum creatinine before initiation and after completion of linezolid or vancomycin treatment. The assessment of adverse events was in accordance with previous study [15]. The cases of eruption included rash due to injection site reactions and allergic reaction in both groups.

For patients with normal baseline hematology values, substantially low post-baseline values were prospectively defined as follows: <75% of the lower limit of the normal (LLN) range for platelet count, hemoglobin, hematocrit and white blood cell count and <50% of the LLN for neutrophil count. For patients with abnormal (low) baseline values, substantially low values were prospectively defined as follows: <75% of baseline for platelet count and white blood cell count, <50% of baseline for neutrophil count, <75% of the LLN and <90% of baseline for hemoglobin and hematocrit. For patients with normal baseline chemistry values, substantially elevated post-baseline values were defined as greater than twice the upper limit of normal (ULN) for alanine aminotransferase, total bilirubin and serum creatinine. For patients with abnormal baseline chemistry values (above ULN), substantially abnormal post-baseline values were defined as greater than twice the baseline value for alanine aminotransferase and serum creatinine and >1.5 times the baseline value for total bilirubin.

2.4. Statistical analysis

The data were expressed as the mean or average values. Statistical significance of the difference was evaluated with Chi-squared test for categorical data and paired *t*-test and unpaired *t*-test for continuous data respectively. Statistical analysis was performed with JMP, version 10.0 (SAS, Tokyo, Japan). A p value of <0.05 was required to achieve statistical significant.

3. Results

3.1. Patients

A total of 68 neonates or infants, received linezolid (n = 32) or vancomycin (n = 36) treatments, were included in this study (Table 1). There were no patients who discontinued administration or dose reduction due to side effects in both groups.

Thus, 42 men and 26 women, with median age of 35 (range: 4–472) days, were included in this study. The median birth weights in linezolid and vancomycin groups were 796 (450–3149) g and 751 (450–3149) g ($p = 0.81$). The median body weights in linezolid and vancomycin groups were 1496.5 (572–9235) g and 1079 (486–6470) g ($p = 0.24$). The median 1-min and 5-min Apgar scores in the linezolid and vancomycin groups were 1 min: 1 (0–7) and 2 (0–9) ($p = 0.79$), and 5 min: 4 (0–8) and 5 (0–10) ($p = 0.54$). Most of patients were received concomitant antimicrobials in the both groups (linezolid group, 96.9%; vancomycin group, 100%). Maximum number of concomitant antimicrobials was 3 in linezolid group and 4 in vancomycin group. Carbapenems was the most common antimicrobial group in both groups (linezolid group, 90.6%; vancomycin group, 72.2%).

The proportion of underlying disease type and infection type were presented in Table 2. Hematologic disease was the most

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