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ORIGINAL ARTICLE

A retrospective cohort study of panipenem/betamipron for adult pneumococcal bacteremia at three teaching hospitals in Japan

Hiromichi Suzuki · Yasuharu Tokuda · Daisuke Shichi · Shigemi Hitomi · Hiroichi Ishikawa · Tetsuhiro Maeno · Hidenori Nakamura

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Abstract Panipenem/betamipron (PAPM/BP) may be highly effective for life-threatening *Streptococcus pneumoniae* infection. However, the efficacy of PAPM/BP for *S. pneumoniae* infections has not been compared with that of other antimicrobial agents. We retrospectively compared PAPM/BP with other carbapenems for treatment of life-threatening infections in newly hospitalized adults with pneumococcal bacteremia. Clinical information for cases of pneumococcal bacteremia was collected from three teaching hospitals in Japan from January 2003 to December 2010. In total, 17 patients who received PAPM/BP therapy and 34 treated with other carbapenems (27 with meropenem, 4 with imipenem/cilastatin, and 3 with biapenem) were identified. The mean age (71 vs. 70 years old), sex distribution (women, 29 vs. 21 %), Charlson comorbidity index (CCI) (1.5 vs. 1.6), and rates of septic shock (29 vs. 38 %), and meningitis (5.9 vs. 8.8 %) did not differ significantly between the two groups. The inpatient mortality rates were lower in the PAPM/BP group (12 vs. 44 %, $p = 0.03$). Multiple logistic regression analysis adjusted for age, sex, CCI, and severe sepsis/septic shock showed that use of other carbapenems was associated with higher in-hospital mortality, with an odds ratio of 6.922 (95 % CI, 1.171–40.92) compared to PAPM/BP therapy. Initial PAPM/BP therapy might have a therapeutic advantage over other carbapenems in treatment of severe *Streptococcus pneumoniae* infections.

Keywords *Streptococcus pneumoniae* · Carbapenem · Panipenem

H. Suzuki (✉)
Department of Clinical Laboratory Medicine, Tsukuba Medical Center Hospital, 1-3-1 Amakubo, Tsukuba, Ibaraki 305-8558, Japan
e-mail: hsuzuki@tmch.or.jp

H. Suzuki · T. Maeno
Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

Y. Tokuda
Department of Medicine, Mito Kyodo General Hospital, University of Tsukuba, Mito, Japan

D. Shichi
Department of Infectious Diseases and Rheumatology, Seirei Mikatahara General Hospital, Hamamatsu, Japan

S. Hitomi
Department of Infectious Diseases, Tsukuba University Hospital, Tsukuba, Japan

H. Ishikawa
Department of Respiratory Medicine, Tsukuba Medical Center Hospital, Tsukuba, Japan

H. Nakamura
Department of Respiratory Medicine, Seirei Hamamatsu General Hospital, Hamamatsu, Japan

Introduction

Streptococcus pneumoniae is a common pathogen and the leading cause of pneumonia and meningitis. Beta-lactam agents are the main treatment options for *S. pneumoniae* infection, and a large international study suggested equal efficacy of different beta-lactam agents for treatment of pneumococcal bacteremia [1]. The value of combined therapy in initial antimicrobial agent selection for pneumococcal bacteremia has been suggested in an observational study [2]; however, a conclusion has yet to be established in this regard [3].

Panipenem/betamipron (PAPM/BP), a carbapenem antimicrobial agent developed in Japan, can be administered intravenously [4]. After its commercial release in 1993, PAPM/BP has been widely used for treatment of life-threatening infections and is thought to be highly effective for *S. pneumoniae* infection based on its excellent in vitro activity against *S. pneumoniae* [5–7]. However, there have only been a few clinical evaluations of PAPM/BP therapy for *S. pneumoniae* infections [8–11] and no comparative studies of the efficacy of PAPM/BP with that of other antimicrobial agents.

Unnecessary use of carbapenems must be avoided to prevent an increase in multidrug-resistant bacteria. In this context, we faced the question "Does PAPM/BP really have an advantage for *S. pneumoniae* infection?" In clinical practice in Japan, PAPM/BP and other carbapenems are mainly used by clinicians for treatment of life-threatening infections. Carbapenems have been shown to not have superior efficacy compared with beta-lactams for treatment of *S. pneumoniae* infections. Thus, we retrospectively compared the efficacy of PAPM/BP therapy with that of other carbapenems in newly hospitalized adults with pneumococcal bacteremia.

Patients and methods

Patients

All hospitalized adult patients with community-acquired pneumococcal bacteremia who visited Seirei Mikatahara General Hospital (SMGH, 934 beds), Seirei Hamamatsu General Hospital (SHGH, 744 beds), and Tsukuba Medical Center Hospital (TMCH, 409 beds) from January 2003 to December 2010 were retrospectively assessed and included in the study. All three hospitals are teaching hospitals equipped with tertiary emergency medical centers. The inclusion criteria were (1) diagnosis of new pneumococcal bacteremia requiring hospitalization and (2) age $\geq$18 years old. The exclusion criteria were (1) medical history of pneumococcal bacteremia; (2) inpatient treatment for pneumococcal bacteremia in hospitals other than those already mentioned; (3) lack of detailed inpatient treatment information; (4) patient refusal to provide personal information for nonmedical purposes; or (5) contraction of hospital-onset pneumococcal bacteremia diagnosed based on new symptoms that developed after hospitalization or from a culture of blood drawn >48 h after hospitalization. After identification of patients, we defined four treatment groups (PAPM/BP, other carbapenems, third-generation cephalosporins, and penicillins) and analyzed the medical background, clinical severity, and outcome in each group.

Data collection

Medical records, nursing databases, and microbiological records from each hospital were reviewed by two physicians qualified as Fellows of the Japanese Society of Internal Medicine, between whom all decisions were made based on consensus. The demographic and background data included age; sex; body weight; residence; energy intake; functional capacity in activities of daily living (ADL) before onset of pneumococcal bacteremia (Katz index [12]); comorbidity, as assessed by the Charlson comorbidity index (CCI) [13]; diagnosis of diabetes mellitus or malignancy; use of dialysis, immunosuppressants (prednisolone $\geq$1 mg/day), or chemotherapy; splenectomy; and administration of antimicrobial agents before blood culture. Clinical and laboratory data included the clinical severity scale score (severe sepsis or septic shock) [14], albumin level, C-reactive protein level, white blood cell count, glomerular filtration rate (GFR) obtained using the Cockcroft–Gault formula, main sources of infection, initial antimicrobial agents used, duration of symptoms from onset to initiation of antimicrobial agent, and immunoglobulin or steroids used. Urine output and lactic acid concentrations were not evaluated as criteria for severe sepsis. The prothrombin time international normalized ratio (PT-INR) was taken to be $\leq$1.5 in cases in which prothrombin time was not determined. In nine patients with unknown body weight, the estimated GFR (eGFR) was calculated using the eGFR estimation formula for the Japanese population [15].

Outcomes

Length of hospital stay, morbidity, and mortality were evaluated as outcomes. Morbidity included reduced functional capacity in ADL (Katz Index) at discharge, development of impaired oral intake, or requirement for oxygen assistance at discharge. Mortality was evaluated based on 14-day, 30-day, and inpatient mortality rates.

Microbiology and dosage of antimicrobial agents

Pneumococcal bacteremia was defined as a case in which *S. pneumoniae* was recovered from at least one blood specimen. Antimicrobial susceptibilities were determined with broth microdilution methods and categorized according to the criteria of the Clinical and Laboratory Standards Institute [16]. Susceptibility results obtained with the disk diffusion method (Tsukuba Medical Center Hospital data before October 2009) were excluded. We also evaluated the initial dosage of each antimicrobial agent. For patients with decreased renal function, the estimated dosage was calculated based on their GFR and the dosing guidelines