

学位論文の要旨

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学位論文名 Efficacy and Safety of Piperacillin/Tazobactam Versus Biapenem in Late Elderly Patients With Nursing- and Healthcare-Associated Pneumonia.

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論文内容の要旨

INTRODUCTION

Pneumonia is associated with an extremely high mortality rate in late elderly patients. Selection of appropriate antibacterial drugs and administration of appropriate doses are important, particularly in late elderly patients. However, the range of current antibiotics is limited, and the development of new antibiotics is difficult. It is therefore necessary to use the existing antibiotics properly. In addition to the efficacy, it is necessary to pay attention to the toxicity of the antibiotics, especially in treating elderly patients with numerous underlying diseases and potential organ dysfunction.

In August 2011, a new concept, nursing- and healthcare-associated pneumonia (NHCAP) was proposed by the Japanese Respiratory Society. NHCAP is a concept focusing on the onset of pneumonia in patients with backgrounds including: (1) stay in a long-term care facility or nursing home, (2) discharge from the hospital within 90 days, (3) elderly or paralyzed patients requiring nursing care, and (4) patients receiving ongoing endovascular repair treatment as outpatients; with many patients falling under this definition being elderly patients. According to the guidelines for NHCAP, piperacillin/tazobactam and carbapenems are listed as the first choice drugs for hospitalized patients with potentially resistant bacteria.

Biapenem was developed in Japan as the fourth carbapenem in 2002. Since biapenem is primarily used in Japan and is not used outside Japan, the clinical data in elderly patients are yet insufficient. Therefore, we firstly planned to evaluate the efficacy and safety of biapenem against pneumonia in the elderly patients.

Piperacillin/tazobactam is a standard drug which is currently used in 94 countries worldwide. As the second study, we retrospectively compared the clinical efficacy and safety of piperacillin/tazobactam and biapenem in the treatment of elderly patients with NHCAP.

MATERIALS AND METHODS

In the first study, the subjects with pneumonia were 65 years of age or older. Biapenem (300 mg) was administered once to three times per day based on the Cockcroft-Gault equation. The clinical efficacy was evaluated based on the improvement in subjective symptoms and objective findings. The primary outcome was the efficacy rate at the end of treatment. We also evaluate the safety based on the side effects that had occurred during treatment.

In the second study, among elderly patients with NHCAP, we extracted 53 patients treated with piperacillin/tazobactam and 53 patients treated with biapenem, who were matched for sex, age, and severity of pneumonia. Piperacillin/tazobactam (2.0 g/0.25 g or 4.0 g/0.5 g) was administered based on the Sanford guide to antimicrobial therapy. Biapenem (300 mg) was administered once to three times per day based on the Cockcroft-Gault equation. The clinical efficacy was evaluated on days three and seven following the administration of therapy, as well as at the end of the treatment. The primary outcome was the clinical efficacy rate at the end of the treatment. The secondary outcome was clinical response (the pneumonia symptoms, chest X-ray score, body temperature, C-reactive protein, and white blood cell count) on days three and seven during treatment. We also evaluated the safety based on the side effects during treatment and bacteriological findings.

RESULTS AND DISCUSSION

In the first study, we confirmed the efficacy and safety of biapenem for the treatment of elderly patients with pneumonia. Biapenem was effective in 85.0% of subject cases. Although four cases experienced hepatic dysfunction and nausea was observed in one case, these adverse effects were not severe so that the administration of drug was continued in all cases. In 13 cases whom the trough value of biapenem was measured, there was no unacceptable side effect and the trough values were generally low. We confirmed that biapenem (300 mg once to three times a day), even in elderly patients, did not accumulate, and that the dosages applied were safe and appropriate.

In the second study, the average ages of the patients in the piperacillin/tazobactam and biapenem groups were 81.8 and 82.1 years, respectively, with most of the patients being middle to older ages. The clinical efficacy at the end of treatment was 96.1% in the piperacillin/tazobactam group and 86.5% in the biapenem group, and the difference was not statistically significant. Significant improvements were noted on day seven in all four parameters (chest X-ray score, body temperature, C-reactive protein, and white blood cell count) in both groups compared with the respective findings before treatment. Significantly faster improvements were observed in the chest X-ray scores ($P<0.01$) and body temperatures on day seven ($P<0.05$) in the piperacillin/tazobactam group than in the biapenem group. Toxicity

profiles were different between the two groups. Hepatic toxicity was significantly higher in the biapenem group ($P<0.05$), whereas nephrotoxicity was significantly more common in the piperacillin/tazobactam group ($P<0.01$). Nephrotoxicity led to a need for a dose reduction or discontinuation of the treatment in seven cases of the piperacillin/tazobactam group. On the other hand, the continuous treatment was feasible in seven cases in the biapenem group, suggesting better continuation of treatment in the biapenem group than in the piperacillin/tazobactam group. The average age of the patients who developed significant nephrotoxicity was as high as 83.2 years. It has been reported that (1) an age above 65 years, (2) a low estimated glomerular filtration rate at baseline, and (3) the use of piperacillin/tazobactam are independent predictors of renal failure. Thus, in addition to the subjects being elderly, the renal impairment due to aging and administration of piperacillin/tazobactam were the causes of the nephrotoxicity. These findings suggest that it is important to select antibiotics with the potential side effects deliberately, although rapid anti-inflammatory effects could be helpful in elderly patients by preventing impaired activities of daily living. Regarding the bacteriological evaluation, drug resistant bacterias, including *Pseudomonas aeruginosa*, were detected in both groups. The bacteriological findings reflected the characteristic of NHCAP. The rate of decrease or disappearance of bacteria was equally good in the two groups.

In the second study, piperacillin/tazobactam provides significantly faster improvements than biapenem. Taking the rapid anti-inflammatory effects of piperacillin/tazobactam into consideration, it is reasonable to use piperacillin/tazobactam for the treatment of NHCAP. On the other hand, significant side effects, particularly nephrotoxicity, were observed following the use of piperacillin/tazobactam. Taking the potential toxicity into account, it is necessary to provide careful follow up after initiating treatment especially in late elderly patients. Serious nephrotoxicity occurred, although the dose administered was determined based on the Sanford guide. These findings suggest that the doses estimated by Sanford guide could be excessive for elderly Japanese patients. To conduct detailed evaluations, including determination of the optimal dose and timing of administration, is necessary for optimizing antibacterial chemotherapy in elderly patients with numerous underlying diseases and potential organ dysfunction. A pharmacokinetic/pharmacodynamic study of piperacillin/tazobactam in elderly patients with NHCAP has been currently in progress in our department. Our future goal is to offer more precise and tailored antibacterial chemotherapy which is based on our original pharmacokinetic/pharmacodynamic analysis performed in elderly Japanese population.

CONCLUSION

Biapenem is as effective as piperacillin/tazobactam, and is safer than the latter in terms of its less nephrotoxicity. Biapenem should be a first line drug for the treatment of elderly NHCAP.

別紙

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- 論文名
1. Evaluation of the efficacy and safety of biapenem against pneumonia in the elderly and a study on its pharmacokinetics.
 2. Efficacy and safety of piperacillin/tazobactam versus biapenem in late elderly patients with nursing- and healthcare-associated pneumonia.
- 発表雑誌名
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1. Fumi Karino, Naoko Deguchi, Hibiki Kanda, Miki Ohe, Keiichi Kondo, Mitsuhiro Tada, Takashige Kuraki, Nobuhiro Nishimura, Hidehiko Moriyama, Kazuro Ikawa, Norifumi Morikawa, Takeshi Isobe
 2. Fumi Karino, Kiyotaka Miura, Hiroshi Fuchita, Naoya Koba, Emiko Nishikawa, Takamasa Hotta, Tamio Okimoto, Shinichi Iwamoto, Yukari Tsubata, Mitsuhiro Tada, Shunichi Hamaguchi, Takeshi Honda, Miki Ohe, Akihisa Sutani, Takashige Kuraki, Hiroyasu Takeyama, Takeshi Isobe