International Journal of Medical Science and Health Research

Vol. 1, No. 02; 2017

ISSN: 2581-3366

Simulation-based Antibiotic Treatment: Meropenem Administration for Elderly Pneumonia Patients

Kouji Aimiya[1, 2, *], Takayoshi Mamiya[1, *], Katsunori Tabuchi[3], Toshiyuki Kita[4], and Masayuki Hiramatsu[1]

[1] Department of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya 468-8503, Japan

[2] Department of Clinical Research, National Hospital Organization Kanazawa Medical Center, 1-1 Shimo-ishibiki-machi, Kanazawa 920-8650, Japan

[3] Department of Pharmacy, National Hospital Organization Kanazawa Medical Center, 1-1 Shimo-ishibiki-machi, Kanazawa 920-8650, Japan

[4]Department of Pulmonary Medicine, National Hospital Organization Kanazawa Medical Center, 1-1 Shimo-ishibiki-machi, Kanazawa 920-8650, Japan

Running title

Meropenemsimulation in elderly pneumonia patients

Contact address

Department of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya 468-8503, Japan

*Corresponding author:E-mail: mamiya@meijo-u.ac.jp

ABSTRACT

Meropenem (MEPM) is a carbapenem antimicrobial used for the treatment of pneumonia. Our previous study revealed that there are no differences on the therapeutic effects of MEPM (0.5 g) between the treatment of twice daily and three-times daily for the elderly pneumonia patients(≥75 years old). However, it is unclear what factor significant are for the elderly pneumonia patients.In this study, the MEPM concentration in the blood was simulated by pharmacokinetics/pharmacodynamics (PK/PD)theory, we estimated the effective number of MEPM administration, and then we evaluated the therapeutic effects. Two elderly patients, who are diagnosed moderate pneumonia patients in our hospital were simulated using the factors, age, sex, body weight and serum creatinine values. It was expected to be effective by the PK/PD-

Vol. 1, No. 02; 2017

ISSN: 2581-3366

based simulation; MEPM treatment twice daily in one case, and three-times daily in other case. Actually, both administrations improved the body temperature, white blood cell and C-reactive protein (CRP), indicating that appropriate treatment of MEPM may prevent the worsening of symptom. These results suggest that it would be very significant to treat the pneumonia patients carefully by considering renal function and conducting the simulations of antimicrobial drugs based on the PK-PD theory.

Keywords: meropenem, elderly patient, pneumonia, simulation

Introduction

Meropenem (MEPM) is a carbapenem antimicrobial widely used for the treatment of infections caused by gram-positive and gram-negative bacteria except for methicillin-resistant *Staphylococcus aureus*, or MRSA (Wakisaka et al., 2015; Hamada et al., 2015). The dosage and frequency of MEPM (0.5 to 1.0 g in 2 to 3 times) recommended for pneumonia patients (Guidelines for the Management of Community Acquired Pneumonia in Adults(2010); Guidelines for Pneumonia in Adults(2017)) already have sufficient therapeutic effects in clinical practice. MEPM is currently administered to elderly pneumonia patients at the same dosage and frequency, but routinely administering MEPM regardless of the age-related decline in kidney function sometimes gives doses higher than necessary for those elderly patients. Therefore, when giving MEPM, we need to consider a more carefully designed dosage regimen taken into account not only kidney function but also the minimum inhibitory concentrations (MICs) determined for pathogenic bacteria, as well as patient information including age and body weight, in order to avoid its excessive dosing (Tanigawara, 2003).

According to our latest report on the dosing frequency of MEPM (0.5 g) and its effects in elderly pneumonia patients, the comparison between twice and three-times daily administration in each indicator: body temperature, C-reactive protein (CRP) levels and white blood cell (WBC) count 3-5 days after the first dose, showed no significant difference in therapeutic effects of MEPM (Aimiya et al., 2018). We also found that even the twice daily administration can potentially have the therapeutic effects in many cases. It is, however, not clear yet under what circumstances the twice daily administration works effectively. If we understand which indicator is used to determine dosing frequency, this will lead to the proper use of antimicrobial and help alleviate the physical and mental burden in elderly patients, which may contribute towards more efficient drug therapy. The first dose of MEPM, in particular, is a key point that helps prevent worsening of the symptoms associated with infections and decrease symptoms.

We computed the duration of the first-dose efficacy of MEPM based on laboratory test results obtained prior to the first dose of MEPM in elderly pneumonia patients who signed the

Vol. 1, No. 02; 2017

ISSN: 2581-3366

informed consent form. A comparison was made between effective dosing frequency obtained from the simulation and actual efficacy of MEPM.

Materials and Methods

1. Patients

Of patients aged 75 and over who had been admitted to the National Hospital Organization Kanazawa Medical Center between July 1 and September 30, 2016, two elderly pneumonia patients whose diagnosis had been made based on patient's background (shown in Figure 1), underlying disorders, physical findings, examinations and chest X-ray images (Sakamoto et al., 2010; Ishihara et al., 2012) and who had been judged preferable to MEPM administration participated in this study.

2. Efficacy assessment by Monte Carlo simulation analysis based on pharmacokinetic/pharmacodynamics (PK/PD) theory and the first dose of MEPM

Among bacteria isolated from patients with community acquired pneumonia (Saito et al., 1999)in our medical center, *Pseudomonas aeruginosa* (MIC = 8 μg/mL; Yamaguchi et al., 2014) highly resistant to MEPM was used for the simulation analysis. The application of PK/PD modeling to MEPM (Omegamon^{TM} ver.3; Pharmacist Support Ltd., provided by Professor NorifumiMorikawa at Hiroshima University) was used to analyze twice or three-times daily administration of 0.5 g MEPM with respect to each of the following patient information: age, sex, body weight and serum creatinine levels. Duration was computed when the T>MIC exceeded 40% because bactericidal effects of carbapenem antimicrobials could be expected at a T>MIC of 40% or higher (Higuchi et al., 2007; Drusano, 2003). Therapeutic assessment for the first dose of MEPM was performed regarding body temperature, WBC count and CRP levels obtained prior to MEPM administration and 4 days after MEPM administration. A-DROP in Guidelines for the Management of Community Acquired Pneumonia in Adultswas used for therapeutic assessment (Saito et al., 1999). This study was approved by an ethics committee of the National Hospital Organization Kanazawa Medical Center prior to commencement (#2017-No.73).

Results

Efficacy determination by simulation and the first dose of MEPM

Case 1: According to the simulation results of the 90-year-old woman (body weight: 27.4 kg, serum creatinine level: 0.46 mg/dL), twice and three-times daily administration achieved a 29% T>MIC and a 44% T>MIC, respectively. Three-times daily dosing was therefore given to the patient. Her laboratory test results obtained 4 days after MEPM administration (body

Vol. 1, No. 02; 2017

ISSN: 2581-3366

temperature: 36.9˚C, WBC count: 4200 cells/μL, CRP level: 1.2 mg/dL) improved compared to those obtained prior to MEPM administration (body temperature: 37.0˚C, WBC count: 7900 cells/μL, CRP level: 4.3 mg/dL).

Case 2: According to the simulation results of the 82-year-old man (body weight: 55.7 kg, serum creatinine level: 1.59 mg/dL), twice and three-times daily administration achieved a 40% T>MIC and a 63% T>MIC, respectively. Twice daily dosing was therefore given to the patient. His laboratory test results obtained 4 days after MEPM administration (body temperature: 36.6˚C, WBC count: 5500 cells/μL, CRP level: 1.1 mg/dL) improved compared to those obtained prior to MEPM administration (body temperature: 36.9˚C, WBC count: 7300 cells/μL, CRP level: 4.1 mg/dL).

According to the assessment using A-DROP, both cases showed the moderate level of pneumonia in both prior to MEPM administration and 4 days after MEPM administration.

Discussion

The main cause of pneumonia is inflammation due to bacterial infection and the only fundamental solution is drug therapy with antibiotic use. Among antibacterial drugs, MEPM has a wide antibacterial spectrum ranging from gram positive bacteria to gram negative bacteria and anaerobic bacteria, and it is also used for severely ill patients with reduced immune function (Wakisaka et al., 2015; Hamada et al., 2015). It is recognized that antimicrobial therapy based on the Pharmacokinetics/ Pharmacodynamics (PK-PD) theory leads the appropriatetherapy for the infection and suppresses the expression of drug-resistant microbials. Additionally, it is suggested that the simulation based on PK-PD theory is very useful when the carbapenem antimicrobials are used (Mikamo et al., 2007). Therefore, in this study, the MEPM concentration in the blood was simulated by PK-PD application, we estimated the effective number of MEPM administration, and then we evaluated the therapeutic effects.

In our hospital, Pseudomonas aeruginosa is sometimes detected with MEPM-resistant bacteria from the community-acquired pneumonia patients.The MIC against Pseudomonas aeruginosa(8 □g/mL) is the highestamong those against 4 bacteria (S. pneumoniae, K. pneumoniae, H. influenzaand P.stuartii; MIC = 1.0□g/mL)which are detected there, therefore we simulated MEPM concentration curve using the MIC = 8□g/mL (Yamaguchi et al., 2014). It was estimated that the MEPM regimens of three-times daily in the Case 1, and twice daily in the Case 2 are effective, and actually administered to the two patients. As results, both administrations improved all of the body temperature, WBC and CRP, suggesting that appropriate treatment of MEPM may prevent the worsening of symptom. There were also no obvious adverse effects of MEPM regarding hepatic and renal functions, at least.

Vol. 1, No. 02; 2017

ISSN: 2581-3366

The initial administration of MEPM is a very important process to prevent severity of the symptom for the elderly pneumonia patients.Pharmacokinetics of MEPM is influenced mainly by renal function (Tanigawara, 2003). Therefore, the renal excretion of MEPM will be considered to be delayed due to decreased renal function with aging.Here the most significant factor may be the serum creatinine level in the patient information of this simulation study.

Conclusion

It would be very significant to treat the pneumonia patients carefully by considering the presumptive causative bacteria of pneumonia from individual patients and conducting the simulations of antimicrobial drugs based on the PK-PD theory, whereas further additional studies are needed.

Acknowledgements

We are thankful to Professor NorifumiMorikawa of Hiroshima University for providing the simulation software, Omegamon^{TM} ver.3. This work was fully supported by Research Grants from National Hospital Organization Kanazawa Medical Center and Meijo University for graduate students.

Conflict of Interest

The authors declare no conflicts of interest.

References

Aimiya K, Mamiya T, Tabuchi K, Kita T, Hiramatsu M, Comparison of twice a day and three times a day meropenem administration in elderly patients in a Japanese community hospital. *Nagoya J Med Sci*. 2018; *In press.*

Drusano G, Prevention of resistance: a goal for dose selection for antimicrobial agents. *Clin Infect Dis*, 2003; 36: 42-50.

Guillemot D, Carbon C, Balkau B, Geslin P, Lecoeur H, Vauzelle-Kervroëdan F, Bouvenot G, Eschwége E, Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. *JAMA* 1998; 279: 365-370.

Hamada Y, Niwa T, Muraki Y, Aoyama S, Ueda H, Okudaira M, A multicenter retrospective analysis of the clinical safety and efficacy of the post-approval meropenem dose in Japanese patients. *Jpn JChemother*, 2015; 63: 560-567.

Vol. 1, No. 02; 2017

ISSN: 2581-3366

Higuchi T, Ota K, Tanabe Y, Suzuki E, Gejyo F, Severity classification and hospitalized elderly patients with community-acquired pneumonia. *Jpn JGeriatr,* 2007; 44: 483-489.

Ishihara N, Nishimura N, Suyama T, Tamaki H, Kanda H, Isobe T, Personalized optimization of meropenem regimen by pharmacokinetic-pharmacodynamic software. *Jpn J Ther Drug Monit*, 2012; 29: 53-60.

Mikamo H, Ninomiya M, Tamaya T, Investigation on administration method of carbapenems. *Jpn J Antibiotics,* 2002; 55: 875-881.

Mikamo H, Tanaka K, Watanabe K, Efficacy of injectable carbapenems for respiratory infections caused by *Streptococcus pneumonia* and *Haemophilusinfluenzae* with Monte Carlo simulation. *Jpn J Antibiotics*, 2007; 60: 47-57.

Saito A, Miki F, Oizumi K, Rikitomi N, Watanabe A, Koga H, Report of the committee for the respiratory system, Japan Society of Chemotherapy, Clinical evaluation methods for new antimicrobial agents to treat respiratory infections. *J InfectChemother,* 1999; 5: 110-123.

Sakamoto N, Sugihara E, Boku S, Fukuda H, Isonuma H, Aiba M, Clinical analysis of mortality in elderly patients with community-acquired pneumonia. *Jpn J Geriatr,* 2010; 47: 47-51.

Tanigawara Y, Recent advances in pharmacokinetics in elderly patients. *Jpn J Geriatr,* 2003; 40: 109-119.

The committee for the Japanese Respiratory Society (JRS) guidelines in management of respiratory infections. The JRS guidelines for the management of community-acquired pneumonia in adults. 2010.

The Japanese Respiratory Society, The committee for the Japanese Respiratory Society (JRS) guidelines in management of respiratory infections. The JRS guidelines for the management of hospital-acquired pneumonia in adults. 2017.

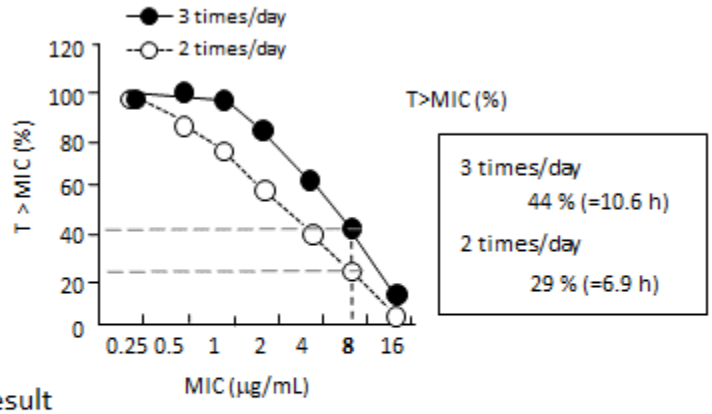
Watanabe A, Tokue Y, Aoki N, Matsuoka H, Yanagihara K, Higa F, Japanese Society of Chemotherapy Antimicrobial Agents Safety Evaluation Standards Committee, Criteria for safety evaluation of antimicrobial agents. *J Infect Chemother,* 2011; 17: 139-147.

Wakisaka K, Tani S, Ishibashi K, Nukui K, Nagao M, Results of a post-marketing surveillance of meropenem administered over 2g/day for serious infection diseases. *Jpn J Antibiotics,* 2015; 68: 257-273.

Yamaguchi K, Ishii Y, Tateda K, Iwata M, Watanabe N, Shinagawa M, Kayaba H, Kimura M, Suwabe A, Kaku M, Abe Y, Kanemitsu K, Taniguchi N, Murakami M, Maesaki S, Kawamura T, Nomura F, Watanabe M, Kanno H, Horiuchi H, Tazawa Y, Kondo S, Misawa S, Takemura H, Nakashima H, Matsuto T, Fujimoto Y, Ishigo S, Gotoh H, Watanabe O, Yagi T, Shimaoka N, Mikamo H, Yamagishi Y, Fujita N, Komori T, Ichiyama S, Kawano S, Nakayama A, Nakamura F, Kohno H, Fukuda S, Kusano N, Nose M, Yokozaki M, Onodera M, Murao K, Negayama K, Nishimiya T, Miyamoto H, Matsunaga A, Yoshimura H, Kohno S, Yanagihara K, Hiramatsu K, Nationwide surveillance of parenteral antibiotics containing meropenem activities against clinically isolated strains in 2012. *Jpn J Antibiotics*, 2014; 67: 73-107.

Case 1

Simulation



Therapeutic result

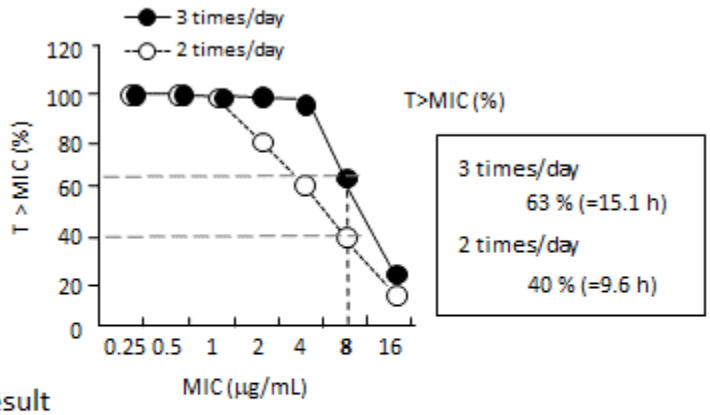
3 times Treatment	Day 0	Day 4
Body Temperature (℃)	37.0	36.9
White blood cell (counts/mm^3)	7900	4200
CRP (mg/dL)	4.3	1.2
Symptom severity by A-DROP	Moderate	Moderate

Vol. 1, No. 02; 2017

ISSN: 2581-3366

Case 2

Simulation



Therapeutic result

2 times Treatment	Day 0	Day 4
Body Temperature (℃)	36.9	36.6
White blood cell (counts/mm^3)	7300	5500
CRP (mg/dL)	4.1	1.1
Symptom severity by A-DROP	Moderate	Moderate

Figure 1. Simulation of meropenem treatment in two elderly pneumonia patients. Actually, meropenem was administered 3 times daily in Case 1 and 2 times daily in Case 2.