〈Original Article〉

Influence of meropenem treatment on hepatic and renal function in Japanese patients with creatinine clearance rates of 10 to 50 mL/min: A single-center retrospective study

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Background: Meropenem is used as empirical therapy for severe sepsis and various infections. It is important to understand the tolerability of meropenem to administer it at a sufficiently high dose (e.g. 1 g or 2 g every 8 or 12 hours) and ensure adequate time above the minimum inhibitory concentration. However, the dose tolerability and risk factors for hepatic and renal dysfunction in meropenem-treated patients with baseline renal dysfunction remain unclear.

Objectives: To confirm the dose tolerability of meropenem and to identify the factors affecting hepatic and renal dysfunction after meropenem treatment in Japanese patients with creatinine clearance rates of 10 to 50 mL/min.

***Methods*:** This was a retrospective, single-center study, where 142 subjects with creatinine clearance rates ranging from 10 to 50 mL/min were administered meropenem between April 1, 2012 and October 31, 2015. Safety was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Abnormal hepatic function was evaluated based on alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels, and abnormal renal function was evaluated using serum creatinine (SCr) levels. Adverse events were considered as worsening if the grade of each item increased from baseline values.

Results: Worsening of ALT, ALP, and SCr grades was observed in 17.9%, 18.3%, and 4.2% of patients, respectively. Dose of 2 g/day or more, treatment duration, or the degree of patient's renal function had no effect on hepatic and renal dysfunction.

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Thus, the risk factors for hepatic and renal dysfunction were not related to meropenem.

Conclusion: Meropenem dose and treatment duration are not risk factors for hepatic and renal dysfunction in Japanese patients with creatinine clearance rates of 10 to 50 mL/min.

Introduction

Meropenem is a carbapenem antibiotic used against gram-positive, gram-negative (including extended-spectrum β-lactamase-producing bacteria and AmpC β-lactamase-producing bacteria), and anaerobic bacteria[1]. Meropenem has proven tolerability, as reported in a comparative investigation of cephems[2]. It is used as empirical therapy for severe sepsis and severe infections such as pneumonia, febrile neutropenia, and bacterial meningitis[1]. Following intravenous administration of meropenem, a small amount is metabolized, while most of it is excreted unaltered via urine[1]. The elimination half-life of meropenem in patients with normal kidney function is 1 h. For patients with impaired renal function, such as those with creatinine clearance rates less than 50 mL/min, the dose or interval of meropenem administration requires adjustment[1]. Importantly, the minimum inhibitory concentration and the mutant prevention concentration (an index for preventing resistant bacteria) are different depending on the bacterial species[3]. Therefore, when meropenem is used for empirical treatment, it should be administered at the highest tolerable dose to ensure adequate time above the minimum inhibitory concentration of most bacteria. However, administration of meropenem at a high-dose of 2 g/day or more has been shown to cause hepatic dysfunction[4~6]. In a questionnaire survey targeting physicians, many physicians had safety concerns regarding high dose of 2 g/day or more administration of meropenem[7], suggesting that administration of meropenem at high doses should be avoided[7].

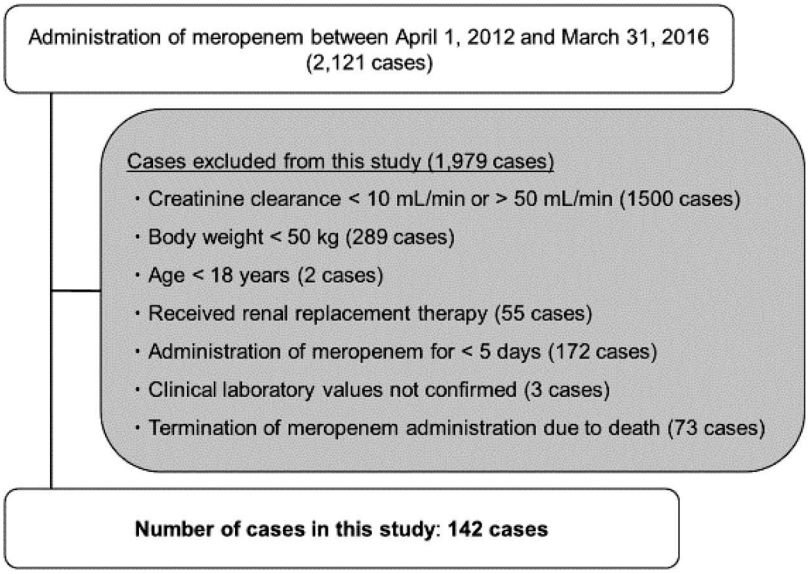
We previously reported the tolerable meropenem dose in Japanese patients with creatinine clearance rates of 50 mL/min or more[8]. We also showed that the frequency of side effects such as hepatic and renal dysfunction was not dependent on meropenem dosage[8]. Regarding the safety of meropenem in Japanese patients with baseline renal dysfunction, although the rate of adverse event occurrence has been reported, the details have not been provided[9]. Furthermore, the dose tolerability and risk factors for hepatic and renal dysfunction in meropenem-treated patients with baseline renal dysfunction remain unclear. In this study, we report meropenem dose tolerability and the factors affecting organ dysfunction during meropenem treatment in Japanese patients with creatinine clearance rates $\geq$10 to $<$50 mL/min.

Patients and Methods

Study design, setting, and subjects

This retrospective study was conducted in an acute care hospital in Osaka, Japan. In total,

Figure 1. Flowchart of study patient selection



Even if there are multiple exclusion criteria for a case, calculation is done for each exclusion criteria.

2,121 patients were treated with brand-name meropenem (Meropen®, Sumitomo Dainippon Pharma Co. Ltd, Osaka, Japan) between April 1, 2012 and March 31, 2016 at the Osaka National Hospital in Osaka, Japan. Of these patients, 1,979 were excluded from the study because their creatinine clearance was ≥50 or <10 mL/min, their body weight was <50 kg, their age was <18 years, they had received renal replacement therapy, their meropenem treatment duration was <5 days, clinical laboratory values were not confirmed, or termination of meropenem administration due to death (Figure 1). The reason for excluding patients with creatinine clearance levels <10 mL/min is that the dose interval for meropenem administration is once every 24 h (Meropen® interview form, July 2018 revision, 15th edition), and therefore the dose would not be 2 g/day or more. The reason for excluding patients with aged <18 years is that creatinine clearance rates were calculated using the Cockcroft–Gault formula[10]. The reason for excluding patients with body weight <50 kg is that to avoid including the study patients with overexposure of meropenem due to low body weight. The reason for excluding patients with meropenem treatment duration <5 days is that drug-induced liver injury is generally occurs between 5 and 90 days after drug ingestion[11]. Subsequently, 142 patients with creatinine clearance rates ≥10 to <50 mL/min were included in the study.

Data collection

We collected data from patient's medical records, including background information (body weight, age, sex, underlying disease, and intensive care unit admission), infectious disease diagnosis,

clinical laboratory data [alanine aminotransferase (ALT), alkaline phosphatase (ALP), and serum creatinine (SCr) levels], concomitant medication use, and meropenem administration duration.

Definitions

Creatinine clearance rates were calculated using the Cockcroft–Gault formula[10].

Safety was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0[12] published by the National Cancer Institute.

Abnormalities in hepatic function were evaluated using ALT and ALP levels, and abnormalities in renal function were evaluated using SCr levels. Adverse events were considered as worsening if the grade of each laboratory data at completion of administration of meropenem increased from the baseline grade (i.e., start of drug administration).

Endpoints

The primary endpoint was worsening hepatic and renal function in meropenem-treated patients with creatinine clearance rates ≥10 to <50 mL/min. The secondary endpoints included (1) differences in hepatic and renal function due to dosage (patients were grouped by meropenem dose: <2 g/day *vs.* ≥2 g/day); (2) differences in hepatic and renal function due to baseline renal function (patients were grouped by creatinine clearance rates: ≥10 to <25 mL/min *vs.* ≥25 to < 50 mL/min); and (3) evaluation of risk factors for hepatic and renal dysfunction during meropenem treatment.

Statistical analysis

Continuous variables are presented as medians (interquartile range), and differences between groups were assessed using the Student's *t*-test. Categorical variable differences between groups were assessed using the chi-square test or Fisher's exact test. Risk factors for hepatic and renal dysfunction were evaluated using univariate and multivariate logistic regression. However, multivariate logistic regression was performed when multiple factors were present in univariate logistic regression. A p-value ≤0.05 indicated statistical significance. All statistical analyses were performed using JMP® 9.0.2 (SAS Institute Inc., Cary, NC, USA).

Ethics

This study was conducted in compliance with the standards of the Declaration of Helsinki and the current ethical guidelines. Approval from the ethics committee board of the Osaka National Hospital, reference number 16028, was obtained. To protect patient privacy, identifying data were encrypted in an electronic database. Written informed consent was exempted because no intervention was involved and patient-identifying data were not included in the study.

Results

Patient baseline characteristics are presented in Table 1. Worsening of ALT, ALP, and SCr levels was observed in 17.9%, 18.3%, and 4.2% of patients, respectively.

Patient characteristics in the <2 g/day and ≥2 g/day groups are presented in Table 2. In the <2 g/day group, the percentage of patients with creatinine clearance <25 mL/min at the start of meropenem administration was higher and elderly patients. In contrast, in the ≥2 g/day group, the number of days of administration of meropenem was longer than that in the <2 g/day group. Although a difference in patient background was observed between the two groups, no difference was observed in worsening of ALT (17.6% *vs.* 18.0%, P=0.96), ALP (18.4% *vs.* 18.2%, P=0.98), and SCr (5.8% *vs.* 2.2%, P=0.19) levels between the <2 g/day and ≥2 g/day groups.

The characteristics of patients with creatinine clearance rates ≥10 to <25 mL/min and those with creatinine clearance rates ≥25 to <50 mL/min are presented in Table 3. In patients with creatinine clearance rates ≥10 to <25 mL/min, the daily dose of meropenem was lower than that in patients with creatinine clearance rates ≥25 to <50 mL/min group, and it was elderly. However, there was no difference in worsening of ALT (4.2% *vs.* 20.7%, P=0.076), ALP (15.8% *vs.* 18.8%, P=1.00), and SCr (4.0% *vs.* 4.3%, P=1.00) levels between patients with creatinine clearance rates ≥10 to <25 mL/min and those with creatinine clearance rates ≥25 to <50 mL/min.

Meropenem dose and treatment duration were not risk factors for hepatic or renal dysfunction in univariate logistic regression. The risk factors for hepatic dysfunction included concomitantly administered drugs (Tables 4 and 5). The risk factors for elevated ALT levels included administration of parenteral nutrition solutions and heparin sodium (Table 4). The only risk factor for elevated ALP was the use of parenteral nutrition solutions (Table 5). On the other hand, no risk factors for renal dysfunction were identified (Table 6).

Discussion

This study was the first to describe dose tolerability and risk factors associated with administering meropenem to Japanese patients with creatinine clearance rates between 10 and 50 mL/min. We report two useful findings. First, the incidence of worsening hepatic and renal function in meropenem-treated patients with creatinine clearance rates between 10 and 50 mL/min was similar to that in patients with creatinine clearance rates of 50 mL/min or more. Second, no factors directly related to meropenem administration, such as daily dose or administration period, were identified as risk factors for hepatic or renal function deterioration.

In previous reports, worsening of hepatic and renal function was observed in 3.4 to 45%[2,4~6,13] and 0.1 to 4.2%[2,4,5] of meropenem-treated patients, respectively. Furthermore, hepatic dysfunction was reportedly higher with high dose meropenem administration (2 or 3 g/day or more)[5,6]. In

Table 1. Patient characteristics and hepatic or renal dysfunction incidence during meropenem treatment

PATIENTS CHARACTERISTICS	
Number of patients	142
Age (years)†	75 (68–81)
Sex (male/female)	108/34
Duration of meropenem administration (days)†	8.5 (6–12)
Dose of meropenem (mg/day)†	2,000 (1,000–3,000)
Intensive care unit patients	48 (33.8%)
Cancer patients	82 (57.7%)
Diagnosis (infectious disease)	
Pneumonia‡	40 (28.2%)
Abdominal infections‡	36 (25.4%)
Blood stream infection	19 (13.4%)
Urinary tract infection	9 (6.3%)
Fever (unknown origin)	10 (7.0%)
Surgical site infection	5 (3.5%)
Pancreatitis	4 (2.8%)
Others‡	19 (13.4%)
Concomitant drugs§	
Parenteral nutrition solutions	59 (41.5%)
Diuretic¶	53 (37.3%)
Other antimicrobials¶¶	39 (27.5%)
NSAIDs¶¶¶	35 (24.6%)
Catecholamine¶¶¶¶	29 (20.4%)
Sedative drug¶¶¶¶¶	28 (19.7%)
Heparin sodium	27 (19.0%)
Acetaminophen	26 (18.3%)
Increase in CTCAE grade	
ALT	25/140 (17.9%)
ALP	21/115 (18.3%)
SCr	6/142 (4.2%)

† Median (interquartile range)

‡ “Pneumonia” includes aspiration pneumonia; “Abdominal infections” include intra-abdominal abscess, cholecystitis, cholangitis, and diffuse peritonitis; “Others” include, skin and soft tissue infection, medical device infection, ileus, febrile neutropenia, and bacterial meningitis.

§ For each concomitant drug category, patients using multiple drugs within a category were only counted once.

¶ Includes furosemide, azosemide, torsemide, spironolactone, canrenoate potassium, and tolvaptan.

¶¶ Includes vancomycin, linezolid, and daptomycin.

¶¶¶ Includes loxoprofen sodium, diclofenac sodium, celecoxib, and flurbiprofen axetil.

¶¶¶¶ Includes dopamine, dobutamine, and noradrenaline.

¶¶¶¶¶ Includes propofol, dexmedetomidine, and midazolam.

ALT = alanine aminotransferase; ALP = alkaline phosphatase; NSAIDs = non-steroidal anti-inflammatory drug; SCr = serum creatinine

Table 2. Comparison of patient characteristics and hepatic and renal function between different meropenem dosing groups

Patient characteristics	Administration dose		p-value
	< 2 g/day	≥ 2 g/day	
Patient numbers	90	52	-
Age (years)‡	74 (67–80)	77 (71–85)	0.017†
Sex (male)	72	36	0.147§
Treatment duration‡	9 (7–13)	7 (6–10)	0.014†
CCr < 25 mL/min	11 (12.2%)	14 (26.9%)	0.027§
Intensive care unit patients	31 (34.4%)	17 (32.7%)	0.83§
Cancer patients	53 (58.9%)	29 (55.8%)	0.72§
Increase in CTCAE grade			
ALT	16/89 (18.0%)	9/51 (17.6%)	0.96§
ALP	14/77 (18.2%)	7/38 (18.4%)	0.98§
SCr	2/90 (2.2%)	3/52 (5.8%)	0.14¶

† Mann–Whitney U test
‡ Median (interquartile range)
§ Chi-square test
¶ Fisher's exact test
ALT = alanine aminotransferase; ALP = alkaline phosphatase; CCr = creatinine clearance; SCr = serum creatinine

Table 3. Comparison of patient characteristics and hepatic and renal function between different meropenem-treated creatinine clearance groups

Patient characteristics	CCr (mL/min)		p-value
	10 ≤ CCr < 25	25 ≤ CCr < 50	
Patient numbers	25	117	
Age (years)†	80 (75–85)	74 (66–80)	0.0038‡
Sex (male)	22	86	0.12‡
Treatment duration†	8 (6–12)	9 (6–12)	0.84‡
Administration dose (mg/day) †	1,000 (500–2,000)	2,000 (1,500–3,000)	0.0015‡
Intensive care unit patients	8	40	0.83§
Cancer patients	16	66	0.49§
Increase in CTCAE grade			
ALT	1/24 (4.2%)	24/116 (20.7%)	0.076¶
ALP	3/19 (15.8%)	18/96 (18.8%)	1.0¶
SCr	1/25 (4.0%)	5/117 (4.3%)	1.0¶

† Median (interquartile range)
‡ Mann–Whitney U test
§ Chi-square test
¶ Fisher's exact test
ALT = alanine aminotransferase; ALP = alkaline phosphatase; CCr = creatinine clearance; SCr = serum creatinine

Table 4. Univariate and multivariate logistic regression analyses to identify risk factors associated with worsening ALT levels in meropenem-treated patients

Factor	Univariate logistic regression			Multivariate logistic regression		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Sex (male)	1.85	0.641–6.735	0.27	-	-	-
Age	1.22	0.141–13.05	0.86	-	-	-
Treatment duration	0.44	0.001–12.83	0.69	-	-	-
Intensive care unit patients	1.41	0.563–3.399	0.46	-	-	-
Administration dose	3.46	0.559–22.89	0.18	-	-	-
Cancer patients	1.32	0.548–3.351	0.54	-	-	-
Concomitant drugs						
Parenteral nutrition solutions	3.21	1.327–8.196	0.01	2.91	1.168–7.599	0.022
Diuretic	0.46	0.469–3.818	0.52	-	-	-
Another antimicrobial ¶	1.28	0.479–3.180	0.61	-	-	-
NSAIDs	2.40	0.942–5.964	0.066	-	-	-
Catecholamine	1.00	0.307–2.783	1.000	-	-	-
Sedative drug	1.41	0.469–3.818	0.52	-	-	-
Heparin sodium	4.31	1.560–10.791	0.005	3.71	1.364–9.964	0.011

NSAIDs = non-steroidal anti-inflammatory drugs

¶ Includes vancomycin, linezolid, and daptomycin.

the present study, meropenem administration resulted in increased ALT, ALP, and SCr levels in 17.9%, 18.3%, and 4.2% of patients, respectively. These results did not differ from those of previous studies using CTCAE criteria for the evaluation of hepatic and renal function[4,8]. In our previous study, worsening of ALT, ALP, and SCr levels was observed in 18.8% (45/240 patients), 18.5% (44/238), and 2.5% (6/240) of patients with creatinine clearance rates of 50 mL/min or more, respectively[8]. These results confirmed reproducibility in the incidence of meropenem-associated hepatic and renal function deterioration.

We also evaluated the effects of baseline renal function and daily meropenem dose; they showed no significant effects on worsening of hepatic or renal function. Therefore, we considered that baseline renal function and daily meropenem dose did not influence hepatic or renal function deterioration. Risk factor analysis for worsening hepatic or renal function did not reveal any risk factors related to meropenem administration, i.e., daily meropenem dose or treatment duration in patients with creatinine clearance ≥10 and <50 mL/min. Accordingly, meropenem daily dose and renal function at baseline were not related to worsening hepatic or renal function. Similar conclusions were obtained in our previous study[8].

In contrast, the use of concomitant medication affected hepatic dysfunction. Specifically,

Table 5. Univariate logistic regression analysis to identify risk factors associated with worsening ALP levels in meropenem-treated patients

Factor	Univariate logistic regression		
	Odds ratio	95% CI	p-value
Sex (male)	1.46	0.482–5.440	0.522
Age	0.35	0.035–3.818	0.382
Treatment duration	0.148	< 0.001–14.540	0.497
Intensive care unit patients	1.94	0.733–5.100	0.179
Administration dose	0.95	0.123–7.135	0.960
Cancer patients	0.683	0.262–1.793	0.434
Concomitant drugs			
Parenteral nutrition solutions	2.87	1.098–7.908	0.031
Diuretic	1.09	0.394–2.845	0.869
Another antimicrobial ¶	0.55	0.149–1.660	0.306
NSAIDs	0.69	0.184–2.076	0.522
Catecholamine	0.87	0.231–2.675	0.819
Sedative drug	1.23	0.367–3.617	0.717
Heparin sodium	0.42	0.063–1.607	0.222

NSAIDs = non-steroidal anti-inflammatory drugs
¶ Includes vancomycin, linezolid, and daptomycin.

parenteral nutrition was a risk factor for increased ALT and ALP levels, and use of heparin sodium was a risk factor for increased ALT. Hepatobiliary complications due to parenteral nutrition solutions[14~18] and elevated hepatic enzymes (such as transaminase) due to heparin administration[19~22] are common. Therefore, when using these medications in combination with meropenem, hepatic function should be monitored.

The mechanism underlying hepatic function deterioration following meropenem treatment is unknown. In general, hepatic dysfunction caused by β-lactam antibiotics, such as cephalosporins, occurs via an immunological mechanism[23,24].

According to the present study, the daily dosage and duration of meropenem treatment were not risk factors for worsening of hepatic or renal function in patients with creatinine clearance rates $\geq$10 and $<$50 mL/min. We concluded that patients infected with multi-drug resistant pathogens or with infections in organs with poor antibiotic penetration could be given empirical therapy with high-dose (2 g/day or more) meropenem at dosing intervals determined by renal function, without affecting hepatic or renal function.

This study has a few limitations. First, it was a single-center retrospective study. Second, the number of cases was limited. Therefore, there could be other factors causing hepatic and renal dysfunction that we did not identify in this study.

In conclusion, meropenem is well tolerated in patients with baseline renal impairment, and

Table 6. Univariate logistic regression analysis to identify risk factors associated with worsening SCr in meropenem-treated patients

Factor	Univariate logistic regression		
	Odds ratio	95% CI	p-value
Sex (male)	0.61	0.115–4.584	0.595
Age	3.04	0.043–665.969	0.638
Treatment duration	0.16	< 0.001–51.852	0.695
Intensive care unit patients	0.98	0.132–5.205	0.980
Administration dose	0.20	0.004–6.703	0.379
Cancer patients	3.83	0.597–74.404	0.171
Concomitant drugs			
Parenteral nutrition solutions	2.95	0.555–21.770	0.205
Diuretic	0.83	0.113–4.426	0.835
Another antimicrobial ¶	1.34	0.180–7.155	0.747
NSAIDs	1.56	0.210–8.375	0.625
Catecholamine	0.77	0.039–5.041	0.811
Sedative drug	2.12	0.283–11.455	0.422
Heparin sodium	0.85	0.043–5.546	0.879

NSAIDs = non-steroidal anti-inflammatory drugs
¶ Includes vancomycin, linezolid, and daptomycin.

its dose and duration are not risk factors for hepatic and renal function deterioration.

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Conflicts of interest

The authors have no conflicts of interest directly relevant to the content of this article.

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