Compatibility of carbapenem antibiotics with nafamostat mesilate in arterial infusion therapy for severe acute pancreatitis: Stabilities of carbapenem antibiotics

Yukihiro Hamada[1], Hiroshi Imaizumi[2], Shirou Miyazawa[2], Mitsuhiro Kida[2], Kazui Souma[3], Wasaburou Koizumi[2], Keisuke Sunakawa[4] and Masakazu Kuroyama[1]

[1] Department of Pharmacy Kitasato University East Hospital
[2] Department of Gastroenterology Kitasato University Hospital
[3] Department of Emergency and Critical Care Medicine, Kitasato University School of Medicine
[4] Infectious Disease Science, Kitasato University, Kitasato Institute for Life Sciences

(Received for publication May 9, 2012)

The effectiveness of continuous regional arterial infusion therapy using protease inhibitors and antibiotics for severe acute pancreatitis has been previously reported. Carbapenem antibiotics, which have a broad antibacterial spectrum, and nafamostat mesilate are often used for this therapeutic approach. We investigated the compatibility of various carbapenem antibiotics with nafamostat mesilate.

Carbapenem antibiotics were dissolved in 30 mL of saline or 5% glucose and the appearance, pH, and stability of the solutions were determined. The changes in each carbapenem antibiotic solution after mixing with nafamostat mesilate were then investigated.

Biapenem and doripenem showed a residual rate of ≥90% at 8 hours after dissolution in saline or 5% glucose and exhibited an appropriate appearance and residual rate (≥90%). After mixing with nafamostat mesilate, biapenem maintained a residual rate of ≥90% for the longest time period (8 hours) and exhibited a slight coloration, followed by doripenem (6 hours) and meropenem dissolved in saline. The other carbapenem antibiotics that were tested exhibited changes in appearance or their residual rate.

Biapenem and doripenem, which exert their effects in a time-dependent manner, can be infused for prolonged periods for the treatment of not only severe acute pancreatitis, but also other severe infections.

Introduction

In severe acute pancreatitis (SAP), pancreatic infectious complications are a critical factor causing poor prognosis, and preventive antibiotic administration has been reported to reduce the frequency of pancreatic infectious complications and the incidence of infectious pancreatic necrosis, significantly improving mortality[1–4]. As a specific therapy to prevent this, the effectiveness of continuous regional arterial infusion therapy (CRAI) with protease inhibitors and antibiotics has been reported[5–9].

Generally, the protease inhibitor, nafamostat mesilate is combined with a carbapenem antibiotic when performing CRAI for SAP[6–10]. This procedure results in the distribution of these drugs to the pancreatic tissue at high concentrations[11–13].

We previously prepared a manual for performing CRAI for SAP[14] using biapenem, which is physically and chemically more stable against nafamostat mesilate than other carbapenem antibiotics, and favorable treatment results have been obtained using this manual[15]. In the present study, we measured the *in vitro* stability of all the carbapenem antibiotics presently available on the Japanese market that are generally used after mixing with nafamostat mesilate.

Material and Methods

The test substances were comprised of the protease inhibitor nafamostat mesilate (Futhan 50, for injection; Torii Pharmaceutical Co., Ltd.) and all the carbapenem antibiotics presently available on the Japanese market: biapenem (Omegacin, for infusion [0.3 g]; Meiji Seika Pharma Co., Ltd.), imipenem/cilastatin sodium (Tienam, for intravenous infusion [0.25 g]; MSD K.K.), panipenem/betamipron (Carbenin, for infusion [0.5 g]; Daiichi Sankyo Co., Ltd.), meropenem (Meropen, vial for infusion [0.5 g]; Dainippon Sumitomo Pharma Co., Ltd.) and doripenem (Finibax, for infusion [0.25 g]; Shionogi & Co., Ltd.). Physiological saline (Otsuka normal saline; Otsuka Pharmaceutical Factory, Inc.) or a 5% glucose injection (Otsuka Glucose Injection 5%; Otsuka Pharmaceutical Factory, Inc.) was used as the solution.

To prepare the test solutions, 1 vial of each carbapenem antibiotic was dissolved in 30 mL of solution based on the doses used in clinical practice[15] to yield solutions containing 10 or 20 mg/mL of biapenem, 16.7 mg/mL of imipenem, 16.7 mg/mL of panipenem, 16.7 mg/mL of meropenem, or 8.3 mg/mL of doripenem. Ten milliliters of each solution was used to determine the appearance, pH and residual rate as the control solution, and was compared with test solutions prepared by adding 2 mL of 5 mg/mL nafamostat mesilate to the solutions containing each carbapenem antibiotic. As a dose of 0.6 g of biapenem is sometimes used for the treatment of SAP at our institution, 2 vials of biapenem were dissolved in 30 mL of solution as an additional test. The solutions were kept at 25℃ and 1000 lx (in a light-exposed chamber). Samplings were performed

at 0 (immediately after mixing), 1, 3, 6, 8, 12 and 24 hours after mixing.

Regarding the compatibility tests and the evaluation methods, the test and control solutions were visually observed and their pH levels were measured. Then, the solutions were filtered with a 0.22 μm pore-size membrane filter and purified water was added to the filtrates for dilution, so as to prepare the sample solutions for high-performance liquid chromatography (HPLC). Referring to the measurement method of KURIHARA *et al.*,[16] these sample solutions were then used for HPLC under the following conditions to measure the peak area of each carbapenem antibiotic and to calculate the peak area ratio for the solution immediately after mixing, enabling the residual titer rate to be obtained: detector, ultraviolet absorption photometer; measurement wavelength, 300 nm; column, Luna 5u C18(2) 100A (250×4.6 mm; Phenomenex); column temperature, constant temperature around 30℃; sample cooler temperature, 5℃; mobile phase (0.1 M phosphate buffer [pH 7.8]: methanol), 92 : 8 for biapenem and imipenem, 87 : 13 for panipenem, and 78 : 22 for meropenem and doripenem; mobile phase flow rate, 1 mL/min; and analysis times, 6 min. for biapenem and imipenem test and control solutions, 10 min. for panipenem test solution, 6 min. for panipenem control solution, 25 min. for meropenem and doripenem test solutions, 11 min. for meropenem control solution, and 7 min. for doripenem control solution.

Results

Table 1-1 shows the sequential residual rates of each carbapenem antibiotic dissolved in saline in the control solutions. Panipenem and meropenem were reduced to less than 90% at 8 hours. When dissolved in 5% glucose, meropenem was reduced to less than 90% at 6 hours, and imipenem and panipenem were reduced to less than 90% at 8 hours, as shown in Table 1-2.

In the compatibility test of each carbapenem antibiotic dissolved in saline with nafamostat mesilate, panipenem precipitated immediately after mixing and imipenem also precipitated 3 hours after mixing. Regarding the residual rates, panipenem was reduced to less than 90% at 3 hours after mixing, and meropenem and doripenem were reduced to less than 90% at 8 hours after mixing, as shown in Table 2-1. Likewise, when dissolved in 5% glucose, panipenem precipitated immediately after mixing and imipenem also precipitated 1 hour after mixing (Table 2-2). As for the residual rate, panipenem was reduced to less than 90% at 3 hours after mixing, meropenem was reduced to less than 90% at 6 hours after mixing, and doripenem was reduced to less than 90% at 8 hours after mixing, as shown in Table 2-2. Biapenem (10 and 20 mg/mL) showed a residual rate of 90% or more, with slight coloration, at 8 hours after mixing (Table 2-2).

Table 1. Compatibility tests of each carbapenem antibiotic in solution.

1-1. Sequential changes in control solutions using saline (25℃, 1000 lx).

		Immediately after mixing	1 hour	3 hours	6 hours	8 hours	12 hours	24 hours
Biapenem (10) control solution	Appearance	Colorless and transparent	No change	No change	No change	No change	Slight progress of coloration, slightly yellow transparent	Obvious coloration, pale yellow transparent
	pH	5.07	4.91	4.82	4.73	4.79	4.71	4.68
	Residual rate (%)	100	99.6	99.0	97.4	95.7	93.5	[87.4]
Biapenem (20) control solution	Appearance	Colorless and transparent	No change	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration, pale yellow transparent	Obvious coloration, yellow transparent	Obvious coloration, yellow transparent
	pH	5.03	4.94	4.89	4.83	4.83	4.81	4.73
	Residual rate (%)	100	99.4	98.5	96.7	94.9	92.0	[86.0]
Imipenem control solution	Appearance	Slightly yellow transparent	No change	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Slight progress of coloration	Obvious coloration, pale yellow transparent
	pH	7.30	7.28	7.21	7.06	6.95	6.83	6.35
	Residual rate (%)	100	99.1	97.9	95.3	93.5	[89.6]	[78.3]

[ ]: Residual rate indicates less than 90%.

Table 1. Compatibility tests of each carbapenem antibiotic in solution. (Continued)

1-1. Sequential changes in control solutions using saline (25℃, 1000 lx). (Continued)

		Immediately after mixing	1 hour	3 hours	6 hours	8 hours	12 hours	24 hours
Panipenem control solution	Appearance	Slightly yellow transparent	No change	No change	Slight progress of coloration, pale yellow transparent	Slight progress of coloration	Obvious coloration, yellow transparent	Marked coloration, yellowish brown transparent
	pH	6.64	6.49	6.37	6.22	6.11	6.00	5.77
	Residual rate (%)	100	99.0	96.2	91.0	[87.2]	[77.7]	[45.7]
Meropenem control solution	Appearance	Slightly yellow transparent	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Slight progress of coloration	Slight progress of coloration	Slight progress of coloration, slightly yellow transparent
	pH	7.78	7.79	7.80	7.76	7.76	7.73	7.67
	Residual rate (%)	100	97.8	95.7	93.3	[88.5]	[85.8]	[81.4]
Doripenem control solution	Appearance	Colorless and transparent	No change	No change	No change	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration, slightly yellow transparent
	pH	5.09	4.94	4.96	4.91	4.87	4.78	4.70
	Residual rate (%)	100	98.4	97.6	93.5	91.2	[88.5]	[85.8]

[ ]: Residual rate indicates less than 90%.

Table 1. Compatibility tests of each carbapenem antibiotic in solution. (Continued)

1-2. Sequential changes in control solutions using 5% glucose injection (25℃, 1000 lx).

		Immediately after mixing	1 hour	3 hours	6 hours	8 hours	12 hours	24 hours
Biapenem (10) control solution	Appearance	Colorless and transparent	No change	No change	No change	No change	Slight progress of coloration, slightly yellow transparent	Obvious coloration, pale yellow transparent
	pH	5.11	4.90	4.89	4.78	4.74	4.77	4.79
	Residual rate (%)	100	99.4	99.1	97.1	96.1	93.4	[87.7]
Biapenem (20) control solution	Appearance	Colorless and transparent	No change	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration, pale yellow transparent	Obvious coloration, yellow transparent	Obvious coloration, yellow transparent
	pH	5.07	4.98	4.96	4.89	4.91	4.87	4.83
	Residual rate (%)	100	99.8	98.0	96.4	94.7	92.5	[86.0]
Imipenem control solution	Appearance	Slightly yellow transparent	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Slight progress of coloration	Obvious coloration, pale yellow transparent	Marked coloration, yellow transparent
	pH	7.39	7.28	7.25	7.13	7.04	6.94	6.59
	Residual rate (%)	100	97.2	94.2	90.5	[87.2]	[81.8]	[69.3]

[ ]: Residual rate indicates less than 90%.

Table 1. Compatibility tests of each carbapenem antibiotic in solution. (Continued)

1-2. Sequential changes in control solutions using 5% glucose injection (25℃, 1000 lx). (Continued)

		Immediately after mixing	1 hour	3 hours	6 hours	8 hours	12 hours	24 hours
Panipenem control solution	Appearance	Slightly yellow transparent	No change	No change	Slight progress of coloration, pale yellow transparent	Slight progress of coloration	Obvious coloration, yellow transparent	Marked coloration, yellowish brown transparent
	pH	6.73	6.56	6.43	6.30	6.22	6.11	5.83
	Residual rate (%)	100	98.2	94.9	90.6	[87.1]	[79.1]	[50.3]
Meropenem control solution	Appearance	Slightly yellow transparent	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Slight progress of coloration	Slight progress of coloration	Obvious coloration, pale yellow transparent
	pH	7.75	7.82	7.82	7.80	7.81	7.79	7.75
	Residual rate (%)	100	95.8	92.0	[84.1]	[77.7]	[72.4]	[57.0]
Doripenem control solution	Appearance	Colorless and transparent	No change	No change	No change	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration, slightly yellow transparent
	pH	4.99	4.99	4.97	4.85	4.90	4.88	4.80
	Residual rate (%)	100	98.4	97.6	93.8	90.9	[88.7]	[86.4]

[ ]: Residual rate indicates less than 90%.

Table 2. Compatibility tests of each carbapenem antibiotic mixed with nafamostat mesilate.

2-1. Sequential changes in mixed solutions using saline (25℃, 1000 lx).

		Immediately after mixing	1 hour	3 hours	6 hours	8 hours	12 hours	24 hours
Biapenem (10) mixed solution	Appearance	Colorless and transparent	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Slight progress of coloration	Obvious coloration, pale yellow transparent	Obvious coloration, pale yellow transparent
	pH	4.30	4.33	4.34	4.36	4.39	4.40	4.48
	Residual rate (%)	100	98.0	96.1	93.0	92.0	[87.6]	[78.9]
Biapenem (20) mixed solution	Appearance	Colorless and transparent	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Obvious coloration, pale yellow transparent	Obvious coloration	Obvious coloration	Obvious coloration, yellow transparent
	pH	4.45	4.48	4.51	4.54	4.54	4.60	4.59
	Residual rate (%)	100	98.5	97.3	94.5	92.3	[88.5]	[80.6]
Imipenem mixed solution	Appearance	Slightly yellow transparent	No change	**Precipitation** No change in color tone, slightly yellow	**Precipitation** Slight progress of coloration	**Precipitation** Slight progress of coloration	**Precipitation** Slight progress of coloration	**Precipitation** Obvious coloration, pale yellow
	pH	6.60	6.65	6.66*	6.50*	6.45*	6.32*	5.84*
	Residual rate (%)	100	99.4	97.9*	95.3*	92.7*	[87.3*]	[68.3*]

*Tentative values due to precipitation. [ ]: Residual rate indicates less than 90%.

Table 2. Compatibility tests of each carbapenem antibiotic mixed with nafamostat mesilate. (Continued)

2-1. Sequential changes in mixed solutions using saline (25℃, 1000 lx). (Continued)

		Immediately after mixing	1 hour	3 hours	6 hours	8 hours	12 hours	24 hours
Panipenem mixed solution	Appearance	**Precipitation (white turbid)** Slightly yellow	**Precipitation (white turbid)** Slightly yellow	**Precipitation (white turbid)** Slight progress of coloration pale yellow	**Precipitation (white turbid)** Obvious coloration, yellow	**Precipitation (white turbid)** Obvious coloration	**Precipitation (white turbid)** Obvious coloration	**Precipitation (white turbid)** Marked coloration, yellowish brown
	pH	5.98*	5.96*	5.89*	5.81*	5.76*	5.66*	5.59*
	Residual rate (%)	100*	96.3*	[89.7*]	[78.9*]	[71.8*]	[56.9*]	[22.2*]
Meropenem mixed solution	Appearance	Slightly yellow transparent	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Slight progress of coloration	Slight progress of coloration	Obvious coloration, pale yellow transparent
	pH	7.68	7.68	7.69	7.68	7.67	7.65	7.61
	Residual rate (%)	100	97.5	95.8	93.1	[88.6]	[85.6]	[80.6]
Doripenem mixed solution	Appearance	Colorless and transparent	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Slight progress of coloration	Obvious coloration, pale yellow transparent	Obvious coloration, pale yellow transparent
	pH	4.31	4.36	4.34	4.35	4.38	4.39	4.45
	Residual rate (%)	100	97.1	95.0	91.2	[86.1]	[81.5]	[73.3]

*Tentative values due to precipitation. [ ]: Residual rate indicates less than 90%.

Table 2. Compatibility tests of each carbapenem antibiotic mixed with nafamostat mesilate. (Continued)

2-2. Sequential changes in mixed solutions using 5% glucose injection (25℃, 1000 lx).

		Immediately after mixing	1 hour	3 hours	6 hours	8 hours	12 hours	24 hours
Biapenem (10) mixed solution	Appearance	Colorless and transparent	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Slight progress of coloration	Obvious coloration, pale yellow transparent	Obvious coloration, pale yellow transparent
	pH	4.29	4.34	4.31	4.40	4.37	4.41	4.50
	Residual rate (%)	100	99.2	97.5	95.2	93.6	[89.2]	[81.8]
Biapenem (20) mixed solution	Appearance	Colorless and transparent	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Obvious coloration, pale yellow transparent	Obvious coloration	Obvious coloration	Obvious coloration, yellow transparent
	pH	4.54	4.56	4.55	4.59	4.62	4.63	4.67
	Residual rate (%)	100	99.2	97.1	94.6	92.8	[89.4]	[81.6]
Imipenem mixed solution	Appearance	Slightly yellow transparent	**Precipitation** No change in color tone	**Precipitation** No change in color tone, slightly yellow	**Precipitation** Slight progress of coloration	**Precipitation** Slight progress of coloration	**Precipitation** Obvious coloration, pale yellow	**Precipitation** Marked coloration, yellow
	pH	6.78	6.88*	6.85*	6.69*	6.62*	6.53*	6.07*
	Residual rate (%)	100	98.0*	96.5*	93.7*	90.0*	[85.7*]	[68.9*]

*Tentative values due to precipitation. [ ]: Residual rate indicates less than 90%.

Table 2. Compatibility tests of each carbapenem antibiotic mixed with nafamostat mesilate. (Continued)

2-2. Sequential changes in mixed solutions using 5% glucose injection (25℃, 1000 lx). (Continued)

		Immediately after mixing	1 hour	3 hours	6 hours	8 hours	12 hours	24 hours
Panipenem mixed solution	Appearance	**Precipitation (white turbid)** Slightly yellow	**Precipitation (white turbid)** Slightly yellow	**Precipitation (white turbid)** Slight progress of coloration, pale yellow	**Precipitation (white turbid)** Obvious coloration, yellow	**Precipitation (white turbid)** Obvious coloration	**Precipitation (white turbid)** Obvious coloration	**Precipitation (white turbid)** Marked coloration, yellowish brown
	pH	6.10*	6.05*	5.99*	5.89*	5.83*	5.74*	5.58*
	Residual rate (%)	100*	96.9*	[89.6*]	[79.9*]	[73.7*]	[58.9*]	[24.7*]
Meropenem mixed solution	Appearance	Slightly yellow transparent	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Obvious coloration, pale yellow transparent	Obvious coloration, yellow transparent	Marked coloration, yellowish brown transparent
	pH	7.71	7.75	7.75	7.73	7.78	7.69	7.67
	Residual rate (%)	100	95.8	92.2	[85.8]	[79.7]	[73.5]	[58.9]
Doripenem mixed solution	Appearance	Colorless and transparent	No change	Slight progress of coloration, slightly yellow transparent	Slight progress of coloration	Slight progress of coloration	Obvious coloration, pale yellow transparent	Obvious coloration, pale yellow transparent
	pH	4.32	4.38	4.38	4.36	4.35	4.39	4.53
	Residual rate (%)	100	97.5	95.4	90.6	[86.9]	[82.4]	[74.8]

*Tentative values due to precipitation. [ ]: Residual rate indicates less than 90%.

Discussion

The prevention of pancreatic infectious complications is important in patients with SAP, and infectious pancreatic necrosis caused by the translocation of enteric bacteria, which are often the causes of such infections, has an extremely poor prognosis[17,18]. In recent years, the usefulness of CRAI for SAP has been reported[9,10,19,20], and the indication for CRAI is generally considered to be necrotizing pancreatitis. However, pancreatic infection and pancreatic necrosis are difficult to predict, and CRAI may be applicable to patients diagnosed as having SAP. By starting CRAI early, we think that pancreatic necrosis may be preventable.

Enteric Gram-negative bacilli, such as *Escherichia coli*[21,22] and *Enterobacter*[22], *Pseudomonas aeruginosa* and MRSA have been separately identified in lesions of infectious pancreatic necrosis[16–23]. Carbapenem antibiotics, which have a broad antibacterial spectrum, show excellent antimicrobial activity against these causative bacteria, with the exception of MRSA, and are considered to be bacteriologically useful. When using carbapenem antibiotics, it is important to prolong the duration of the drug concentration above the minimum inhibitory concentration (MIC) from the standpoint of the pharmacokinetics-pharmacodynamics (PK-PD)[24,25], and excellent effects can be expected by prolonging the administration time and increasing the number of doses. In CRAI, a syringe pump is used to infuse carbapenem antibiotics at higher concentrations than usual. Therefore, when considering which antibiotics should be used, the selection of an antibiotic that is stable against nafamostat mesilate for a long period of time and that can be infused in combination with nafamostat mesilate is desirable. Regarding biapenem, higher residual rates at concentrations of both 10 and 20 mg/mL were observed, compared with the residual rates for other carbapenem antibiotics (Tables 2-1, 2-2), supporting our choice of this drug for CRAI. The reason for the lower residual rates in this study, compared with those in previous reports[15], was thought to be that higher concentrations of each carbapenem antibiotic were used. For general CRAI, the combination of nafamostat mesilate and imipenem/cilastatin or meropenem has often been used[5,6,9,10,20]. However, when the number of infusion routes is limited, the infusion of nafamostat mesilate is often temporarily discontinued; instead, only imipenem/cilastatin or meropenem is infused. With the use of biapenem and doripenem, the techniques required for the infusion of imipenem/cilastatin, such as catheter irrigation and catheter air removal, become unnecessary, reducing catheter difficulties. We have experienced crystal precipitation when using panipenem/betamipron and imipenem/cilastatin in clinical practice, and crystal precipitation was also seen in the present study immediately or at 1 hour after mixing. Therefore, these drugs should be used with caution. The usefulness of biapenem and doripenem was also suggested from the viewpoint of risk management.

As biapenem has been reported to be more effectively distributed to the pancreas than imipenem/cilastatin in an animal model for SAP[26], these results suggest that biapenem may have a

beneficial effect on CRAI for SAP. It may be needed to evaluate the bacteriological efficacy in the future.

References

1) Golub, R.; F. Siddiqi & D. Pohl: Role of antibiotics in acute pancreatitis: A meta-analysis. J. Gastrointest. Surg. 2: 496～503, 1998
2) Pederzoli, P.; C. Bassi, S. Vesentini, *et al.*: A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg. Gynecol. Obstet. 176: 480～483, 1993
3) Bassi, C.; G. Mangiante, M. Falconi, *et al.*: Prophylaxis for septic complications in acute necrotizing pancreatitis. J. Hepatobiliary Pancreat. Surg. 8: 211～215, 2001
4) Bassi, C.; M. Falconi, G. Talamini, *et al.*: Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. Gastroenterol. 115: 1513～1517, 1998
5) Takeda, K.; S. Matsuno, M. Sunamura, *et al.*: Continuous regional arterial infusion of protease inhibitor and antibiotics in acute necrotizing pancreatitis. Am. J. Surg. 171: 394～398, 1996
6) Takeda, K.; S. Matsuno, M. Ogawa, *et al.*: Continuous regional arterial infusion (CRAI) therapy reduces the mortality rate of acute necrotizing pancreatitis: results of a cooperative survey in Japan. J. Hepatobiliary Pancreat. Surg. 8: 216～220, 2001
7) Anai, H.; H. Sakaguchi, H. Uchida, *et al.*: Continuous arterial infusion therapy for severe acute pancreatitis: correlation between CT arteriography and therapeutic effect. J. Vasc. Interv. Radiol. 10: 1335～1342, 1999
8) Okada, T.; H. Komoriyama & H. Uchida: Continuous arterial infusion of protease inhibitor in intensive care acute pancreatitis [in Japanese]. Shuchu Chiryo 9: 555～562, 1997
9) Piaścik, M.; G. Rydzewska, J. Milewski, *et al.*: The results of severe acute pancreatitis treatment with continuous regional arterial infusion of protease inhibitor and antibiotic: a randomized controlled study. Pancreas 39: 863～867, 2010
10) Shirai, K.; K. Tanjou, K. Shinohara, *et al.*: The effectiveness of continuous regional arterial infusion therapy with meropenem in severe acute pancreatitis compared with imipenem: A prospective, randomized study [in Japanese]. Jpn. J. Gastroenterol. Surg. 41: 1～11, 2008
11) Mikami, Y.; K. Takeda, K. Matsuda, *et al.*: Rat experimental model of continuous regional arterial infusion of protease inhibitor and its effects on severe acute pancreatitis. Pancreas 30: 248～253, 2005
12) Kakugawa, Y.; K. Takeda, M. Sunamura, *et al.*: Effect of continuous arterial infusion of protease inhibitor on experimental acute pancreatitis induced by closed duodenal loop obstruction. Nihon Shokakibyo Gakkai Zasshi 87: 1444～1450, 1990
13) Satoh, H.; M. Harada, S. Tashiro, *et al.*: The effect of continuous arterial infusion of gabexate mesilate (FOY-007) on experimental acute pancreatitis. J. Med. Invest. 51: 186～193, 2004
14) Hamada, Y.; H. Imaizumi, H. Naito, *et al.*: Development of a guideline for continuous regional arterial infusion of biapenem in a patient with severe acute pancreatitis [in Japanese]. J. Jpn. Soc. Hosp. Pharm. 43: 187～190, 2007
15) Hamada, Y.; H. Imaizumi, M. Watanabe, *et al.*: Continuous regional arterial infusion therapy with biapenem and nafamostat mesilate for severe acute pancreatitis [in Japanese]. J. Jpn. Pancreas Soc. 23: 578～586, 2008

16) Kurihara, Y.; J. Kizu & S. Hori: Simple and rapid determination of serum carbapenem concentrations by high-performance liquid chromatography. J. Infect. Chemother. 14: 30～34, 2008
17) Furuya, T.; T. Soeno & M. Komatsu: Strategy for bacterial translocation in acute pancreatitis. Nihon Shokakibyo Gakkai Zasshi 101: 502～509, 2004
18) Isaji, S. & S. Uemoto: Pathophysiology and management of infectious complications in sever acute pancreatitis [in Japanese]. Tan to Sui. 23: 825～830, 2002
19) Takeda, K.; J. Yamauchi, K. Shibuya, *et al.*: Benefit of continuous regional arterial infusion of protease inhibitor and antibiotic in the management of acute necrotizing pancreatitis. Pancreatology 1: 668～673, 2001
20) Imaizumi, H.; M. Kida, H. Nishimaki, *et al.*: Efficacy of continuous regional arterial infusion of a protease inhibitor and antibiotic for severe acute pancreatitis in patients admitted to an intensive care unit. Pancreas 28: 369～373, 2004
21) Acosta, J. M.; O. M. Rubio Galli, R. Rossi, *et al.*: Effect of duration of ampullary gallstone obstruction on severity of lesions of acute pancreatitis. J. Am. Coll. Surg. 184: 499～505, 1997
22) Senninger, N.; F. G. Moody, J. C. Coelho, *et al.*: The role of biliary obstruction in the pathogenesis of acute pancreatitis in the opossum. Surgery 99: 688～693, 1986
23) Takeyama, N.: Pathophysiology, diagnosis and treatment of severe acute pancreatitis infectious complication with severe acute pancreatitis. J. Biliary Tract & Pancreas 27: 31～36, 2006
24) Craig, W. A.: Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin. Infect. Dis. 26: 1～10; quiz 11～12, 1998
25) Craig, W. A.: Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect. Dis. Clin. North Am. 17: 479～501, 2003
26) Muto, Y.; Y. Mikami, S. Sakakibara, *et al.*: Pharmacokinetic and pharmacodynamic properties of biapenem, a carbapenem antibiotic, in rat experimental model of severe acute pancreatitis. Pancreas 36: 125～132, 2008

重症急性膵炎（SAP）動注療法におけるカルバペネム系抗菌薬とnafamostat mesilate（NM）の配合変化試験
—カルバペネム系抗菌薬の安定性—

浜田幸宏[1)]・今泉　弘[2)]・宮澤志朗[2)]・木田光広[2)]・
相馬一亥[3)]・小泉和三郎[2)]・砂川慶介[4)]・黒山政一[1)]

[1)] 北里大学東病院薬剤部
[2)] 北里大学医学部消化器内科学
[3)] 北里大学医学部救命救急医学
[4)] 北里大学北里生命科学研究所

近年，重症急性膵炎（SAP）に対する蛋白分解酵素阻害薬・抗菌薬持続動注療法（以下，動注療法）の有効性を示す報告が散見される。その動注療法では広域抗菌スペクトルを有するカルバペネム系抗菌薬とnafamostat mesilate（NM）が用いられることが多い。我々は，日本の臨床で上市されている全カルバペネム系抗菌薬とNMとの配合後のカルバペネム系抗菌薬の配合変化について検討した。カルバペネム系抗菌薬を生理食塩液または5%ブドウ糖30mLで溶解し，外観，pHおよび安定性について観察または測定した。また，各カルバペネム系抗菌薬溶液とNM溶液との配合後の変化について検討した。各カルバペネム系抗菌薬の生理食塩液および5%ブドウ糖液で溶解後8時間まで残存率が90%以上を示したのは，Biapenem（BIPM）とDoripenem（DRPM）であり，外観および残存率（90%以上）とも問題ないと判断された。NMと各カルバペネム系抗菌薬を配合後の変化については，僅かな着色と90%以上の残存率を示したのはBIPMの8時間が最も長く，次いで，DRPMの6時間，生理食塩液で溶解したMEPMであった。他のカルバペネム系抗菌薬では外観および残存率の変化を認めた。時間依存的に効果を発揮するカルバペネム系抗菌薬ではSAPのみに限らず他の重症感染症においてもBIPMおよびDRPMは点滴時間を延長した投与が可能と考えられた。