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Original

Usefulness of Continuous Regional Arterial Infusion with Doripenem and Protease Inhibitors for Severe Acute Pancreatitis

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Abstract: Doripenem (DRPM) is a relatively new drug belonging to the carbapenem antibiotic group. We hypothesized that the pharmacological characteristics of DRPM could make it useful in the treatment of severe acute pancreatitis (SAP). We investigated the usefulness of continuous regional arterial infusion (CRAI) with DRPM and protease inhibitors for SAP. Two hundred and forty-two patients with SAP were admitted to Showa University Hospital between November 2002 and June 2013. Of these, 53 patients were treated with CRAI with carbapenem antibiotics and nafamostat mesilate (NM), a serine protease inhibitor, via the celiac and superior mesenteric arteries. Clinical outcomes were evaluated retrospectively in 34 patients treated with DRPM and 19 patients undergoing non-DRPM therapy (meropenem $n=11$, imipenem $n=6$; biapenem $n=2$). The median time to commencement of oral intake was significantly shorter in the DRPM than non-DRPM group (9 vs 14 hospital days, respectively; $P<0.01$). In addition, the rate of walled-off necrosis in the DRPM group tended to be lower than in the non-DRPM group (37.5 vs 64.7%, respectively, $P=0.069$). The results of the present study suggest that CRAI with DRPM and NM for SAP could have equivalent therapeutic effects to CRAI with other carbapenem antibiotics and NM.

Key words: continuous regional arterial infusion, doripenem, protease inhibitor, severe acute pancreatitis

Introduction

Severe acute pancreatitis (SAP), although a benign disease, is associated with high mortality and is often refractory to treatment. The mortality rate of SAP has been reported to be approximately 30%¹.

Guidelines regarding pancreatitis have been amended using a revision of the Atlanta International Classification². In these new guidelines, the definition, severity assessment, and treatment strategies for SAP have been revised. SAP is diagnosed when there is associated organ failure that is refractory to therapy for 48 hr.

In current practice, patients are observed for 4 weeks for the development of walled-off necro-

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sis (WON), a complication of infectious pancreatitis, which, if it occurs, is then treated by the recommended therapeutic approach of necrosectomy using a low invasive approach³). Infectious pancreatic complications are an important prognostic factor for SAP; it is reported that continuous regional arterial infusion (CRAI) with antibiotics and protease inhibitors is effective in preventing infectious pancreatic complications and reducing mortality following SAP^{4, 5}). Recently, studies have been published describing CRAI with carbapenem antibiotics⁶⁻¹¹). Based on the results of these studies, we adopted CRAI with carbapenem antibiotics and protease inhibitors for the treatment of SAP. SAP is associated with a high mortality rate. Therefore, it is very difficult to perform a prospective study for SAP.

The aim of the present study was to evaluate the usefulness of CRAI with doripenem (DRPM) and the serine protease inhibitor nafamostat mesilate (NM) for SAP. DRPM is a relatively new drug belonging to the carbapenem antibiotic group. We hypothesized that the pharmacological characteristics of DRPM could make it useful in the treatment of SAP. We compared the safety and efficacy of CRAI with DRPM and NM for SAP with non-DRPM therapy (i.e. treatment with other carbapenem antibiotics) by assessing adverse events and the mortality of SAP following treatment.

Material and methods

Two hundred and forty-two patients with SAP were admitted to Showa University Hospital between November 2002 and June 2013. Of these, 53 patients underwent treatment with CRAI with carbapenem antibiotics and NM via the celiac and superior mesenteric arteries. Clinical outcomes, such as infectious complications and mortality, were reviewed retrospectively and compared between the 34 patients who received DRPM and the 19 patients who were treated with non-DRPM therapy (meropenem [MEPM] n = 11; imipenem [IPM] n = 6; biapenem [BIPM] n = 2).

In Japan, the prognostic factors and computed tomography (CT) grading for acute pancreatitis¹²), developed by the Research Committee of Intractable Diseases of the Pancreas (Ministry of Health, Labour and Welfare), are used for the assessment of the severity of acute pancreatitis (Table 1).

CRAI was used in patients with severe acute necrotizing pancreatitis, defined as a lack of enhancement of pancreatic parenchyma on contrast-enhanced (CE) CT. The drugs administered by CRAI were NM (240 mg/day) together with either 1.5 g/day DRPM (0.5 g every 8 hr), 2 g/day MEPM (1 g every 12 hr), 2 g/day IPM (1 g every 12 hr), or 1.2 g/day BIPM (0.6 g every 12 hr). The antibiotic used was chosen at the discretion of the attending physician.

Continuous variables are expressed as median values with the range in parentheses. Statistical analyses were performed using StatMate III software (ATMS, Tokyo, Japan). Data were analyzed by the Mann-Whitney *U*-test and Chi-squared test, with $P < 0.05$ considered significant.

The present retrospective study was approved by the Ethics Committee of Showa University Hospital.

Table 1. Japanese severity scoring system for acute pancreatitis (Ministry of Health, Labour and Welfare of Japan, 2008 revision)

Prognostic factors (1 point for each factor)	
1. Base excess ≤ -3 mEq/l or shock (systolic blood pressure < 80 mmHg)	
2. $P_aO_2 \leq 60$ mmHg (room air) or respiratory failure (requiring ventilatory management)	
3. BUN ≥ 40 mg/dl or creatinine ≥ 2.0 mg/dl or oliguria (daily urine output < 400 ml even after intravenous fluid resuscitation)	
4. Lactate dehydrogenase ≥ 2 ULN	
5. Platelet count $\leq 100,000/\text{mm}^3$	
6. Serum Ca ≤ 7.5 mg/dl	
7. C-Reactive protein ≥ 15 mg/dl	
8. No. positive measures in SIRS criteria ≥ 3	
9. Age ≥ 70 years	
CT grade based on contrast-enhanced CT	
1. Extrapancreatic progression of inflammation	
Anterior pararenal space	0 points
Root of mesocolon	1 point
Beyond lower pole of kidney	2 points
2. Hypo-enhanced lesion of the pancreas	
The pancreas is conveniently divided into three segments (head, body, and tail)	
Localized in each segment or only surrounding the pancreas	0 points
Extends to two segments	1 point
Occupies entire two segments or more	2 points
1 + 2 = total score	
Total score = 0 or 1	Grade 1
Total score = 2	Grade 2
Total score ≥ 3	Grade 3
Assessment of severity	
If the prognostic factors score is ≥ 3 or CT grade is ≥ 2 , the disease is graded as 'severe'	
The systemic inflammatory response syndrome (SIRS) criteria include body temperature $> 38^\circ\text{C}$ or $< 36^\circ\text{C}$, heart rate > 90 b.p.m., respiratory rate > 20 breaths/min or $P_aCO_2 \leq 32$ torr, and white blood cell counts $> 12,000$ cells/ mm^3 , < 4000 cells/ mm^3 , or $> 10\%$ immature (band) forms.	
BUN, blood urea nitrogen; ULN, upper limit of normal; CT, computed tomography.	

Results

The median age of the 53 SAP patients (41 men, 12 women) was 49 years (range 15 ~ 85 years). Disease etiology included alcoholic pancreatitis in 34 patients, gallstones in two, idiopathic pancreatitis in 13, and other diseases in the remaining four patients. The median Japanese prognostic factors score within 48 hr of admission was 4 points (range 0 ~ 8 points). CE-CT Grade 2 disease was present in 30 patients, whereas Grade 3 disease was present in 23 patients. The median Acute Physiology and Chronic Health Evaluation (APACHE) II score was 10 points (range 0 ~ 31 points), and the median sequential organ failure assessment (SOFA) score was 2 points (range 0 ~ 10 points). The median day of commencement of CRAI was Hospital Day 1 (range Days 1 ~ 4), the median duration of CRAI was 5 days (range 3 ~ 7 days), and the mortality rate was 9.4%.

There were no significant differences in patient characteristics between the DRPM and non-DRPM groups in terms of age, sex, etiology, Japanese prognostic factors score, CE-CT grade, APACHE-II score, SOFA score, starting day of CRAI, and duration of CRAI (Table 2). No

Table 2. Patient characteristics in doripenem (DRPM)-treated and -untreated (non-DRPM) patients

	DRPM group (n = 34)	Non-DRPM group (n = 19)	P value
Age (years)	51 (19 ~ 85)	48 (15 ~ 83)	NS
No. men / women	27 / 7	14 / 5	NS
Etiology (alcohol / gallstones / idiopathic / others)	24 / 1 / 7 / 2	10 / 1 / 6 / 2	NS
Japanese prognostic factors score (points)	3 (0 ~ 7)	4 (1 ~ 8)	NS
CE-CT grade (1 / 2 / 3)	0 / 22 / 12	0 / 8 / 11	NS
APACHE-II score (points)	11 (0 ~ 28)	9 (1 ~ 31)	NS
SOFA score (points)	3 (0 ~ 10)	2 (0 ~ 10)	NS
Start time of CRAI (hospital day)	1 (1 ~ 3)	1 (1 ~ 4)	NS
Duration of CRAI (days)	5 (3 ~ 5)	5 (3 ~ 7)	NS

Data are presented as median values with the range in parentheses, or as the number of patients in each group. CE-CT, contrast-enhanced computed tomography; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; CRAI, continuous regional arterial infusion.

significant differences were observed between the two groups with regard to the disappearance of abdominal pain, duration of administration of antibiotics, early organ dysfunction rate, late severe infection rate, surgery rate, duration of admission, and mortality. The median day of commencement of oral feeding was significantly earlier in the DRPM than non-DRPM group (9 vs 14 hospital days, respectively; $P < 0.01$). The rate of WON tended to be lower in the DRPM than non-DRPM group (37.5% vs 64.7%, respectively; $P = 0.069$; Table 3). Adverse events due to CRAI with DRPM and NM for SAP included increased serum bilirubin levels in five patients (two patients had increased aspartate aminotransferase and alanine aminotransferase levels), one case of subarachnoid hemorrhage (SAH), and one case of obstruction of the artery of the lower extremity.

Discussion

When acute pancreatitis is suspected, its severity needs to be determined so that appropriate treatment can be administered. In severe cases, strict circulatory and respiratory management are necessary.

In Showa University Hospital, CRAI is performed in patients with severe acute necrotizing pancreatitis, and continuous hemodiafiltration (CHDF) is performed in patients with SAP with organ dysfunction. Further, we provide early enteral nutrition as infection prophylaxis for SAP.

In Japan, it is not considered necessary to administer antibiotics prophylactically to patients with mild acute pancreatitis because of the low rate of infectious complications and mortality. Although prophylactic administration of antibiotics for SAP can improve the prognosis and decrease the incidence of infectious pancreatic complications, it is necessary to consider the antibacterial spectrum, pancreatic tissue concentration, and dosing period of antibiotics for SAP.

Table 3. Clinical outcomes in doripenem (DRPM)-treated and -untreated (non-DRPM) patients

	DRPM group (n = 34)	Non-DRPM group (n = 19)	P value
Disappearance of abdominal pain (hospital day)	5 (2 ~ 12)	5 (3 ~ 15)	NS
Start day of oral intake (hospital day)	9 (4 ~ 35)	14 (10 ~ 93)	<0.01
Duration of administration of antibiotics (days)	12 (3 ~ 57)	13 (3 ~ 143)	NS
Early organ dysfunction rate	64.7% (22 / 34)	84.2% (16 / 19)	NS
Late severe infection rate	13.3% (4 / 30)	17.6% (3 / 17)	NS
Surgery rate	2.9% (1 / 34)	5.3% (1 / 19)	NS
WON rate	37.5% (12 / 32)	64.7% (11 / 17)	NS (0.069)
Duration of admission (days)	21 (3 ~ 115)	25 (3 ~ 172)	NS
Mortality rate	8.8% (3 / 34)	10.5% (2 / 19)	NS

Data are given as median values with the range in parentheses, or as percentages with the number of patients / total number of patients in parentheses.

WON, walled-off necrosis.

Interestingly however, one published study in 2006 does not recommend prophylactic antibiotic therapy in patients with SAP¹³⁾.

Buchler *et al*¹⁴⁾ examined pancreatic tissue concentrations of different antibiotics and reported that imipenem (carbapenem antibiotics), ofloxacin, and ciprofloxacin (new quinolone) had high pancreatic tissue concentrations and extensive bactericidal activity against most bacteria. Therefore, we examined the usefulness of prophylactic antibiotics in SAP in the present study. There have been some reports published regarding the prophylactic use of antibiotics for severe pancreatitis¹⁵⁻²⁶⁾. The efficacy of prophylactic antibiotics for acute pancreatitis was first reported after the introduction of carbapenem antibiotics in the 1990s, including a report regarding the use of imipenem by Pederzoli *et al*¹⁵⁾. Recently, carbapenem antibiotics for SAP have been recommended in Japan⁷⁻¹⁰⁾.

Some placebo-controlled double-blind studies have evaluated transvenous prophylactic antibiotic therapy^{21, 22)}. These studies suggest that prophylactic antibiotic therapy for SAP does not necessarily lead to decreases in infectious pancreatic complications and mortality rate. However, these studies varied in the type of antimicrobial agent used, the route of administration, and the day on which antibiotics were started. Therefore, denying early prophylactic antibiotic therapy based on these studies is not appropriate.

Conversely, a randomized controlled trial (RCT) on early prophylactic antibiotic therapy for SAP reported decreases in infectious pancreatic complications and mortality rate with such therapy²⁵⁾. Manes *et al*²²⁾ conducted an RCT using MEPM for necrotizing pancreatitis. They divided patients into two groups based on the timing of commencement of antibiotic administration (i.e. at admission and after CE-CT confirmation of the pancreatic necrotic area). Pancreatic infection occurred in 13% of patients in the former group, compared with 31% of patients in

the latter group, with extrapancreatic infection observed in 17% and 45% of patients, respectively. Pancreatic and extrapancreatic infection rates in the former group were significantly lower than in the latter group. In addition, the former group had lower surgery rates and a shorter period of admission than patients in the latter group. Therefore, the results of the study of Manes *et al*²²⁾ suggest that the time of initiation of antibiotic therapy is an important determinant of patient outcome.

CRAI for acute necrotizing pancreatitis was reported by Takeda *et al*⁴⁾, and came to be recognized as appropriate therapy for SAP. The purpose of CRAI is to directly deliver a high concentration of the protease inhibitor and antibiotic to the site of inflammation and necrotic tissue by intra-arterial injection to prevent local pancreatic inflammation and infection. NM acts as a protease inhibitor at low concentrations and as an anticoagulant at high concentrations. It is estimated that local pancreatic concentrations of drugs administered by intra-arterial injection for CRAI can reach levels nine fold higher, or more, than those seen after intravenous infusion²⁷⁾. Takeda *et al*⁴⁾ reported that NM inhibits the extension of pancreatic necrosis by its anticoagulant action in the microcirculation, and is effective for the prevention of vasospasm and vascular occlusion. In that study, intraperitoneal infections, infections due to pancreatic necrosis, and mortality were significantly lower in the NM than non-NM group.

Hayashi *et al*⁶⁾ have reported the usefulness of CRAI via the celiac artery, whereas Takagi and Isaji⁵⁾ have reported the usefulness of CRAI via the superior mesenteric artery.

In studies that divided patients with SAP into CRAI and non-CRAI groups, infectious pancreatic complications, surgical rate, and mortality were lower in the CRAI than non-CRAI group^{7, 8)}. It has also been reported that patients who received CRAI for SAP with gabexate mesilate as the protease inhibitor had a shorter duration until the disappearance of abdominal pain, lower systemic inflammatory response syndrome (SIRS) positive scores, and a shorter duration of hospitalization than patients in the non-CRAI group⁹⁾.

Ishikawa *et al*¹⁰⁾ reported on the usefulness of CRAI with NM and IPM for SAP. The mortality rate was significantly lower in the group that started CRAI within 3 days of the onset of SAP compared with the group that started CRAI after 3 days after onset (0% vs 66.7%, respectively). Ishikawa *et al*¹⁰⁾ concluded that the timing of CRAI initiation is extremely important, and that CRAI should be initiated within 3 days of the onset of SAP for greater efficacy.

An RCT of CRAI for SAP was first reported by Piascik *et al*¹¹⁾. In that study, 78 patients were randomly divided within 72 hr from the onset of acute pancreatitis and hospitalization into two groups (n = 39 in each): a CRAI group and a non-CRAI group. The CRAI group was treated continuously with 240 mg/day NM and 1 g/day IPM for 5 days as an arterial infusion via one of the arteries perfusing the pancreas, following which IPM was given intravenously (0.5 g every 8 hr) for at least 9 days. The non-CRAI group received IPM (0.5 g every 8 hr) intravenously for 14 days. The mortality rate was lower in the CRAI than non-CRAI group, indicating that CRAI for SAP with a protease inhibitor and antibiotic is effective in preventing adverse events and reducing mortality rates.

Recently, a pharmacokinetic–pharmacodynamic theory was proposed^{28, 29)}. β -Lactam antibiotics,

such as carbapenem antibiotics, are drugs with time-dependent bactericidal activity. In vivo, the proliferative inhibitory effect and maximal bactericidal action correlate with the time for which the drug concentration exceeds its minimum inhibitory concentration (MIC; %T>MIC).

In the present study, we chose DRPM as the antibiotic to be evaluated for the following reasons: (1) DRPM is highly effective against aerobic Gram-negative and Gram-positive bacteria, as well as anaerobic bacteria, and it suppresses the growth of antimicrobial-resistant *Pseudomonas aeruginosa*; (2) DRPM, MEPM, and IPM exhibit potent activity, with an MIC₉₀ of 4, 16, and 32 µg/ml, respectively, and DRPM is clinically effective against *P. aeruginosa* infection; (3) DRPM does not show any cross-resistance with MEPM and IPM against *P. aeruginosa*; (4) incompatibility between DRPM and protease inhibitors is low; and (5) DRPM is a drug with little effect on the central nervous system³⁰⁻³⁶.

In addition, on the basis of changes in plasma concentrations in healthy adults in a Phase I study¹⁴), it has been suggested that as the number of doses of DRPM increases, the time above the MIC of DRPM increases. In the present study, the incidence of WON in the DRPM group tended to be lower than in the non-DRPM group, indicating the clinical efficacy of CRAI with DRPM and NM. One study compared the MIC₉₀ of DRPM, IPM, and MEPM for the main microorganism strains affected by them. In most strains, the MIC₉₀ of DRPM was lower than that of IPM and MEPM²⁹).

In the present study, it is possible that synergistic actions between DRPM and NM led to the observed decrease in the incidence of WON.

In conclusion, the results of the present study suggest that CRAI with DRPM and NM for SAP could provide equivalent therapeutic effects to those seen following CRAI with other carbapenem antibiotics and NM.

Conflict of interest disclosure

The authors have no sources of funding or conflicts of interest to declare.

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