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Serum Concentrations of Antibiotics During Severe Invasive Surgery Such as Esophagectomy for Esophageal Cancer

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This study was performed to confirm the antibiotic regimen during a severe invasive surgery, such as esophagectomy, with a long procedure and a large amount of normal volumes of infusion. Ten patients with esophageal cancer were enrolled in this study, and cefmetazole sodium concentrations in serum were measured during esophagectomy. The ranges of minimum inhibitory concentrations for 90% of isolates of cefmetazole sodium for microorganisms in our institutions for 8 years were investigated. The maximum concentration was 83.9 μg/mL just after the completion of infusion, and its half-life was 1.5 hours. Serum concentration of cefmetazole sodium was kept above 16 μg/mL for 4 hours during esophagectomy. It was kept above 32 μg/mL for 2.5 hours after injection. There are almost no differences in the pharmacokinetics of cefmetazole sodium between common use and during esophagectomy. In addition, additive infusion of antibiotics 4 hours after the first infusion was recommended during esophagectomy.

Key words: Antibiotics – Serum concentration – MIC_{90} – Esophagectomy

The guidelines for the administration of antibiotics during surgical treatment were published by the Centers for Disease Control and Prevention (CDC) in 1999.[1] The CDC recommends that therapeutic levels of the antimicrobial agent in both serum and tissues be maintained throughout the operation and until, at most, a few hours after the closure of incision. Many types of operation are included in this "operation," although the volumes of bleeding and infusion, as well as the operation time, differ in each surgical operation. Esophageal cancer surgery, which is one of the most invasive

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operations, requires a long operation time and a large amount of infusion. Furthermore, blood transfusion is also required in some cases. Therefore, although a different schedule for antibiotics seems to be required for esophagectomy in comparison with other cancer surgeries, the schedule for antibiotic administration during esophagectomy has not been established yet. The aims of this study were to investigate the use of antibiotics and to establish the clinical effect of antibiotic infusion during invasive esophageal cancer surgery.

Materials and Methods

Patients

Ten patients with esophageal cancer were enrolled in this study. All patients underwent esophagectomy via right thoracotomy and laparotomy with 2- or 3-field lymphadenectomy, and a gastric tube pulled up though the posterior mediastinal route was anastomosed with cervical esophagus in the left neck region. Furthermore, all patients underwent placement of an ileostomy tube for enteral feeding. Informed consent to participate in this study was obtained from all patients before surgery. The characteristics of these patients and details of the operation are described in Table 1. None of the patients received antibiotics for at least 48 hours before surgery.

Just before the first skin incision, a solution containing 1 g of the cephamycin antibiotic, cefmetazole sodium (Cefmetazon Intravenous, Sankyo Co Ltd, Tokyo, Japan)[2] in 100 mL of normal serine was administered intravenously for 30 minutes using an infusion pump (Telfusion TE 16s, Terumo Co, Tokyo, Japan). No other antibiotics were given to these patients on the day of operation.

Blood samples (5 mL) were collected through an arterial pressure line before sodium cefmetazole injection, and at 15, 30, 90, 120, 180, 240, and 360 minutes after the injection. After these samples were centrifuged immediately, the serum was separated and was stored at –80°C until assay. Patients were carefully monitored for clinical or biologic signs of infection.

Concentrations of cefmetazole sodium

Cefmetazole sodium concentrations in serum were assayed by high-performance liquid chromatography[3] using an integrated high-performance liquid chromatography system (LC-10A, Shimadzu Co, Kyoto, Japan). The assays were performed by a third party without the knowledge of clinical data.

Table 1 Clinical findings

	Values
Patients	
Sex, male/female	10/0
Age, y	62.7 ± 10 (48–76)
Location (Ce/Ut/Mt/Lt)	1/1/3/5
pT (T0/T1/T2/T3/T4)	1[a]/1/1/6/1
pN (N0/N1)	3/7
M (M0/M1)	10/0
Preoperation	
BUN	14.9 ± 5.2
Cr	0.75 ± 0.16
CCr	79.6 ± 22.4
AST	25 ± 7.5
ALT	22.2 ± 13.2
T-bil	0.76 ± 0.3
Operation	
Operation time, min	455 ± 72 (360∼605)
Within 6 hours of the beginning of the operation	
Bleeding volume, mL	469 ± 300 (120∼1240)
Infusion volume, mL	3560 ± 590 (2610∼4400)
Blood transfusion, mL	0
Balance, mL	2330 ± 440 (2015∼3320)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ce, cervical esophagus; Cr, creatinine; CCr, creatinine clearance; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; T-bil, total bilirubin; Ut, upper thoracic esophagus.

[a]T0 patient: no residual carcinoma by neoadjuvant chemoradiation.

Minimum inhibitory concentrations for 90% of cefmetazole

The range of minimum inhibitory concentrations for 90% (MIC_{90}) of isolates of cefmetazole sodium for microorganisms detected in our institutions between January 1996 and December 2010 was investigated (MicroScan WalkAway, Dade MicroScan Inc, West Sacramento, California; Vitek, Bio Meriéux Ltd, L'Etoile, France). These pathogens were collected from the respiratory tract, gastrointestinal tract, urinary tract, skin, and wounds of patients treated at our institutions. The results of MIC_{90} of cefmetazole sodium for clinical isolates were analyzed every 7 years, from January 1996 to December 2003, and from January 2004 to December 2010. The sensitivity of cefmetazole sodium against each microorganism was determined by National Committee for Clinical Laboratory Standards (NCCLS; present CLSI: US clinical examination standardization society).[4]

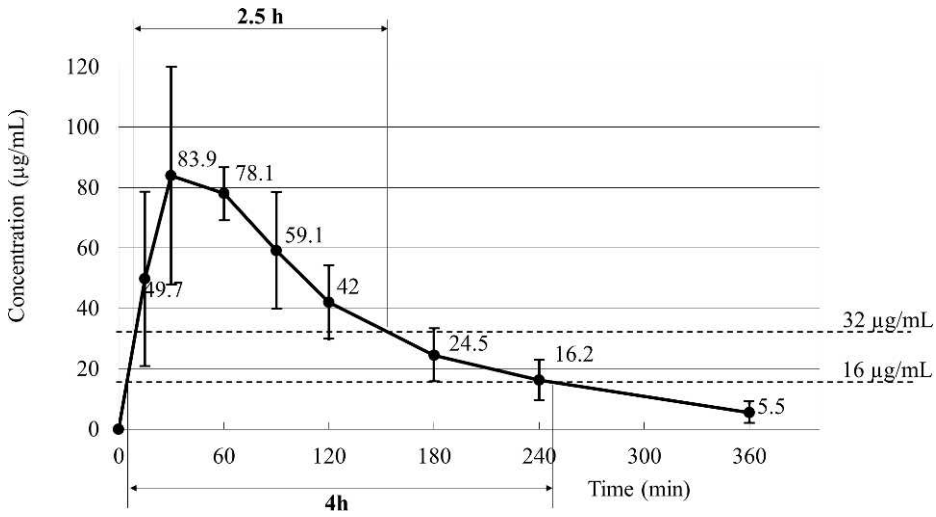

Fig. 1 Serum concentration of cefmetazole sodium after venous administration of 1 g for 30 minutes in 10 patients.

Statistical analysis

The ratios of the number of resistant microorganisms versus those of microorganisms showing sensitivity and intermediate sensitivity to cefmetazole sodium in the former and latter 7-year periods were compared using the χ^2 test. A *P* value of less than 0.05 was considered to indicate a significant difference.

Results

Antibiotic concentrations

Serum concentrations of cefmetazole sodium are shown in Fig. 1. The maximum concentration was 83.9 ± 35.9 μg/mL (mean ± SD; range, 43.8–144.5 μg/mL) 30 minutes after administration of antibiotics. The mean concentrations of antibiotics at 60, 90, 120, 180, 240, and 360 minutes were 78.1, 59.1, 42, 24.5, 16.2, and 5.5 μg/mL, respectively. The half-life of the antibiotics was about 90 minutes.

MIC_{90} for bacteria

MIC_{90} of cefmetazole sodium for clinical isolates showed little change over the 14 years of this study. Cefmetazole sodium affected most of the representative bacteria at 16 μg/mL; exceptions were methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*. The resistance rate of cefmetazole against bacteria in two seasons (1996–2003 and 2004–2010) was *Escherichia coli*: 2.0% and 3.1%, *Klebsiella pneumoniae*: 5.2% and 2.9%, *Klebsiella oxytoca*: 1.0% and 0.0%, *Proteus mirabilis*: 0.0% and 0.0%, *S aureus* except MRSA: 1.9% and 4.5%, MRSA: 83.9% and 68.8%, *S epidermidis*: 56.2% and 35%, *P aeruginosa*: 0.0% and 0.0%, respectively (Tables 2 and 3). There is no significant difference between the two seasons against the representative bacteria.

Discussion

Instructions of the antimicrobial agent

The maximum serum concentration of cefmetazole sodium was reported to be 76.2 μg/mL just after intravenous infusion at a dose of 1 g for 60 minutes.[5] Its half-life was reported to be approximately 1.2

Table 2 MIC_{90} of cefmetazole sodium against clinically detected microorganisms in our hospital 1997–2003[a]

	Sensitive				Resistant
Intestinal bacteria	2	4	8	16	>32
E coli		418	14	10	9
K pneumoniae		410	5	4	23
K oxytoca		99			1
Morganella morganii		34	28	3	4
P mirabilis		31			
Proteus vulgaris		12	1	1	2
Enterobacter cloacae		2			121
Enterococcus faecalis					289
Enterococcus faecium			1	1	112
Staphylococcus					
S aureus	602	4	5	5	12
S aureus (MRSA)	52	98	98	140	2024
S epidermidis	40	16	26	46	164
Pseudomonas aeruginosa					19

[a]N = 4986 isolates.

Table 3 MIC_{90} of cefmetazole sodium against clinically detected microorganisms in our hospital 2004–2010[a]

	Sensitive				Resistant
Intestinal bacteria	2>	4	8	16	>32
E coli	110	8	5	2	4
K pneumoniae	61	7			2
K oxytoca	4				
M morganii					
P mirabilis		2			
P vulgaris					
E cloacae			1		18
E faecalis				2	977
E faecium				14	241
Staphylococcus					
S aureus		17		4	1
S aureus (MRSA)			2	3	11
S epidermidis		1	2	10	7
Pseudomonas aeruginosa					170

[a]N = 1686 isolates.

hours. Mashimo *et al*[6] reported that its maximum serum concentration was 85.3 μg/mL under the same conditions. In the present study regarding esophagectomy, the maximum concentration was 83.9 μg/mL just after intravenous infusion at the same dose for 30 minutes, and its half-life was approximately 1.5 hours. There were differences in the time of intravenous infusion, but the pharmacokinetics of cefmetazole sodium were almost same during esophageal surgery. The infusion in esophagectomy had little effect on the pharmacokinetics of cephamycin antibiotic.

In the experimental study using mice, cefmetazole sodium was excreted in the urine and bile juice, and tissue concentrations of the kidney and liver are elevated.[5] Furthermore, radiation levels in the kidneys, urinary bladder, gallbladder, liver, blood, lung, and intestinal cavity were high in monkey whole-body autoradiograms using radiolabeled cefmetazole sodium.[7] In addition, the concentration in human ascites was maintained at a high level. These data suggested that the high serum level of cefmetazole sodium was in accord with high concentrations in various tissues. Therefore, we examined serum concentration of cefmetazole sodium only, but our data showed an association with the same or higher concentration of cefmetazole sodium in the operation area (ascites, intestinal cavity, and serum).

Serum concentration of cefmetazole sodium was kept above 16 μg/mL for 4 hours during esophagectomy, and above 32 μg/mL for 2.5 hours after injection. Most MRSA and *S epidermidis* could not survive in the presence of the antibiotic at 32 μg/mL. Time above the MIC of 32 μg/mL was 62.5% (2.5 h/4 h; Fig. 1). Our data suggested that a second antibiotic injection should be administered about 4 hours after the first infusion in operations lasting longer than 4 hours (Fig. 2). In such cases, we could keep the time above the MIC of 32 μg/mL higher than 62.5% (5 h/8 h) during operations lasting even for about 8 hours. Time above MIC (32 μg/mL) of 62.5% is acceptable. Therefore, additive infusion of antibiotics 4 hours after the first infusion is recommended during esophagectomy. Another important point is the serum antibiotics concentration at closure on wound infection. Zelenitsky *et al*[8] demonstrated the critical effect of

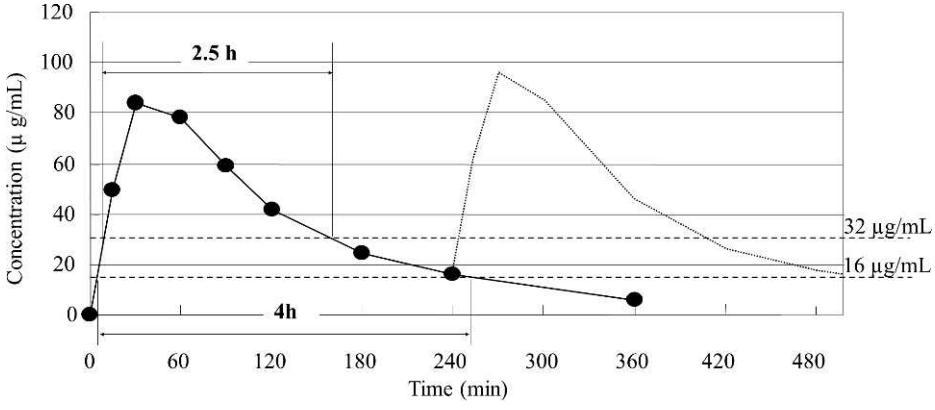

Fig. 2 Serum concentration of cefmetazole sodium after venous administration of 1 g for 30 minutes in 10 patients. If we added the second 1 g of cefmetazole sodium at 4 hours after the first infusion, the serum concentration of cefmetazole sodium would be drawn as the dotted line. This line was created by the curve of the first infusion and the half-life of this drug. Serum concentration of cefmetazole sodium was maintained above 32 μg/mL for 150 minutes, and above 16 μg/mL for 240 minutes.

the antibiotic concentration at closure on wound infection and suggested a significant association between the concentration of antibiotics and other well-established risk factors, like the timing of preoperative antibiotic administration and surgery duration.

Drug-resistant successive change

For inspection of the antimicrobial agent usage, a sensitivity test of antimicrobial agent for bacteria periodically in a hospital setting is important. In these 14 years, there were few changes in the susceptibility for bacteria of cefmetazole. In these past 14 years, we have used cefem antimicrobial agent of the first generation/the second generation as the first choice for a postoperative infection prevention antimicrobial agent. It is not necessary to change the type of antibiotic or method of use during surgical operation. It is necessary to choose a postoperative antimicrobial agent in order to control postoperative infection systematically.

We think that this study realizes the importance of and gives important data for a real direction for uses of antimicrobial agents in esophageal cancer surgery, which is one of the most invasive operations and requires a long operation time and a large amount of infusion.

Conclusions

The concentration of cefmetazole sodium was maintained until 4 hours after administration. When operation time is longer than 4 hours, additional administration of antibiotics is recommended for severe invasive surgery, such as esophagectomy for esophageal cancer.

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