Note

Pharmacokinetics of Prophylactic Ampicillin–Sulbactam and Dosing Optimization in Patients Undergoing Cardiovascular Surgery with Cardiopulmonary Bypass

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Antibiotic concentrations must be maintained at an adequate level throughout cardiovascular surgery to prevent surgical site infection. This study aimed to determine the most appropriate timing for intraoperative repeated dosing of ampicillin–sulbactam, a commonly used antibiotic prophylaxis regimen, to maintain adequate concentrations throughout the course of cardiovascular surgery with cardiopulmonary bypass (CPB). The total plasma concentrations of ampicillin were monitored in 8 patients after ampicillin (1 g)–sulbactam (0.5 g) administration *via* initial intravenous infusion and subsequent CPB priming. Pharmacokinetic parameters were estimated and used to predict the free plasma concentrations of ampicillin. The mean values for the volume of distribution, elimination rate constant, elimination half-life, and total clearance of ampicillin were 15.8±4.1 L, 0.505±0.186 h^{-1}, 1.52±0.47 h, and 7.72±2.72 L/h, respectively. When ampicillin (1 g)–sulbactam (0.5 g) was intravenously administered every 3, 4, 6, and 12 h after the start of CPB, the predicted free trough plasma concentrations of ampicillin were 15.20, 8.25, 2.74, and 0.13 μg/mL, respectively. Therefore, an every-6-h regimen was needed to maintain the free ampicillin concentration at more than 2 μg/mL during cardiovascular surgery with CPB. We suggest that the dose and dosing interval for ampicillin–sulbactam should be adjusted to optimize the efficacy and safety of treatment, according to the minimum inhibitory concentrations for methicillin-sensitive *Staphylococcus aureus* isolates at each institution. Registration number: UMIN000007356.

Key words ampicillin; sulbactam; cardiovascular surgery; prophylaxis; cardiopulmonary bypass

The United States Centers for Disease Control National Nosocomial Infections Surveillance system demonstrated that surgical site infection (SSI) is the most frequently reported nosocomial infection, accounting for 14–16% of such infections among hospitalized patients and 38% in surgical patients.[1)] According to the Japan Nosocomial Infections Surveillance Open Report 2013, the incidence of SSI in cardiovascular surgery was 1.5–4.8%.[2)]

Postoperative SSIs are a major cause of postoperative morbidity and mortality in patients undergoing cardiac surgery. SSIs of the sternal wound and underlying mediastinum occur in 0.4–4% of cardiac surgical operations.[3)] The administration of antibiotic prophylaxis in patients treated with cardiothoracic operations can reduce the rate of SSI, and placebo-controlled trials of cardiothoracic antibiotic prophylaxis have found a benefit in preventing postoperative wound infections.[4)]

Cardiopulmonary bypass (CPB) is a technique that is nearly exclusively used by cardiac surgeons and has profound effects on the volume of distribution (V_d, L) and elimination kinetics for a variety of drugs, including commonly used antibiotic prophylaxis agents.[3)] Antibiotic prophylaxis should be selected according to the type of surgery, with administration starting within 60 min of the skin incision. When the duration of the cardiovascular operation is expected to exceed the time in which therapeutic level of the antibiotic prophylaxis agent can be maintained, additional antibiotic prophylaxis drugs should be infused.[1,3)] *Staphylococcus aureus* is the common pathogen involved in the epidemiology of SSI after cardiac surgery. Other major pathogens include *S. epidermidis*, *Enterococcus* spp. and Gram-negative organisms.[5)] Ampicillin–sulbactam is a combination drug consisting of beta-lactam and a beta-lactamase inhibitor, with a broad-spectrum anti-aerobic/anti-anaerobic activity. Thus, ampicillin–sulbactam and cefazolin are the most commonly used antibiotics in cardiovascular surgery. Notably, ampicillin–sulbactam was superior to cefazolin as a prophylactic agent against infections caused by methicillin-resistant *S. aureus* and borderline-susceptible *S. aureus* in a guinea pig model.[6)] From both effectiveness and cost perspectives, ampicillin–sulbactam is the most commonly used antibiotic prophylaxis regimen in breast cancer surgery and neurosurgery cases.[7,8)] Therefore, the dose and dosing interval for ampicillin–sulbactam must be carefully determined in order to achieve the proper plasma concentration in each patient.

Kara *et al.* reported that the rate of mortality and morbidity was higher with CPB (on-pump) than without CPB (off-pump), showing more importance of antibiotic prophylaxis for surgery with CPB.[9)] In patients undergoing cardiovascular surgery without CPB, we previously reported the pharmacokinetics of ampicillin–sulbactam and optimization of dosing regimens for prophylaxis.[10)] However, the pharmacokinetics of ampicillin in patients receiving cardiovascular surgery with CPB as an an-

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tibiotic prophylaxis regimen for SSIs has not been examined.

The aim of this study was to investigate the pharmacokinetics of ampicillin in patients undergoing cardiovascular surgery with CPB and to determine the most appropriate timing for intraoperative dosing in order to maintain adequate drug concentrations throughout the operation.

PATIENTS AND METHODS

Patients This study was approved by the Ethics Review Board of Kagoshima University Hospital. Eight adult patients who received ampicillin–sulbactam as antibiotic prophylaxis regimen during cardiovascular surgery with CPB between October 2009 and August 2010 at Kagoshima University Hospital were included in this study. The exclusion criteria were patients on dialysis, neonates, infants and children.

On-Pump Cardiovascular Surgery Procedures In this study, CPB was conducted using an extracorporeal pump and membrane oxygenator (Senko Medical Instrument Manufacturing Co., Ltd., Saitama, Japan). The CPB circuit was primed with 1500–1700 mL of lactated Ringer's solution and ampicillin (1 g)–sulbactam (0.5 g) (combined dose of 1.5 g). All patients received heparin to achieve an active clotting time of >480 s. The pump flow rate was individually calculated (2.4–2.6 L/min/m^2) and adjusted to maintain a mean arterial pressure of 60–80 mmHg. After the initiation of CPB, each patient was cooled under hypothermia (25–34°C) until the end of the surgical procedure.

Measurement of the Total Concentrations of Ampicillin in the Plasma Ampicillin (1 g)–sulbactam (0.5 g) was intravenously administered for 0.001–0.85 h before the start of surgery, followed by administration for 30 s in the CPB priming solution. Venous blood samples were collected every 30 min before and during CPB from the first administration and before the second administration at the start of CPB. The total concentrations of ampicillin in the plasma were measured using HPLC with minor modifications of the methods described by Martin *et al.*[11] For ampicillin, the intra- and inter-day accuracy (as absolute values of the relative error of the mean) and precision (as the coefficient of variation) were within 10%.

Pharmacokinetic Analysis Pharmacokinetic analyses of ampicillin before and after CPB were performed using the MULTI program.[12] Total concentration–time data for ampicillin were fitted to a standard one-compartment model with zero-order input and first-order elimination. The pharmacokinetic parameters for V_d and total clearance (CL, L/h) were estimated in each patient.

Prediction of the Free Concentrations of Ampicillin in the Plasma Based on the means of the estimated V_d and CL values, the free concentration of ampicillin in the plasma was predicted using the MULTI program,[12] where the fraction of plasma protein binding was assumed to be 20%[13] simulated using the pharmacokinetic parameters obtained after ampicillin (1 g)–sulbactam (0.5 g) administration *via* the initial intravenous infusion (0.25 h) and subsequent CPB priming (30 s). In the assessment of the drug concentrations, a value of 2 μg/mL was employed as a threshold (pharmacodynamic target) for the free concentration of ampicillin in the plasma, because the minimum inhibitory concentration of ampicillin–sulbactam for 90% of clinical isolates (MIC_{90}) of methicillin-sensitive *Staphylococcus aureus* (MSSA) was estimated to be 2 μg/mL in 2010[14] in Japan.

RESULTS

The patients included six males and two females, with a mean age of 61.9±12.4 years (mean±standard deviation (S.D.)), body weight (BW) of 56.4±9.5 kg, blood urea nitrogen level of 19.2±3.5 mg/dL, serum creatinine level of 1.1±0.4 mg/dL and creatinine clearance (CL_{cr}) of 65.6±25.7 mL/min. Diseases requiring cardiovascular surgery were as follows: valvular heart disease (n=6), coronary atherosclerosis (n=3), thoracic aortic aneurysm (n=1) and aortic root dilatation (n=1).

Figure 1 shows the observed and simulated ampicillin concentrations in eight patients. The estimated values of V_d and CL were as follows: 11.3 L and 5.76 L/h in patient A (CL_{cr}=96.7 mL/min, BW=48 kg); 10.7 L and 4.01 L/h in patient B (CL_{cr}=48.3 mL/min, BW=48 kg); 11.8 L and 9.72 L/h in patient C (CL_{cr}=73.4 mL/min, BW=65 kg); 15.3 L and 7.53 L/h in patient D (CL_{cr}=33.6 mL/min, BW=46 kg); 17.5 L and 13.07 L/h in patient E (CL_{cr}=28.2 mL/min, BW=65 kg); 20.73 L and 6.58 L/h in patient F (CL_{cr}=76.8 mL/min, BW=70 kg); 19.6 L and 7.72 L/h in patient J (CL_{cr}=77.4 mL/min, BW=50 kg); and 19.4 L and 7.36 L/h in patient H (CL_{cr}=90.2 mL/min, BW=59 kg). No correlation was observed between the values for CL (4.01–13.07 L/h) and CL_{cr} (28.2–96.7 mL/min), although ampicillin is a renally excreted drug.[10] The mean elimination rate constant (k_e) and elimination half-life ($t_{1/2}$) of ampicillin were 0.505±0.186 h^{-1} and 1.52±0.47 h, respectively (Table 1).

By predicting the free trough concentrations of ampicillin in the plasma, we developed a model adjusting for the dose and interval of ampicillin–sulbactam with CPB. The predicted free trough concentrations of ampicillin in the plasma at the 3-, 4-, 6- and 12-h intervals at the start of CPB were 15.20, 8.25, 2.74 and 0.13 μg/mL, respectively. Ampicillin (1 g)–sulbactam (0.5 g) (combined dose of 1.5 g every 6 h) should be administered intravenously to obtain a free trough concentration of ampicillin of >2 μg/mL.

DISCUSSION

This study examined the pharmacokinetics of prophylactically administered ampicillin–sulbactam in patients undergoing cardiovascular surgery with CPB. The doses and intervals of ampicillin–sulbactam during cardiovascular surgery with CPB were then assessed based on the estimated pharmacokinetic parameters, together with the presumed susceptibility to MSSA.

The mean V_d, k_e, $t_{1/2}$ and CL values of ampicillin to be 15.8 L, 0.505 h^{-1}, 1.52 h and 7.72 L/h, respectively (Table 1), in eight patients with a CL_{cr} of 65.6±25.7 mL/min. The drug concentrations may be profoundly altered during CPB, albeit mainly as a result of changed V_d and k_e, resulting in underdosing.[15] In this study, the pharmacokinetic parameters of ampicillin were compared before and after CPB. The V_d of after CPB was slightly increased compared to that observed before CPB. However, the mean V_d, k_e, $t_{1/2}$ and CL values obtained before and after CPB were very similar (data not shown). Therefore, we estimated the pharmacokinetic parameters for V_d and CL in each patient. We previously reported that the V_d of ampicillin in patients undergoing cardiovascular surgery

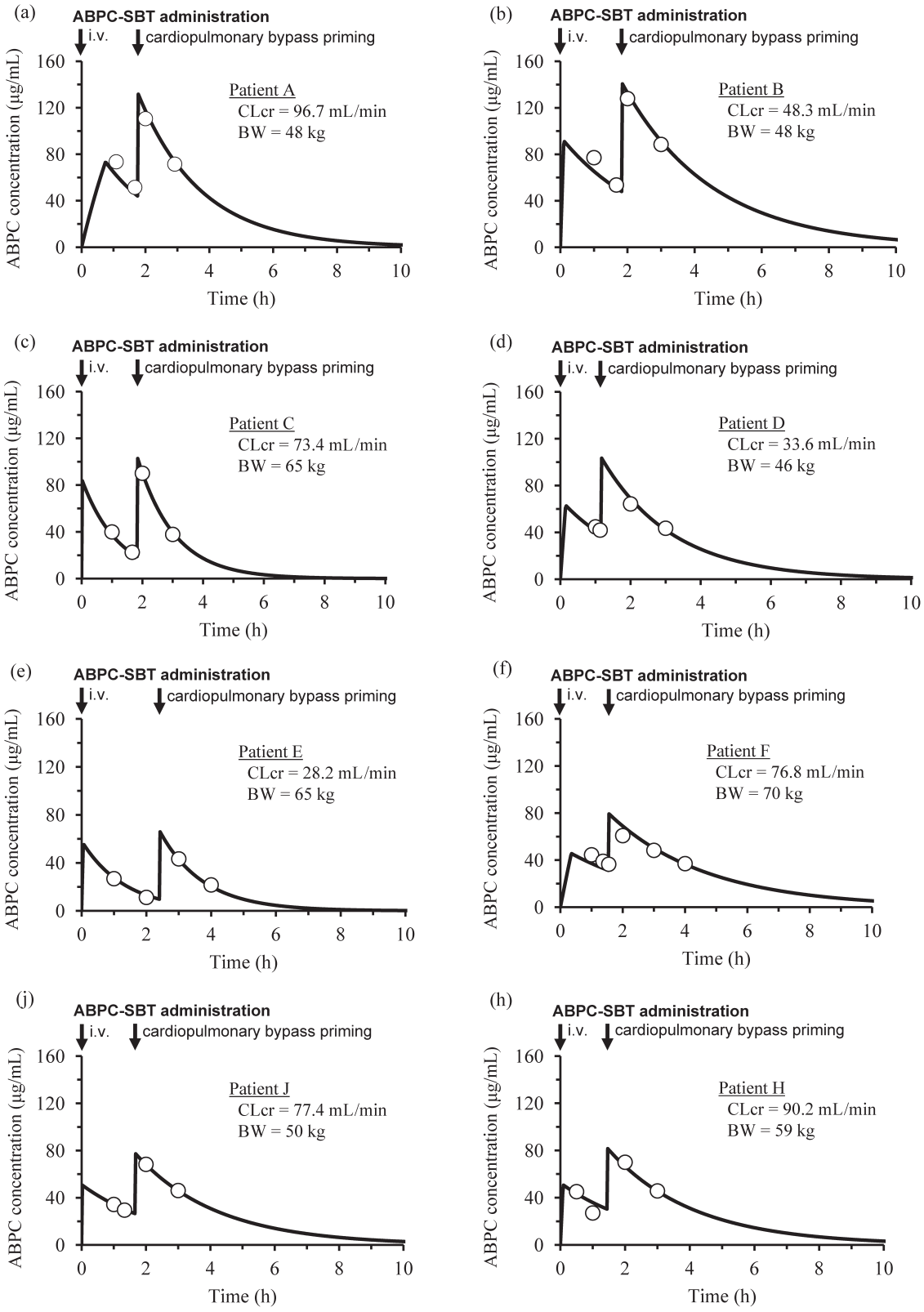

Fig. 1. (a)–(h) Observed Total Plasma Concentrations (○) and Simulation Curves Obtained Using the Pharmacokinetic Parameters (Table 1) in Eight Patients after Ampicillin (ABPC, 1 g)–Sulbactam (SBT, 0.5 g) Administration *via* Initial Intravenous (i.v.) Infusion (0.001–0.85 h) and Subsequent Cardiopulmonary Bypass Priming (30 s)

CL_{cr}, creatinine clearance; *BW*, body weight.

without CPB was 13.2±3.1 L, the k_e was 0.652±0.246 L, the $t_{1/2}$ was 1.32±0.94 h and the *CL* was 8.45±3.31 L/h, respectively, in 40 patients with a CL_{cr} of 62.8±24.8 mL/min.[10] Meanwhile, Blum *et al.* reported that the V_d of ampicillin was 0.22±0.04 L/kg (14.5±3.1 L (per 76.8 kg)), the $t_{1/2}$ was 1.41±0.65 h and the *CL* was 218.6±52.4 mL/min (13.1±3.1 L/h)

Table 1. Pharmacokinetic Parameters of Ampicillin ($n=8$)

	Mean±S.D. (range)
V_d (L)	15.8±4.1 (10.7–20.7)
CL (L/h)	7.72±2.72 (4.01–13.107)
k_e (h^{-1})	0.505±0.186 (0.317–0.826)
$t_{1/2}$ (h)	1.52±0.47 (0.84–2.18)

V_d, volume of distribution; CL, total clearance; k_e, elimination rate constant; $t_{1/2}$, elimination half-life.

in patients with a CL_{cr} of 78.6±20.5 mL/min.[16]

Postoperative mediastinitis developed after 126 (1.32%) of 9557 consecutive cardiac surgery operations. In the case of cardiac surgery, *S. aureus* and coagulase-negative staphylococci are the most commonly isolated organisms,[17] and proper antibiotic prophylaxis reduces the incidence of SSI. Hence, the choice of antibiotic, as well as the dose, timing and duration of prophylaxis, is important. Prophylaxis significantly reduced the SSI rate (4.8%) in the prophylaxis group when compared with that observed in the control group (13.7%). In addition, the mean SSI-related cost was higher in the control group than in the prophylaxis group.[7] Therefore, the use of an antibiotic effective against the causative pathogen, which in the case of cardiac surgery is *S. aureus*, in order to achieve a concentration above MIC during the entire operation is recommended.[18] The pharmacokinetics of cefamandole was recently examined in 69 males undergoing coronary artery bypass grafting. The investigators suggested that most suitable dosing regimen to ensure optimal antibacterial activity with cefamandole for the entire cardiosurgical operation, in terms of the ability to achieve a drug concentration higher than the MIC_{90} against the causative pathogen, may be the administration of 2 g intravenously at the time of induction anesthesia plus 2 g administered intraoperatively after CPB.[19] If antibiotic prophylaxis has a short elimination $t_{1/2}$, the most important aspect for ensuring an optimal pharmacodynamic antibacterial activity during prophylaxis in patients undergoing CBP is represented by the need for redosing at no more than 3 or 4 h after the start of the operation.[20] Certainly, when ampicillin (1 g)–sulbactam (0.5 g) (combined dose of 1.5 g) was administered every 6 h in this study, the ampicillin concentration was maintained at more than 2 μg/mL of MIC_{90} for MSSA during cardiovascular surgery with CPB. Moreover, as high plasma concentrations of the drug may increase the risk of adverse reactions, the dose and interval of ampicillin–sulbactam in patients should be determined by referring to the MIC_{90} for MSSA at each institution.

This study has some limitations. The pharmacokinetic parameters were estimated in only eight patients with CPB. Mainly due to the small number of patients, no correlation was observed between CL and CL_{cr}, although ampicillin is a renally excreted drug. Further pharmacokinetic studies in a larger number of patients with CPB are needed to create a nomogram equation (such as $CL=0.103\times CL_{cr}+1.98$),[10] which will make it possible to more individualize the dosing interval according to the renal function.

In conclusion, this study investigated the pharmacokinetics of ampicillin–sulbactam administered for surgical prophylaxis in patients undergoing cardiovascular surgery with CPB. Based on the assessment using both the pharmacokinetic parameter values and the presumed susceptibility to MSSA, we suggest that ampicillin (1 g)–sulbactam (0.5 g) should be administered intravenously every 6 h in order to maintain the ampicillin concentration at more than 2 μg/mL during cardiovascular surgery with CPB. These results provide useful information on the use of antibiotic prophylaxis regimens for optimizing ampicillin–sulbactam therapy to ensure the efficacy and safety of the treatment.

Conflict of Interest The authors declare no conflict of interest.

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