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Original Research

Absorption Kinetics of Subcutaneously Administered Ceftazidime in Hypoperfused Guinea Pigs

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ABSTRACT

Background: Pneumonia is the most common cause of death in patients with severe motor and intellectual disabilities (SMID), and intravenous ceftazidime (CAZ) is a widely used treatment for such infections. However, intravenous administration in patients with SMID may be difficult because of insufficient vascular development.
Objectives: The aim of our study was to determine the feasibility of subcutaneous drug administration by mentholated warm compresses (WMCs) as an alternative delivery method for ceftazidime in patients with SMID.
Methods: CAZ was subcutaneously administered to the abdominal region of naphazoline-treated hypoperfused guinea pigs, which were used as a hemodynamic model of patients with SMID. MWCs or warm compresses (WCs) were applied to the injection site to increase blood flow. We calculated the cumulative CAZ absorption over time by using the deconvolution method.
Results: Application of MWCs or WCs increased blood flow at the administration site and increased CAZ plasma levels. Application of MWCs or WCs after subcutaneous CAZ injection led to higher CAZ plasma levels than the mutant prevention concentration for a longer period than was observed for CAZ administration without the application of MWCs or WCs.
Conclusions: The application of MWCs or WCs enhanced subcutaneous CAZ absorption by increasing blood flow. MWCs and WCs are considered to be safe and routine methods to induce defecation after surgery on the digestive system; thus, the combination of these methods and subcutaneous CAZ administration is a potential method for treating pneumonia in patients with SMID.

Introduction

People with severe motor and intellectual disabilities (SMIDs) exhibit abnormal muscle tone, dysfunctional swallowing, and respiratory and gastrointestinal disorders.[1] Inhalation of saliva and vomiting leads to the development of pathogenic bacteria in the respiratory system, causing repetitive or chronic respiratory infections.[2] The most common cause of death in patients with SMID is aspiration pneumonia.[3,4]

The preferred treatments for aspiration pneumonia are administration of a third-generation cephalosporin or penicillin combined with a β-lactamase inhibitor. A survey of antibiotic use at the National Rehabilitation Center for Children with Disabilities (between April 1, 2008, and March 31, 2009) found that frequently used antibiotics were the penicillin-based piperacillin sodium and ceftazidime (CAZ), a third-generation cephalosporin. The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy Guidelines for the Treatment of Infectious Diseases: Respiratory Infections also state that the treatment of hospital-acquired aspiration pneumonia should cover gram-negative rod bacteria, including *Pseudomonas aeruginosa*, and CAZ covers a wider range of gram-negative rod bacteria than does piperacillin sodium.[5] The efficacy of CAZ is determined by the time during which CAZ blood concentrations exceed the MIC of the drug to inhibit the growth of wild-type bacteria.[6] Moreover, to prevent the occurrence of CAZ-resistant bacteria, it is necessary to consider the mutant prevention concentration (MPC) in addition to the MIC.[7]

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People with SMID are often bedridden for long periods of time during which their movements are limited.[8] In these people, vascular development may be insufficient, and blood vessels of sufficient thickness may be difficult to target for intravenous administration of CAZ for pneumonia treatment. It is necessary to consider alternative administration routes that can be used simply and reliably, and thus we focused on the subcutaneous route of administration for the treatment of pneumonia with CAZ in patients with hypoperfusion. This route of administration is simpler than the intravenous route, and reduces the incidence of peripheral phlebitis and systemic infections.[9]

Patients with SMID often experience symptoms caused by disturbances in the autonomic nervous system.[10,11] In particular, skin blood flow may be reduced by constriction of the skin blood vessels due to elevated sympathetic nervous system tone.[12] Subcutaneous blood flow may be slower in patients with severe disabilities compared with healthy individuals; therefore, low drug absorption rates due to limited blood flow, which lead to sub-MIC or sub-MPC blood levels, must be considered when treating such patients.

We have previously reported[13] that reduced cutaneous blood flow decreased skin permeation of nicardipine hydrochloride, and that the addition of a strong permeation enhancer that had been screened in vitro to the formulation most likely caused the observed decrease in cutaneous blood flow. Thus, it is important that methods that promote absorption increase blood flow at the site of drug administration.

Hot compresses applied locally to the site of drug administration have been shown to increase local subcutaneous blood flow through vasodilation.[14] Mentholated warm compresses (MWCs) and warm compresses (WCs) are used widely in clinical settings to induce defecation after gastrointestinal tract surgery, and their safety is well established.[15–17]

In our study we investigated the use of MWC and WC methods to enhance the absorption of subcutaneously administered drugs with the goal of reaching blood levels that exceed the MIC and MPC in patients with hypoperfusion. The vasoconstrictor naphazoline was used to produce hypoperfusion in guinea pigs as a model of reduced blood flow in patients with SMID.[18]

Methods

Materials

Naphazoline nitrate was purchased from Wako Pure Chemical Industries (Osaka, Japan). Ceftazidime was obtained from GlaxoSmithKline Co Ltd (Tokyo, Japan). Cephalexin hydrate (CEX) was purchased from Sigma Chemical Co Ltd (St Louis, Missouri). Mentha oil was acquired from Yoshida Pharmaceutical Co Ltd (Saitama, Japan). All other chemicals and solvents were of reagent grade or HPLC grade and used without further purification.

Animals

Male Hartley guinea pigs (Japan SLC, Shizuoka, Japan) of identical age (7 weeks, 450–500 g; n = 42) were reared under constant temperature (22°C ±2°C) and humidity (55% ± 5%), with a 12-hour light cycle from 7 AM to 7 PM. Feed and water were supplied ad libitum. All experiments using animals were approved by the Institutional Animal Care and Use Committee of Josai University (approval No. H22043-2010/05/14).

Blood flow measurement using laser Doppler flowmetry

Guinea pigs were anesthetized with urethane (1.5 g/kg IP), and blood flow in the abdominal region was measured using a laser Doppler flow meter (Peri Flux PF3; Perimed KB Co, Lund, Sweden).[13] Animals were divided into 3 groups (saline group, n = 8; naphazoline group, n = 4 each). A 0.15 or 1.5 mg/kg dose of naphazoline was administered to guinea pigs to induce hypoperfusion. Control animals received a physiologic saline solution injection into the femoral muscle. The laser Doppler probe (6 mm diameter; Perimed KB Co) was attached to the shaved abdominal skin, and blood flow was measured for 6 hours. Blood flow was measured every 5 seconds for 3 minutes, and the mean of these measurements was used for each blood flow value. The data are represented as changes in blood flow (ie, percent of initial flow).

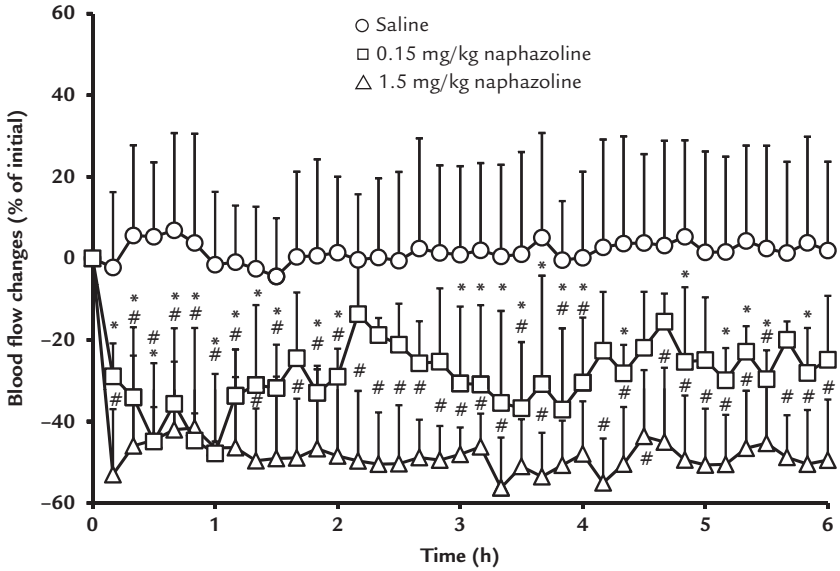

Figure 1. Blood flow changes in hypoperfused guinea pigs. Guinea pigs received an intramuscular injection of saline and either 0.15 mg/kg naphazoline or 1.5 mg/kg naphazoline as a vasoconstrictor, 150 minutes after anesthesia. Blood flow was measured every 10 minutes for 6 hours. Each point represents the mean (SD) (saline group, n = 8; 0.15 mg/kg naphazoline group, n = 4; 1.5 mg/kg naphazoline group, n = 4). $^{*}P < 0.05$ (0.15 mg/kg vs. saline). $^{\#}P < 0.05$ (1.5 mg/kg vs saline).

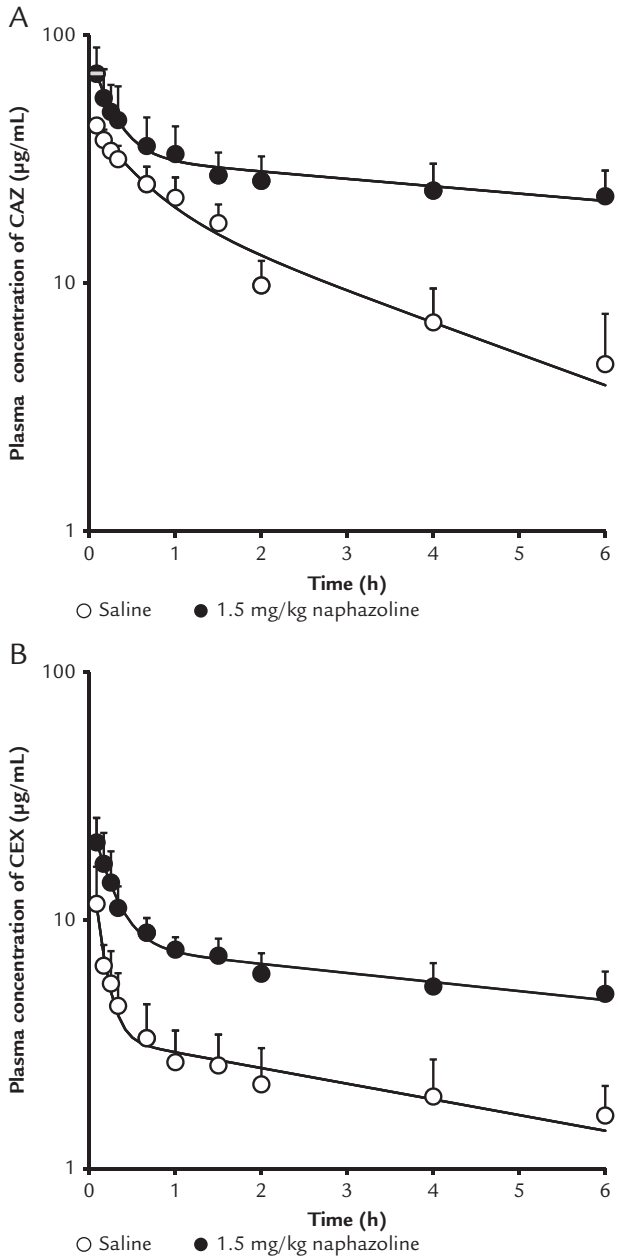

Figure 2. Plasma concentration-time curves after intravenous injection of (A) ceftazidime (CAZ) and (B) cephalexin hydrate (CEX), following intravenous injection of saline or naphazoline into the jugular vein. Each point represents the mean (SD) (saline group, n = 3; 1.5 mg/kg naphazoline group, n = 5). The solid line indicates the model fit using a 2-compartment model.

Pharmacokinetics of CAZ and CEX after intravenous administration

Animals were divided into 2 groups (saline group, n = 3; 1.5 mg/kg naphazoline group, n = 5). Immediately after the intramuscular administration of naphazoline (1.5 mg/kg) or saline (as a control), CAZ (17 mg/kg) and CEX (7 mg/kg) were injected into the jugular vein. The dose of 17 mg/kg represents the converted clinical dose (1 g/administration for a 60-kg adult). Blood samples (0.25 mL) were taken from the contralateral jugular vein at different time intervals (5, 10, 15, 20, 40, 60, 90, 120, 240, and 360 minutes) for 6 hours, and immediately centrifuged (4°C; 3000 g; 10 minutes) to collect plasma, which was stored at –45°C until the analysis. Heparin sodium (5 U/mL) was used as an anticoagulant for plasma sampling. The plasma concentration-time profile of CAZ and CEX were analyzed by 2-compartment model, where the plasma concentrations after intravenous administration are described as follows:

$$C(t) = \frac{D(\alpha - K_{21})}{V_1(\alpha - \beta)} e^{-\alpha t} + \frac{D(K_{21} - \beta)}{V_1(\alpha - \beta)} e^{-\beta t} \quad (1)$$

where α and β are constants, V_1 is the volume of drug within the central compartment, V_2 is the volume of drug within the peripheral compartment, K_{21} is the migration rate constant for migration from the peripheral to central compartment, K_{12} is the migration rate constant for migration from the central to peripheral compartment, K_{10} is the elimination rate constant for elimination from the central compartment, and CL_{tot} is the total body clearance.

The value of α, β, V_1, and K_{21} were estimated by fitting the above equation 1 to the concentration-time curve after intravenous administration using MULTI to the nonlinear least-squares method (algorithm; Gauss-Newton method).[19] The values obtained for α, β, V_1, and K_{21} were used in equations 2 to 7 to calculate the other parameters.

$$t_{1/2\alpha} = \frac{0.693}{\alpha} \quad (2)$$

$$t_{1/2\beta} = \frac{0.693}{\beta} \quad (3)$$

$$V_2 = \frac{K_{12} \cdot V_1}{K_{21}} \quad (4)$$

$$K_{12} = \alpha + \beta - K_{21} - K_{10} \quad (5)$$

$$K_{10} = \frac{\alpha\beta}{K_{21}} \quad (6)$$

$$CL_{tot} = \frac{D\alpha\beta}{A\beta + B\alpha} \quad (7)$$

Subcutaneous administration of CAZ to hypoperfused guinea pigs

Animals were divided into 4 groups (n = 3 each) according to the dose level, and injection volume. CEX, which has a high urinary excretion rate, was coadministered with CAZ to correct a decrease in the elimination rate of CAZ in naphazoline-treated animals. Guinea pigs were anesthetized by intraperitoneal administration of urethane (1.5 g/kg). Naphazoline saline solution (1.5 mg/kg) was injected into the femoral muscle to reduce blood flow 2.5 hours after anesthesia administration. Intravenous administration of a CEX saline solution (7 mg/kg) in the jugular vein immediately followed. A CAZ saline solution (17 mg/320 μL [1D1V], 17 mg/640 μL [1D2V], 34 mg/320 μL [2D1V], or 34 mg/640 μL [2D2V]) was subcutaneously administered over a 30-minute period at 2 sites in the abdominal region. After CAZ administration, blood samples (0.25 mL) were taken from the contralateral jugular vein at predetermined times (0, 5, 10, 15, 20, 40, 60, 90, 120, 180, 240, 300, and 360 minutes) for 6 hours and immediately centrifuged to collect plasma. The supernatant was 1 stored at –45°C until analysis, in which plasma concentrations of CAZ and CEX were determined using an HPLC system. In addition, the blood flow at the administration sites was measured using a laser Doppler flow meter.

Effect of the mentholated warm compress on CAZ subcutaneous absorption

Animals were divided into 3 groups (n = 3 each). To prepare an MWC, mentha oil (0.5 mL) was dripped into warm tap water (65°C; 500 mL) to prepare saturated mentha water.[20] The MWC consisted of a towel (11 × 33 cm) that was soaked in saturated mentha water until its temperature reached 65°C. The administration site was covered with the MWCs immediately after CAZ administration, and

Table I
Pharmacokinetic parameters of ceftazidime (CAZ) and cephalexin hydrate (CEX) in hypoperfused guinea pigs after intravenous administration.

	CAZ		CEX	
Parameter	Without naphazoline	With naphazoline	Without naphazoline	With naphazoline
α^{*}, 1/h	1.87 ± 0.97	4.02 ± 1.62	8.75 ± 2.88	4.41 ± 1.25
β^{*}, 1/h	0.29 ± 0.12	0.07 ± 0.05	0.15 ± 0.12	0.08 ± 0.06
$t_{1/2\alpha}$, h	0.20 ± 0.15	0.18 ± 0.09	0.08 ± 0.03	0.15 ± 0.05
$t_{1/2\beta}$, h	1.81 ± 0.64	13.05 ± 9.13	4.95 ± 1.46	8.97 ± 3.15
$V_1^{\dagger}$, mL	157.94 ± 9.20	86.64 ± 11.58	149.49 ± 34.97	114.20 ± 13.01
$V_2^{\ddagger}$, mL	80.83 ± 22.13	139.95 ± 62.24	674.66 ± 287.87	231.44 ± 22.10
$K_{21}^{\S}$, 1/h	1.06 ± 0.78	1.59 ± 0.70	1.59 ± 0.65	1.38 ± 0.48
$K_{12}^{\|\|}$, 1/h	1.76 ± 1.28	2.84 ± 1.66	6.60 ± 2.28	3.19 ± 0.62
$K_{10}^{\P}$, 1/h	0.70 ± 0.20	0.19 ± 0.09	0.83 ± 0.03	0.31 ± 0.20
$CL_{tot}^{\#}$, L/h	0.10 ± 0.03	0.02 ± 0.01	0.13 ± 0.03	0.03 ± 0.02

* Constants.
† Volume of drug within the central compartment.
‡ Volume of drug within the peripheral compartment.
§ Migration rate constant for migration from the peripheral to central compartment.
‖ Migration rate constant for migration from the central to peripheral compartment.
¶ Elimination rate constant for elimination from the central compartment.
# Total body clearance.

the MWCs were entirely covered with plastic cling wrap to prevent mentha water evaporation. WCs that did not contain mentha oil were similarly applied to the administration site. In addition, the abdomen was wrapped with a towel. The MWCs or WCs were replaced every 30 minutes, and they were replaced a total of 13 times during the duration of the experiment. To ensure that the mentha water saturation of the administration site was maintained, mentha oil was added 5 minutes before the MWCs were changed.

HPLC separation and quantification of CAZ and CEX

A 7.0% (vol) perchloric acid solution (100 μL) was added to each plasma sample (100 μL), and this mixture was centrifuged for 15 minutes (4°C; 13,000 g). The supernatant (20 μL) was injected into the HPLC system to determine CAZ and CEX plasma concentrations.

The HPLC system consisted of a pump (LC-10ATvp; Shimadzu Corp, Kyoto, Japan), a degasser (DGU-12A; Shimadzu Corp), a column oven (CTO-10Avp; Shimadzu Corp), a column (TSK-gel ODS-80TM, 5 μm, 4.6 × 250 mm; TOSOH Corp, Tokyo, Japan), and an ultraviolet detector (SPD-6A; Shimadzu Corp). A mobile phase consisting of 9:91 (v/v) acetonitrile:10 mM phosphate buffer (pH 3.0) was used for elution. The flow rate was 1.0 mL/min, the column temperature was 50°C, and the detector operated at a wavelength of 258 nm.

Under the HPLC condition for the analysis of CAZ, the peaks of CAZ and CEX appeared on the chromatogram of the ultraviolet detector at 8.8 and 15.8 minutes, respectively. From the standard deviation of the response and the slope of the calibration line, the detection limit for CAZ was calculated to be 0.02 μg/mL, whereas the detection limit for CEX was 0.05 μg/mL. Similarly, the lower limit of quantification for CAZ was calculated to be 0.06 μg/mL, whereas that of CEX was 0.13 μg/mL. A calibration line was produced every time the HPLC pump was stopped.

Estimation of CAZ absorption rate by the deconvolution method

The deconvolution method was used to estimate subcutaneous CAZ absorption rates (Research Institute of TTS Technology, Saitama, Japan).[21] The time course of the subcutaneous absorption rate, I(θ), was estimated from the time course of the blood concentration after subcutaneous (C[t]) and intravenous (W[t]) administrations. C(t) is the response function, W(t) is the weight function, and I(θ) is the input function.[21,22] C(t) is expressed as follows:

$$C(t) = \int_0^t W(t-\theta)\cdot I(\theta)\cdot d\theta \quad (8)$$

The volume of distribution of CAZ and its elimination rate constant were decreased by naphazoline-induced hypoperfusion; thus, correction of the weighting function was necessary to estimate the absorption rate of CAZ. Ratios comparing the pharmacokinetic parameters of CEX in hypoperfused guinea pigs and normal guinea pigs were determined. The pharmacokinetic parameters of CAZ in normal guinea pigs were multiplied by these ratios to estimate the pharmacokinetic parameters of CAZ in hypoperfused guinea pigs. Using these parameters as weighting functions, and the CAZ plasma level-time curve after subcutaneous administration in hypoperfused guinea pigs as a response function, the time-course of cumulative CAZ absorption was estimated using the deconvolution method. The average absorption rate was used to compare the absorption rates between administration methods. The average absorption rate is the slope of the cumulative absorption profile.[23]

Statistical analysis

All data are presented as mean (SD). Differences in blood flow and plasma concentrations of CAZ among the groups were analyzed using ANOVA. When an ANOVA showed a significant effect ($P < 0.05$), Tukey's honest significant difference test was used as a post-hoc test to compare means, and differences were considered to be significant if the value of P was < 0.05. All analyses were conducted using software from the R Project for Statistical Computing (R version 2.15.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

Blood flow measurement using laser Doppler flowmetry in hypoperfused guinea pigs

After administration of 0.15 and 1.5 mg/kg naphazoline, blood flow immediately decreased by 30% and 50%, respectively, compared with baseline. The reduction of blood flow caused by 1.5 mg/kg naphazoline administration persisted until the end of the measurement period (Figure 1).

Effects of naphazoline on the disposition of CAZ after intravenous administration

The CAZ and CEX plasma concentration-time curve after intravenous CAZ and CEX administration following intramuscular administration of naphazoline or saline is shown in Figure 2, and the corresponding pharmacokinetic parameters are presented in Table I.

The elimination of CAZ, determined using a 2-compartment model, was significantly altered, most likely due to a blood flow reduction after naphazoline administration, and had to be corrected to estimate the subcutaneous absorption rate of CAZ. Thus, intravenous coadministration of CEX, which has a high urinary excretion rate,[24] was performed at the same time as subcutaneous CAZ administration. The elimination parameters of CAZ were then determined based on the changes observed in the elimination parameters of CEX.

CAZ subcutaneous absorption profile in hypoperfused guinea pigs

We hypothesized that CAZ blood levels would be approximately equivalent after intravenous administration of identical doses per time unit (eg, 17 mg for 1D1V and 1D2V or 34 mg for 2D1V and 2D2V). However, doubling the volume of vehicle (2V) resulted in significantly increased CAZ blood levels compared with the original vehicle volume (1V) (Figure 3A). CAZ blood levels exceeded its MIC_{90} (16 μg/mL) under all conditions of administration.[25,26] However, in the 1D1V condition, CAZ blood levels did not exceeded the MPC (32 μg/mL),[27] which was exceeded in the other conditions.

Blood flow changes occurring during CAZ subcutaneous administration are shown in Figure 3B. Blood flow rapidly decreased after naphazoline administration in all conditions, and then reached a constant rate. No difference was observed among groups. Figure 3C shows the CAZ cumulative absorption profile estimated using the deconvolution method. The subcutaneous absorption of CAZ was not complete 6 hours after CAZ administration in the 1D1V and 2D1V groups, whereas almost all of the administered CAZ was absorbed in the 1D2V and 2D2V groups.

Effect of WMCs on CAZ subcutaneous absorption in hypoperfused guinea pigs

MWCs and WCs were applied to the 1D1V group. CAZ plasma levels were markedly increased in both the MWC and WC groups compared with the control group, and were approximately 4 and 6 times higher, respectively, than in the control group 6 hours after administration (Figure 4A). Naphazoline administration resulted in a blood flow decrease, which was partially inhibited by the application of an MWC or a WC (Figure 4B). Figure 4C shows the cumulative CAZ absorption as estimated using the deconvolution method. CAZ absorption after subcutaneous administration was about 84.0% complete in the MWC group (14.1 mg absorbed) after 6 hours, whereas 60.0% of the administered CAZ was absorbed in the WC group. The average absorption rate throughout the period of experimentation was increased compared with the 1D1V group by the application of WCs or MWCs (1D1V, 0.013 mg/min; with WC, 0.027 mg/min; with MWC, 0.039 mg/min). The increased absorption that was produced by application of an MWC or WC reached levels equivalent to those of the 1D2V and 2D1V groups (Figure 3C).

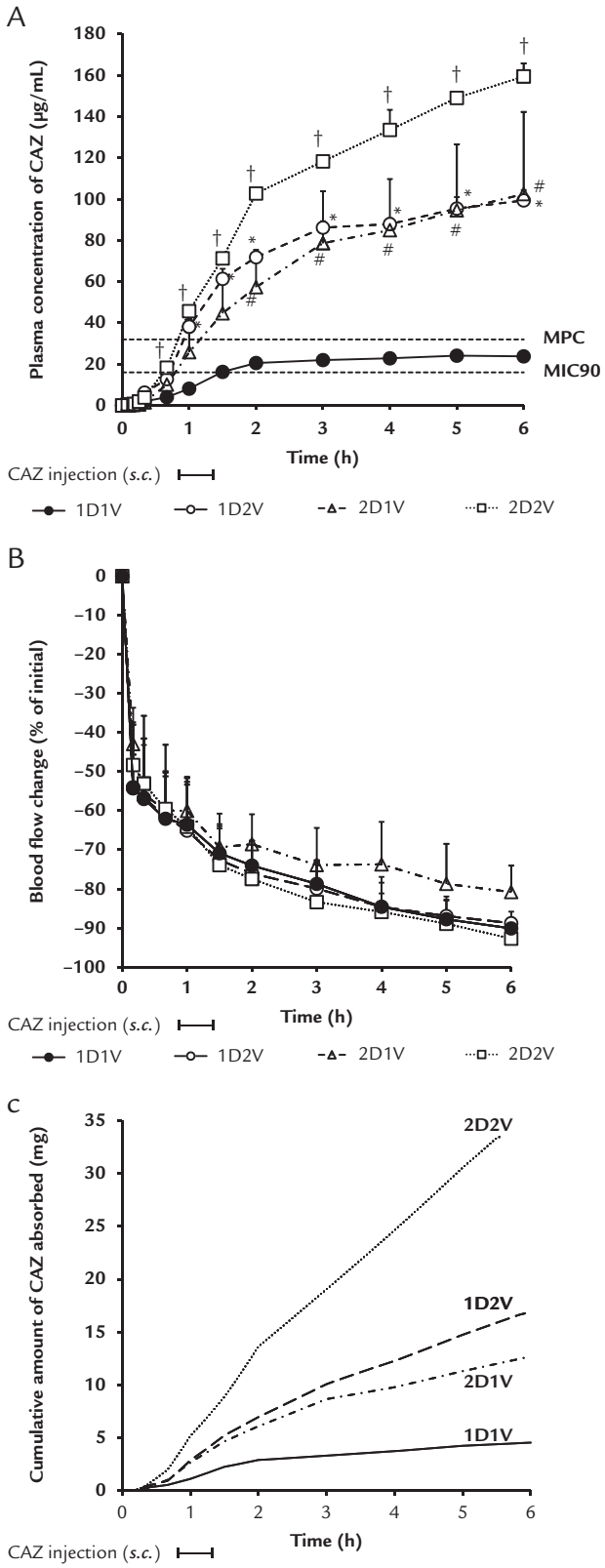

Figure 3. Plasma concentrations of ceftazidime (CAZ) and blood flow changes after subcutaneous injection in hypoperfused guinea pigs. CAZ was administered subcutaneously at a dose of 17 mg (1D) or 34 mg (2D) over a 30-minute time period in different vehicle volumes (1V or 2V). (A) CAZ plasma concentration-time curves. (B) Corresponding blood flow changes. (C) Cumulative amounts of absorbed CAZ as obtained by the deconvolution method. Each point represents the mean (SD) (n = 3). $^{*}P < 0.05$ (1D2V vs 1D1V). $^{\#}P < 0.05$ (2D1V vs 1D1V). $^{\dagger}P < 0.05$ (2D2V vs 1D1V).

Discussion

Abdominal subcutaneous blood flow was reduced by intramuscular administration of naphazoline. In the 0.15 mg/kg

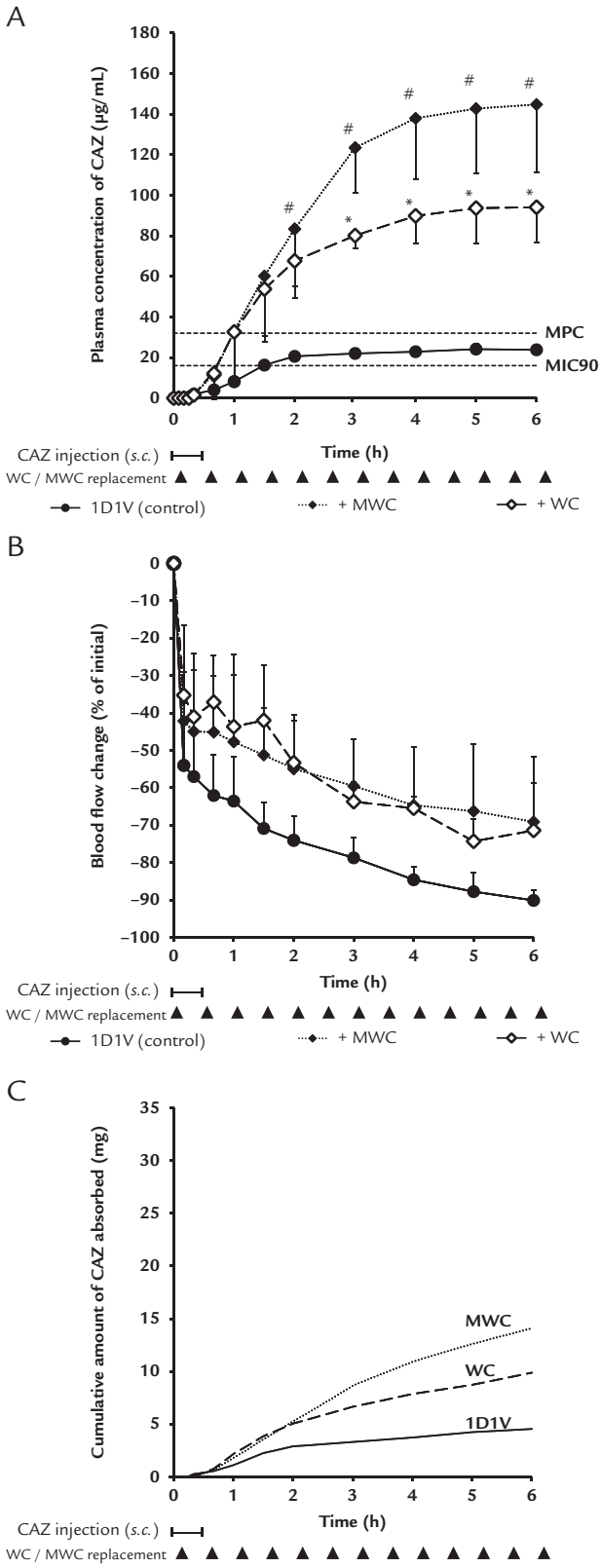

Figure 4. Effects of mentholated warm compresses (MWCs) and warm compresses (WCs) on cefazidime (CAZ) subcutaneous absorption in hypoperfused guinea pigs. CAZ was administered subcutaneously at a dose of 17 mg (1D) over a 30-minute time period (1D1V). (A) CAZ plasma concentration-time curves. (B) Blood flow changes. (C) Cumulative amounts of absorbed CAZ as obtained by the deconvolution method. Each point represents the mean (SD) (n = 3). $^{*}P < 0.05$ (+WC vs 1D1V). $^{\#}P < 0.05$ (+MWC vs 1D1V).

naphazoline group, a significant decrease in blood flow compared with the saline group was observed for only 2 hours after administration. In contrast, naphazoline at a dose of 1.5 mg/kg reduced abdominal subcutaneous blood flow for 6 hours. The dose of naphazoline used to produce hypoperfused guinea pigs was therefore set at 1.5 mg/kg. Naphazoline administration decreased the K_{10} (elimination rate constant) of CAZ (Table I). Because the CAZ doses per unit of time were equivalent in the 1D1V and 1D2V groups, as well as the 2D1V and 2D2V groups, we expected plasma levels of CAZ to be equivalent within these pairs of treatment groups. However, doubling the volume of vehicle resulted in elevated CAZ levels. It has been previously reported that subcutaneously administered drugs spread horizontally in the subcutaneous tissue at the site of administration.[28] Therefore this finding may indicate that the subcutaneous area that came into contact with CAZ was increased (Figure 3).

MWCs and WCs were applied to the injection site to alter local blood flow. MWCs and WCs are frequently used to promote defecation by inducing intestinal peristalsis in clinical settings.[15–17] Plasma CAZ concentrations were increased compared with those in the control group by the application of MWCs and WCs to the administration site. Reduced blood flow due to naphazoline administration was shown to recover slightly due to MWC and WC application.

In intermediate air temperatures, skin temperature increases as skin blood flow increases, because skin temperature is generally dependent on skin blood flow. Although differences in effects on skin temperature between MWCs and WCs were not observed in our study, different effects on skin and core body temperatures for these treatments have been reported under a variety of conditions. Moreover, it has also been reported that MWCs elevated skin temperature and body core temperature, and maintained elevated core body temperature for significantly longer than WCs.[20] It is possible that MWCs induced a greater absorption enhancement than WCs because of their effects on deep blood flow (Figure 4). The laser Doppler flowmetry probe measures flow at the dermoepidermal interface, where skin blood flow is most abundant. It is not possible currently to measure blood flow that influences the absorption of drugs in tissues deeper than the skin with this method.

Consideration of the MPC is advocated in addition to the MIC as a means of preventing the occurrence of resistant bacteria. In general, the growth of wild-type bacteria is prevented when the concentration of antibiotics in the blood exceeds the MIC. If mutant bacteria with acquired resistance coexist with wild-type bacteria, then the mutant population will survive antibiotic exposure at the MIC. However, as the concentration of antibiotics is increased further, mutant bacteria are killed in addition to wild-type bacteria. The concentration at which this effect occurs is known as the MPC.[7] In our study, a therapeutic effect equivalent to that of intravenous administration was obtained by increasing the dose of CAZ or vehicle volume per unit time. However, doubling the vehicle volume might be clinically difficult, because subcutaneous administration rates > 1 mL/min can be painful.[9,29,30] On the other hand, the application of WCs or MWCs to the site of CAZ subcutaneous administration may be expected to increase its therapeutic effect without changing its infusion rate. Furthermore, this method prevents the development of drug-resistant mutants, because CAZ blood levels achieved through this method exceed the MPC.

Conclusions

The subcutaneous administration of CAZ in combination with MWCs or WCs is a potential alternative to intravenous CAZ

administration, and should be investigated clinically for the treatment of pneumonia in patients with hypoperfusion associated with SMID.

Acknowledgments

Tsuyoshi Ebihara and Shinji Oshima contributed the data analysis, data interpretation and writing. Kousuke Ohara, Akio Negishi and Shigeru Ohshima contributed the literature search and figure creation. Mitsuyoshi Okita and Sayumi Shiina contributed the data collection. Hiroyuki Iwasaki, Akira Yoneyama and Eiji Kitazumi contributed the study design for clinical practical application. Daisuke Kobayashi contributed the study design, the overall responsibility of the article and the writing.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

References

[1] Goto K, Uemura A, Imai K, et al. A survey focused on the medical care of the short-term stay service for patients with severe motor and intellectual disabilities. *Iryo.* 2011;65:533–538.
[2] Teramoto S, Fukuchi Y, Sasaki H, et al. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. *J Am Geriatr Soc.*. 2008;56:577–579.
[3] Baba K. The treatment and care of child/adult with severe motor and intellectual disabilities. *Jpn J Genet Counsel.*. 2002;23:197–204.
[4] Fukuda K, Nakagawa Y. The relationship between the gross motor function and the causes of death in persons with sever motor and intellectual disabilities. *No to Hattatsu.* 2013;45:38–43.
[5] Mikasa K, Aoki N, Aoki Y, et al. The JAID/JSC Guideline to Clinical Management of Infectious Diseases (Respiratory infections). *Kansenshogaku Zasshi.* 2014;88:1–109.
[6] Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis.* 1998;26:1–12.
[7] Drlica K. The mutant selection window and antimicrobial resistance. *J Antimicrob Chemother.* 2003;52:11–17.
[8] Hanaoka T, Mita K, Hiramoto A, et al. Survival prognosis of Japanese with severe motor and intellectual disabilities living in public and private institutions between 1961 and 2003. *J Epidemiol.* 2010;20:77–81.
[9] Sasson M, Shvartzman P. Hypodermoclysis: an alternative infusion technique. *Am Fam Physician.* 2001;64:1575–1578.
[10] Yang TF, Chan RC, Kao CL, et al. Power spectrum analysis of heart rate variability for cerebral palsy patients. *Am J Phys Med.* 2002;81:350–354.
[11] Veugelers R, Benninga MA, Calis EA, et al. Prevalence and clinical presentation of constipation in children with severe generalized cerebral palsy. *Dev Med Child Neurol.* 2010;52:216–221.
[12] Suzuki Y, Kobayashi M, Kuwabara K, et al. Skin temperature responses to cold stress in patients with severe motor and intellectual disabilities. *Brain Dev.* 2013;35:265–269.
[13] Kobayashi D, Kawabata S, Sugibayashi K, et al. *In vitro/in vivo* difference in enhanced skin permeation of nicardipine hydrochloride by the 1-menthol-ethanol system. *Skin Pharmacol.* 1996;9:130–136.
[14] Okada K, Yamaguchi T, Minowa K, et al. The influence of hot pack therapy on the blood flow in masseter muscles. *J Oral Rehabil.* 2005;32:480–486.
[15] Iwazaki M, Nomura S. Examination of the relaxing effects of the local warm pack application – comparison of the influences of two treatments warm pack application to the back and warm foot soaks. *Journal of Japanese Society of Nursing Research.* 2005;28:33–43.
[16] Fukada J, Kamakura Y, Hibino T, et al. Effects of hot compresses applied to back regions using different temperatures. *Journal of Japanese Society of Nursing Research.* 2007;30:75–83.
[17] Hishinuma M, Hiramatsu N, Kasuga M, et al. The effect on bowel sounds of very hot compresses applied to the lumber region. *J Jpn Acad Nurs Sci.* 1997;17:32–39.
[18] Greiner JV, Udell IJ. A comparison of the clinical efficacy of phenitamine maleato naphazolines hydrochloride ophthalmic solution and dopatadine hydrochloride ophthalmic solution in the conjuntival challenge model. *Clin Ther.* 2005;27:568–577.
[19] Yamaoka K, Tanigawara Y, Nakagawa T, et al. A pharmacoknetic analysis program (MULTI) for microcomputer. *J Pharm Dyn.* 1981;4:879–885.
[20] Araki K, Sugama T, Nakayama M, et al. Influence of mentholated compress applied on the abdomen on the skin temperature and intestinal peristalsis. *Jpn J Nurs Sci.* 2003;49:609–611.
[21] Sato K, Oda T, Sugibayashi K, et al. Estimation of blood concentration of drugs after topical application from *in vitro* skin permeation data. I. Prediction by convolution and confirmation by deconvolution. *Chem Pharm Bull.* 1988;36:2232–2238.
[22] Pithavala YK, Soria I, Zimmerman CL. Use of the deconvolution principle in the estimation of absorption and pre-systemic intestinal elimination of drugs. *Drug Metab Dispos.* 1997;25:1260–1265.
[23] Miyamoto M, Natsume H, Iwata S, et al. Improved nasal absorption of drugs using poly-L-arginine: effects of concentration and molecular weight of poly-L-arginine on the nasal absorption of fluorescein isothiocyanate-dextran in rats. *Eur J Pharm Biopharm.* 2001;52:21–30.
[24] Nakagawa T, Haginaka J, Yamaoka K, et al. High speed liquid chromatographic determination of cephalexin in human plasma and urine. *J Antibiot.* 1978;31:769–775.
[25] Yuki A, Shimojima M, Arai K, et al. Susceptibility for *Pseudomonas aeruginosa* in Saitama prefecture. *The Saitama Journal of Medical Technology.* 2007;54:284–289.
[26] Takeda S, Nakai T, Wakai Y, et al. *In vitro* and *in vivo* activities of a new cephalosporin, FR264205, against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother.* 2007;51:826–830.
[27] Henrichfreise B, Wiegand I, Luhmer-Becker I, et al. Development of resistance in wild-type and hypermutable *Pseudomonas aeruginosa* strains exposed to clinical pharmacokinetic profiles of meropenem and ceftazidime simulated in vitro. *Antimicrob Agents Chemother.* 2007;51:3642–3649.
[28] Brown EA, Metcalf TG, Slanetz LW. Visualization of the fate of injections of water-in-oil emulsions by means of radiopaque media, II. *Ann Allergy.* 1961;19:1016–1018.
[29] Borgna PC, Franchini M, Gandini G, et al. Subcutaneous bolus injection of deferoxamine in adult patients affected by onco-hematologic diseases and iron overload. *Haematologica.* 1998;83:788–790.
[30] Franchini M, Gandini G, de Gironcoli M, et al. Safety and efficacy of subcutaneous bolus injection of deferoxamine in adult patients with iron overload. *Blood.* 2000;95:2776–2779.