Pharmacokinetic and Adsorptive Analyses of Administration of Oral Voriconazole Suspension via Enteral Feeding Tube in Intensive Care Unit Patients

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For intensive care unit (ICU) patients, injectable voriconazole (VRCZ) is difficult to use because the patients often develop acute kidney injury. Since many ICU patients have consciousness disturbance, oral ingestion of tablet formulation is also difficult, and administration of a suspension via enteral feeding tube is required when using VRCZ. In this study, we investigated the in vitro adsorption property of oral VRCZ to feeding tube and performed pharmacokinetic analysis of VRCZ prepared by powdering and simple suspension for ICU patients. VRCZ was tube-administered to five ICU patients at a loading dose of 300 mg and plasma VRCZ concentrations before and at 1, 2, 4, 8, 12 h after the first dose were measured using HPLC. Pharmacokinetic parameters were calculated by non-compartmental model analysis. The recovery rate of VRCZ after infusion of the suspension through feeding tube was 89.8 ± 8.3%, but the cumulative rates after the first and second re-infusion were 102.7 ± 20.7% and 99.3 ± 10.3%, respectively, suggesting almost no residual drug in the tube after re-infusion. Metabolic phenotype was extensive metabolizer (EM) in two patients and intermediate metabolizer (IM) in three patients. The values of total clearance (CLtot/F) calculated by moment analysis were 0.51 and 0.55 L/h/kg in two EM patients, and 0.09, 0.29 and 0.31 L/h/kg in three IM patients. The CLtot/F was apparently lower in IM patients compared to EM. In conclusion, powdered and suspended VRCZ administered via enteral feeding tube showed pharmacokinetics depending on CYP2C19 gene polymorphism, similar to that observed in usual oral administration.

Key words voriconazole; tube administration; CYP2C19 polymorphism; pharmacokinetic analysis; adsorption

INTRODUCTION

Many patients in intensive care unit (ICU) have high-risk factors for the development of invasive candidiasis, such as central venous catheterization, frequent use of broad-spectrum antimicrobials, increased use of immunosuppressive agents or corticosteroids, and respiratory management with a ventilator. Empirical therapy for invasive candidiasis is recommended for patients with high fever and inflammatory findings persisting for a long time even after with administration of therapeutic antibacterial agents. The first choices of empiric anti-Candida therapy are echinocandin and fosfluconazole, while voriconazole (VRCZ) is one of the alternative drugs.

VRCZ is a second-generation triazole antifungal agent and is indicated for the treatment of invasive fungal infections by non-albicans Candida spp., Aspergillus spp. and Cryptococcus spp. This drug has pharmacokinetic properties such as superior distribution to tissues and high bioavailability. The availability of different dosage forms including intravenous and oral formulations allows selection of the administration route. VRCZ is extensively metabolized in the liver, predominantly mediated by the CYP2C19 enzyme. Allelic polymorphism of CYP2C19 has been reported and the metabolic phenotypes are categorized into extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM) according to a combination of mutations of CYP2C19*2 (681G > A; rs4244285) and CYP2C19*3 (636G > A; rs17878459). The total clearance of VRCZ has been reported to be approximately 0.46 times for IM and 0.35 times for PM compared with EM.5)

Since VRCZ is water insoluble, the injection formulation contains sulfobutylether-β-cyclodextrin (SBEDC) for solubilizing the drug. The urinary excretion rate of unchanged VRCZ is extremely low, but SBEDC is not metabolized and is excreted in urine through the kidney. SBEDC was reported to accumulate in patients with renal impairment.5,7) Therefore, restricted use of intravenous VRCZ is recommended for patients with creatinine clearance of 50 mL/min or lower. As many ICU patients have renal impairment, use of intravenous VRCZ tends to be avoided. Although oral VRCZ can be used in ICU patients, many patients have difficulties ingesting the tablet by mouth due to disturbance of consciousness. Hence, it is necessary to powder and suspend the oral formulation and administer the suspension via the enteral feeding tube when oral VRCZ is used for ICU patients.

In this study, we investigated the in vitro adsorption property of VRCZ suspension to enteral feeding tube and performed pharmacokinetic analysis of the powdered and suspended VRCZ in ICU patients.

PATIENTS AND METHODS

Subject The study enrolled five patients who received a powdered and suspended preparation of oral VRCZ admin-
istered via an enteral feeding tube between September 2016 and November 2017 in ICU of Oita University Hospital. The clinical and laboratory data were extracted from medical records. Creatinine clearance (CCr) was calculated using the Cockcroft–Gault equation. This study was approved by the ethics committee (Approval No. 1025) and human genome research ethics committee of Oita University (Approval No. P-13-14). Written informed consent was obtained from either the patients or their legally authorized representatives.

**Recovery Rate of VRCZ after Infusion through Enteral Feeding Tube**

Recovery of VRCZ after infusion in enteral feeding tube was evaluated by an *in vitro* experiment. Using the simple suspension method, VRCZ tablets (300 mg) were powdered using porcelain mortar and pestle and then suspended in 20 mL of distilled water at 55 °C. After stirring for 10 min, the suspension was drawn into an injection syringe and injected into a tube for enteral feeding (in our ICU, a balloon catheter for gastrointestinal imaging (Fuji Systems, Tokyo, Japan) is used). The enteral tube is derived from silicone rubber, and the surface is coated with a hydrophilic polymer. The three-way stopcock at the inlet is composed of polycarbonate and polypropylene. Then, the infused suspension was collected into a beaker. The enteral feeding tube was rinsed twice by infusing with 20 mL of distilled water at room temperature to ensure that no drug remains in the tube (a procedure routinely used clinically in our hospital). The first and second re-infused eluents were also collected. The VRCZ concentrations in each solution before and after infusion via the tube were measured by HPLC. The recovery rate after infusion through the tube was calculated using the concentrations before and after infusion.

**Administration to Patients and Sample Collection**

Using the simple suspension method, VRCZ tablets were powdered and dissolved in 20 mL of distilled water at approximately 55 °C followed by incubation for 10 min. After cooling to around body temperature, the suspension was administered at a dose of 300 mg (loading dose) through the enteral feeding tube between meals, and flushed twice with 20 mL of distilled water at room temperature. Blood samples were collected before and at 1, 2, 4, 8, and 12 h after the first dose. Blood was collected from an indwelling artery line into heparinized tubes. Blood samples were centrifuged at 1900 g at 4 °C for 5 min, and plasma samples were frozen immediately and stored at −40 °C until measurement.

**VRCZ Assay**

VRCZ concentrations in plasma samples or suspensions were quantified using the partially modified method of Suzuki *et al.* To 500 µL of plasma or suspension in a glass tube, 30 µL of ketoconazole (500 µg/mL) in 100% methanol was added as internal standard, followed by 200 µL of sodium hydroxide (0.1 mol/L). The mixture was then briefly vortexed and extracted with 3 mL of diethyl ether for 5 min, followed by centrifugation at 1500 g for 5 min. The organic layer was transferred into a glass tube and evaporated to dryness under a gentle stream of nitrogen at 40 °C, and the residue was reconstituted in 250 µL of mobile phase. Fifty microliters of the sample were injected into a HPLC system (Alliance model e2695; Waters, Milford, MA, U.S.A.) equipped with a reversed-phase C18 packed column (Cosmosil 5C18, 4.6 mm i.D. × 150 mm, Nacalai Tesque, Kyoto, Japan) followed by UV detection at 260 nm. Phosphate buffer (0.05 mol/L, pH 6.0)/acetonitrile/methanol (350/450/200, vol/vol/vol) was used as the mobile phase, at a flow rate of 0.7 mL/min. The column temperature was maintained at 40 °C throughout all experiments, while the sample temperature was maintained at 20 °C.

**Pharmacokinetic Analysis**

Pharmacokinetic parameters were calculated by non-compartmental model analysis using the Excel® (Microsoft) macro program MOMENT, created and validated by Tabata *et al*. Log-linear trapezoidal rule was adopted in this calculation. To minimize Akaike’s information criterion, which was incorporated in the macro program, the last three points of the plasma concentration–time curve were used for linear regression. The area under the curve (AUC) was calculated with linear regression of integration to infinite time.

**RESULTS**

**Recovery Rate of VRCZ in Feeding Tube Infusion**

As shown in Table 1, the recovery rate after infusion of the VRCZ suspension was 89.8 ± 8.3%. The tube was rinsed twice by re-infusing distilled water to ensure no residual drug in the tube. The cumulative recovery rate after the first re-infusion was 102.7 ± 20.7% and that after the second re-infusion was 99.3 ± 10.3%. These results suggested that almost all of the powdered and suspended VRCZ administered via the enteral feeding tube would gain access to the gastrointestinal tract.

**Pharmacokinetic Parameters of VRCZ in Each Patient**

Patient characteristics are shown in Table 2. VRCZ was administered at a loading dose of 300 mg twice daily in all patients and the maintenance dose was 150 or 200 mg twice daily. Figure 1 shows the plasma concentration–time profiles after first loading of VRCZ in each patient. Plasma concentrations were confirmed in all patients, suggesting absorption of the drug after feeding tube administration of powdered and suspended VRCZ. Pharmacokinetic parameters of individual patients are shown in Table 3. The mean pharmacokinetic profile was: plasma concentration at 1 h after administration (C max); 1.81 ± 0.64 µg/mL, AUC; 27.1 ± 27.1 h*µg/mL, t 1/2; 12.7 ± 8.1 h, mean residence time; 18.2 ± 11.9 h, total clearance/bioavailability (CL tot/F);
0.35 ± 0.19 L/h/kg and distribution volume at steady state (Vdss)/F; 4.9 ± 1.3 L/h. Metabolic phenotype was EM in two patients and IM in three patients. The values of CLtot/F calculated by moment analysis were 0.51 and 0.55 L/h/kg in two EM patients, and 0.09, 0.29 and 0.31 L/h/kg in three IM patients. The CLtot/F was apparently lower in IM patients than in EM, which was similar to that observed in usual oral administration.5)

DISCUSSION

Injectable VRCZ is difficult to use for ICU patients because they often have acute renal injury. On the other hand, since many ICU patients have consciousness disturbance, they have difficulties in ingesting tablets orally, and administration of a powdered and suspended preparation via the enteral feeding tube is required when using VRCZ. In this study, evaluation of adsorption of VRCZ to feeding tube confirmed almost 100% recovery rate after re-infusion with water twice. Furthermore, pharmacokinetic analysis of tube administration of a powdered and suspended VRCZ preparation revealed a similar plasma concentration profile as that of usual oral administration.5)

In our in vitro study, the recovery rate of VRCZ after the initial tube infusion was 89.8 ± 8.3%, suggesting that a part of the drug was not recovered from the tube (Table 1). VRCZ is highly lipophilic. When dissolved in solvents containing high proportions of water, some drugs, particularly highly lipophilic and peptide drugs, are known to adsorb to polypropylene tubes. According to our previous report, daptomycin, the cyclic lipopeptide drug, adsorbed to polypropylene tubes when water is selected as the solvent for the drug.14) Moreover, since itraconazole, a triazole antifungal drug with high lipophilicity like voriconazole, also adsorbed to polypropylene tube in a solvent with a high proportion of water, 100% methanol was used as the solvent for the drug to avoid adsorption in our previous report.15) As the surface of the enteral feeding tube is coated with a hydrophilic polymer, VRCZ is unlikely to show adsorptivity to the tube itself. In contrast, the three-way stopcock at the inlet is composed of polycarbonate and polypropylene. Therefore, adsorption of VRCZ to the three-way stopcock was suspected to be the reason why a part of the drug was not be recovered from the tube. However, the cumulative recovery rate after re-infusion with water was 102.7 ± 20.7%, confirming no adsorption to the tube after rinsing. We speculate that during the first infusion, some solid particles of the drug remained on the tube surface, but re-infusion with 20 mL of distilled water at room temperature allowed recovery of almost all the drugs. Although we did not evaluate prolonged stability at 55 °C, the recovery study suggested that almost all the VRCZ in the preparation would be administered via the feeding tube into the patient. However, recovery rates showed a high standard deviation, and that after the first re-infusion was ±20.7%. To investigate the in vitro recovery rate of in vivo infusion method, we used the quite concentrated VRCZ suspension of approximately 2500 µg/mL. The high standard deviation may stem from the insufficient dissolution owing to the insolubility of VRCZ in water and error by thousandfold diluting so that concentrations of the suspension fit within the calibration curve range of the quantification method. This is a limitation of our study.

Next, we evaluated the plasma concentration–time profiles and calculated pharmacokinetic parameters after the first (loading) dose to check whether VRCZ was absorbed following passage through the feeding tube. The values of CLtot/F calculated by moment analysis in two EM patients were 0.51 and 0.55 L/h/kg, and those in three IM patients were

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**Table 2. Demographic and Clinical Data of Subjects**

| No. of patients (n) | 5 |
| Nos. of males/females (n) | 4/1 |
| Age (years) | 65 [62–85] |
| Height (cm) | 161.5 [150.0–167.6] |
| Body weight (kg) | 53.9 [38.3–83.8] |
| Loading dose (mg/d) | 300 × 2 |
| Maintenance dose (mg/d) | 150 × 2 or 200 × 2 |
| AST (U/L) | 39.4 [10.9–134.5] |
| ALT (U/L) | 27.1 [3.0–148.1] |
| γ-GTP (U/L) | 99.6 [13.3–648.1] |
| Albumin (g/dL) | 2.89 [2.77–3.02] |
| Total bilirubin (mg/dL) | 0.93 [0.53–3.84] |
| CRP (mg/dL) | 6.87 [2.17–14.14] |
| CCr (mL/min) | 33.3 [22.6–109.3] |

Data are expressed as number of patients or median [range]. AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, CRP: C-reactive protein, CCr: creatinine clearance.
The maximum concentration in EM phenotype of IM patients. Previous study indicated that mean maximum sample of five patients. In the future, it is necessary to collect administration. The limitation of this study is a very small on CYP2C19 gene polymorphism similar to that of usual oral administered powdered and suspended VRCZ was dependent feeding tube-water twice. Furthermore, pharmacokinetic study in ICU patients revealed that the pharmacokinetics of feeding tube-administered powdered and suspended VRCZ was dependent on CYP2C19 gene polymorphism similar to that of usual oral administration. The limitation of this study is a very small sample of five patients. In the future, it is necessary to collect more cases and perform detailed pharmacokinetic analysis.

**Conflict of Interest** The authors declare no conflict of interest.

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**Table 3. Metabolic Phenotype and Pharmacokinetic Parameters of Each Patient**

| Patient | Metabolic phenotype | Gender (f/m) | Age (year) | Weight (kg) | Dose/weight (mg/kg) | AST (U/L) | ALT (U/L) | γ-GTP (U/L) | Albumin (g/dL) | Total bilirubin (mg/dL) | CRP (mg/dL) | CL\(_{\text{tot/F}}\) (L/h/kg) | V\(_{dss/F}\) (L/kg) | AUC (h*µg/mL) | MRT (h) | CL\(_{\text{tot/F}}\) of patient 2 | t\(_{1/2}\) (h) | V\(_{dss}\) (L/kg) |
|---------|---------------------|-------------|-----------|-------------|-------------------|----------|----------|------------|----------------|------------------------|------------|------------------------|----------------|---------------|--------|--------------------------|--------|-------------|
| Patient 1 | EM | f | 62 | 38.3 | 7.83 | 23.0 | 11.9 | 13.3 | 2.89 | 0.91 | 2.37 | 1.26 | 15.3 | 8.5 | 12.7 | 0.51 | 6.5 |
| Patient 2 | IM | m | 85 | 45.8 | 6.55 | 51.7 | 81.1 | 99.6 | 2.77 | 1.09 | 8.93 | 2.40 | 74.7 | 26.9 | 39.1 | 0.09 | 3.4 |
| Patient 3 | IM | m | 65 | 53.9 | 5.57 | 10.9 | 3.0 | 61.2 | 1.09 | 0.93 | 14.14 | 2.07 | 19.3 | 8.6 | 12.7 | 0.29 | 5.9 |
| Patient 4 | IM | m | 63 | 83.8 | 3.58 | 134.5 | 148.1 | 648.1 | 3.08 | 3.84 | 6.78 | 0.99 | 6.5 | 7.8 | 10.7 | 0.55 | 4.8 |
| Patient 5 | IM | m | 77 | 50.0 | 6.00 | 39.4 | 27.1 | 105.0 | 3.02 | 0.53 | 3.79 | 2.32 | 19.5 | 11.5 | 15.7 | 0.31 | 4.8 |

EM: extensive metabolizer, IM: intermediate metabolizer, f: female, m: male, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, CRP: C-reactive protein, C\(_{\text{max}}\): plasma concentration at 1 h after administration, AUC: area under the curve, MRT: mean residence time, CL\(_{\text{tot}}\): total clearance, F: bioavailability, V\(_{dss}\): distribution volume at steady state.
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