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Disposition of voriconazole during continuous veno-venous haemodiafiltration (CVVHDF) in a single patient

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***Objectives*: To determine whether voriconazole dosage adjustment is required during continuous veno-venous haemodiafiltration (CVVHDF).**

***Methods*: Voriconazole pharmacokinetics were studied in a critically ill patient under CVVHDF. The analysis was carried out for 12 h following a 6 mg/kg dose. Voriconazole concentrations were measured by HPLC in blood inlet and outlet lines and in dialysate.**

***Results*: The total body clearance of voriconazole was 20.3 L/h, with a terminal half-life of 13.7 h and a distribution volume of 399 L. The estimated sieving coefficient was 0.53 and the filtration-dialysis clearance 1.2 L/h.**

***Conclusions*: CVVHDF does not significantly affect voriconazole disposition and requires no dosage adjustment.**

Keywords: antifungals, renal failure, dialysis, pharmacokinetics

Introduction

Voriconazole is a new triazole antifungal agent with a broad spectrum activity against *Candida*, *Aspergillus* and *Cryptococcus neoformans*.[1–4] It is 58% protein bound and extensively metabolized by the liver. It exhibits non-linear pharmacokinetics, possibly due to saturable first pass metabolism and systemic clearance.[3] Voriconazole disposition has not yet been studied in patients receiving renal replacement therapy through continuous veno-venous haemodiafiltration (CVVHDF).[5] However, its administration to such patients may be medically indicated. We report the case of a patient who received voriconazole under renal support through CVVHDF, in whom voriconazole blood and dialysate levels were determined over an interval of administration.

Materials and methods

Patient

A 70-year-old, 60 kg female patient with chronic renal insufficiency (baseline serum creatinine 195 μmol/L) was admitted to the Intensive Care Unit for adult respiratory distress syndrome due to *Pneumocystis carinii* pneumonia. The patient's condition deteriorated; she developed pancreatitis, disseminated intravascular coagulation and acute renal failure requiring the initiation of CVVHDF treatment. The CVVHDF apparatus was a PRISMA CFM (Hospal, Lyon, France) provided with a 0.9 m^2 polyacrylonitrile hollow fibre filter (AN69 HF, Multiflow 100, Hospal, Lyon, France) connected through a double lumen venous catheter. The treatment conditions were set to 120 mL/min blood flow, 500 mL/h pre-dilution flow, patient subtraction of 220 and 1000 mL/h counter-current dialysate solution flow. A deterioration of the respiratory status was observed and a reassessment revealed the presence of *Aspergillus fumigatus* in the cultures. Treatment with intravenous voriconazole (6 mg/kg twice at a 14 h interval as loading dose, followed by 4 mg/kg every 12 h) was begun. The patient died 8 days later from multiple organ failure.

Drug sampling and assay

The analysis was carried out on the second 6 mg/kg dosing after patient's informed consent had been obtained, with blood samples being collected from the 'arterial' and 'venous' lines and dialysate samples from the output line. The administered dose was assessed with precision by recording the infused volume (137 mL) and measuring the voriconazole concentration in a sample of the infused solution. The residual urine was collected over the 12 h dosing

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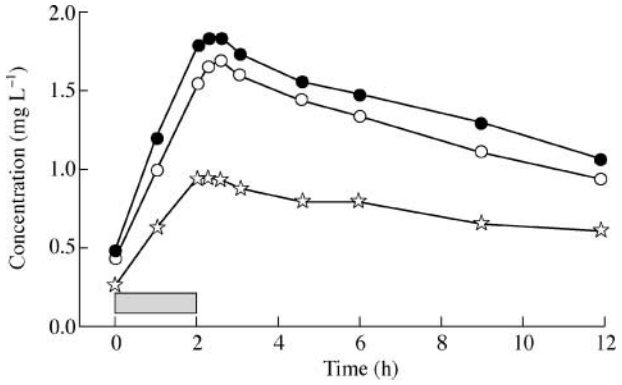

Figure 1. Voriconazole concentration–time profiles in 'arterial' and 'venous' line and in dialysate. Closed circles, 'arterial' concentrations; open circles: 'venous' concentrations; stars, dialysate concentrations; shaded rectangle, time of infusion.

interval for voriconazole determination. Blood samples were centrifuged and plasma, dialysate, urine and infused solution samples stored at −20°C until analysis.

Voriconazole concentrations were measured by an HPLC method[6] after solid phase extraction, using a reversed-phase Luna-5 μm C_{18} column (250 × 4.5 mm) at room temperature. The mobile phase consisted of 0.01 M N,N,N′,N′-tetramethylethylenediamine phosphate buffer (adjusted to pH 7.4 with phosphoric acid) added to acetonitrile (55:45); detection was made by UV at 254 nm. The lower limit of quantification was 0.2 mg/L, and the inter- and intra-day coefficients of variation were lower than 12% at all concentration levels.

Pharmacokinetic analysis

The concentration–time curves resulting from the 'arterial', 'venous' and dialysate lines are shown in Figure 1. Plasma voriconazole concentration–time data were analysed using non-compartmental calculations, with the AUC being estimated by the log-trapezoidal method (without extrapolation beyond the dosing interval). The total body clearance was estimated as the dose divided by AUC, the apparent terminal elimination rate constant (λ_z) by log-linear least square regression, with elimination half-life ($t_{1/2}$) derived as $\log(2)/\lambda_z$ and terminal volume of distribution (V_z) as CL_{TOT}/λ_z. The renal clearance was obtained as the ratio of voriconazole excreted unchanged in urine over AUC. A sieving coefficient was calculated as the ratio of concentration in dialysate over 'arterial' blood. Then a filtration-dialysis clearance was estimated as the product of S_c multiplied by total filtrate and dialysate flow (detailed calculations according to Ref. 7).

Results and discussion

The resulting pharmacokinetic parameters are listed in Table 1. These parameters do not differ from those reported in patients without renal impairment: Purkins *et al.*[3] observe an average AUC of 43 mg·h/L for a 5 mg/kg dose on day 7; the same authors in a different study[8] report an average AUC of 13 mg·h/L both after a 6 mg/kg loading dose and after 10 days of treatment at 3 mg/kg twice daily, with CL_{TOT} values ranging from 13 to 36 L/h. These results are in accordance with the predominant extrarenal elimination of voriconazole, making its pharmacokinetics poorly sensitive to renal impairment.[9] Moreover, renal substitution by CVVHDF appears to contribute to drug elimination by only 6%. This percentage is about four times higher than the 1.5% reported in the literature for the renal excretion of drug in healthy volunteer.[9] This difference may be explained by the renal handling of voriconazole, with a significant physiological reabsorption of the filtered drug by renal tubules, whereas CVVHDF replaces only the filtration component.

Table 1. Pharmacokinetic parameters of voriconazole in a patient undergoing CVVHDF treatment

Pharmacokinetic parameter	Value	Units
Dose	337	mg
C_{max}	1.84	mg/L
AUC	16.6	mg·h/L
Terminal elimination half-life ($t_{1/2}$)	13.7	h
Total body clearance (CL_{TOT})	20.3	L/h
Terminal volume of distribution (V_Z)	399	L
Renal clearance (CL_R)	0.14	L/h
Sieving coefficient (S_C)	0.53	
Filtration-dialysis clearance (CL_{FD})	1.2	L/h

In conclusion, the pharmacokinetics of voriconazole in our patient appeared not significantly affected by CVVHDF. In this situation, we would recommend administration of a standard dose adjusted to the patient's general condition. Voriconazole having non-linear pharmacokinetics, the contribution of renal replacement therapy to its total clearance might however increase with high dosages.

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