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Vancomycin clearance during continuous venovenous haemofiltration in critically ill patients

Abstract  Objective: To study the pharmacokinetics of vancomycin in critically ill patients with acute renal failure treated with continuous venovenous haemofiltration (CVVHF).  
Design: Open-label study.  
Setting: Hospital pharmacy centre and medical intensive care unit of the University Medical Centre Utrecht.  
Materials and methods: In a laboratory setting, the sieving coefficient (s) of vancomycin by polyacrylonitrile (PAN) haemofilters of different surface areas was studied. In one patient, the pharmacokinetics of vancomycin were studied following a single dose of vancomycin. Another patient was treated with a vancomycin dosing regimen based on data from the literature, but high trough concentrations made dose reduction necessary after 24 h of withholding therapy. After two doses of 250 mg, serum and ultrafiltrate samples were collected for pharmacokinetic evaluation.  
Intervention: CVVHF with the following operational characteristics: blood flow 200 ml/min, ultrafiltrate flow 25 ml/min, postdilution, PAN 06 hollow fibre haemofilter.  
Measurements and results: The average sieving coefficient in vitro was 0.73 ± 0.06, 0.86 ± 0.11, and 0.80 ± 0.06 for the PAN 03, 06, and 10 haemofilters, respectively. Changes in the sieving coefficient by increasing the ultrafiltration rate were not clinically significant. The first patient was given a single dose of vancomycin, 1000 mg by intravenous infusion. The following pharmacokinetic data were obtained: apparent volume of distribution (Vd) 55.8 l, terminal half-life time (t1/2 term) 15.4 h, total clearance (Cltot) 2.5 l/h, CVVHF clearance (CLCVVHF, form 1) 1.4 l/h, and body clearance (Clbody) 1.1 l/h. The average sieving coefficient during the study period was 0.89 ± 0.03. In the second patient, the pharmacokinetics of vancomycin were studied following dose reduction: Vd 41.7 l, t1/2 term 20.3 h, Cltot 1.4 l/h, CLCVVHF, form 1 1.4 l/h, and Clbody < 0.1 l/h. The average sieving coefficient during the study period was 0.88 ± 0.03. The cumulative amount of vancomycin removed by means of CVVHF during the 12-h study period was 245 mg in patient 1 and 228 mg in patient 2.  
Conclusion: CVVHF with a PAN 06 haemofilter effectively removed vancomycin in two critically ill patients. The amount of vancomycin removed with CVVHF was about 250 mg per 12 h. A clear difference in body clearance in the two patients was observed. Our dosage recommendation for vancomycin in critically ill patients receiving CVVHF is a loading dose of 15–20 mg/kg followed after 24 h by 250 to 500 mg twice daily with close monitoring of the serum and ultrafiltrate vancomycin concentration.  
Key words Vancomycin · CVVHF · Intensive care
Introduction

Haemofiltration is a convection-based alternative method to haemodialysis in the treatment of acute renal failure and volume overload. Haemofiltration is particularly useful in critically ill patients with haemodynamic instability. Continuous venovenous haemofiltration (CVVHF) was introduced as an alternative to continuous arteriovenous haemo(dia)filtration (CAVH(D)F) and has potential benefits over CAVH(D)F such as CVVHF does not need a large bore arterial catheter, the blood flow through the extracorporeal circuit is pump driven, and the total ultrafiltrate flow can be set at a desired level. CAVH(D)F was reported to be effective in the clearance of drugs, and many reports on adjustment of dosing regimens have been published [1–5]. CVVHF was also shown to be effective in the clearance of drugs [6–14]. In general, drugs with a molecular weight less than 5000 Da, low plasma protein binding, small volume of distribution, and low endogenous clearance are effectively removed by CVVHF [1, 15]. Many drugs used in critically ill patients meet these criteria, complicating dosing regimens in patients receiving CVVHF.

However, additional factors such as altered binding to plasma proteins, capillary leakage, hepatic and/or renal failure, and changes in volume of distribution complicate drug dosing in critically ill patients but are not always taken into account. Knowledge of optimum dosing regimens of drugs like antibiotics, long-acting vasoactive drugs, and potentially toxic drugs in critically ill patients is crucial, but far from complete. Mathematical models, data derived from CAVH(D)F, and data derived from patients with renal failure in an otherwise stable condition are helpful in the development of dosing regimens in critically ill patients on CVVHF. However, we have to study the pharmacokinetics of drugs in this patient category because of the aforementioned potential drawbacks of overdosing with toxic drugs or underdosing with drugs necessary in the treatment of these patients.

We studied the pharmacokinetics of vancomycin in vitro and in two critically ill patients receiving CVVHF. Additionally, a dosing recommendation based on our observations is proposed.

Materials and methods

Haemofiltration technique

Vascular access was obtained by insertion of a double-lumen dialysis catheter (Quinton, Mahukar, catheter, 11.5 F × 16 cm) in to a central vein. The blood flow through the extracorporeal circuit was maintained at 200 ml/min (12 l/h) by the roller pump of the Gambro AK100 dialysis machine equipped with haemofiltration mode. We used a polyacrilonitrile haemofilter (PAN 06, Asahi Medical, Tokyo, Japan) in the intensive care ward. The total ultrafiltrate rate was set at 1600 ml/h with replacement of 1500 ml/h resulting in a net ultrafiltration rate of 100 ml/h. Shiwa SH 44-hep substitution fluid (Shiwa, 4519 Glandorf, Germany) was rein infused into the venous drip chamber to maintain fluid and electrolyte balance (postdilution).

In vitro work

During three separate in vitro sessions, the sieving coefficient of vancomycin was studied in a PAN haemofilter with different surface areas (0.3, 0.6, and 1.0 m²). For this purpose, packed cells were resuspended with fresh frozen plasma (neither suitable for patient aims) to a haematocrit of about 0.30 and a total volume of about 2 l. Thereafter 5000 E heparin and 100 mg of vancomycin were added. The system was allowed to equilibrate for 30 min and CVVHF was started. The blood flow was maintained at 200 ml/min. The ultrafiltration rate was increased stepwise at 500, 1000, 1500, and 2000 ml/h. The ultrafiltrate volume was rein infused as Shiwa SH 44-hep substitution fluid administered into the venous drip chamber (postdilution) to maintain total volume. After changes in the ultrafiltrate and substitution rate, the system was allowed to equilibrate for 30 min.

The ultrafiltrate was continuously sampled during collection periods of 60 min by means of a pull pump connected to the proximal part of the ultrafiltrate outlet tube using a T-piece and a side line. The flow rate of the pull pump was set at 10 ml/h. The vancomycin concentration was determined in the 10 ml ultrafiltrate aliquot represented the average ultrafiltrate concentration during the collection period of 1 h. The total ultrafiltrate volume was checked.

Blood samples were collected at the midpoint of an ultrafiltrate collection period for measurement of the serum vancomycin concentration.

Patients

The pharmacokinetics of vancomycin were studied in two patients with septic shock and multiple organ dysfunction syndrome (MODS) receiving CVVHF. Both patients were anuric (19 and 46 ml over 24 h, respectively). The pharmacokinetics were studied over 15 and 12 h, respectively.

In patient 1, a 53-year-old male (weight 85 kg), the pharmacokinetics of vancomycin after a single dose of vancomycin were studied. Vancomycin 1000 mg was administered as a continuous intravenous infusion over 60 min. The patient had had a cardiac transplant 4 years before and was admitted to the intensive care unit because of pneumonia. Later on during the course of his disease MODS developed, and CVVHF was started for fluid and metabolic control. The day before the study took place his pulmonary situation had deteriorated and there was a clinical suspicion of ventilator-associated pneumonia. New cultures were taken, and vancomycin was added to the antimicrobial therapy (imipenem/cilastatin). The patient had an hyperdynamic circulation, and during the study his haemodynamic situation deteriorated. Inotropic support had to be expanded and fluid infusion was given to maintain the pulmonary artery wedge pressure (PAWP) at 14 mm Hg. The patient’s clinical condition deteriorated and he died 17 h after the start of the study.

In patient 2, a 39-year-old female (weight 80 kg), the pharmacokinetics of vancomycin were studied on the 6th day of therapy. She was resuscitated following an out-of-hospital cardiac arrest. She had possible anoxic encephalopathy with remaining brain stem function and developed acute renal failure. CVVHF was star-