Journal of the Formosan Medical Association (2016) 115, 560–570

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Pharmacokinetics of vancomycin in adults receiving extracorporeal membrane oxygenation

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Received 12 August 2014; received in revised form 17 May 2015; accepted 20 May 2015

KEYWORDS
critical care;
extracorporeal membrane oxygenation;
pharmacokinetics;
therapeutic drug monitoring;
vancomycin

Background/purpose: Extracorporeal membrane oxygenation (ECMO) alters the pharmacokinetics (PK) of vancomycin in neonates; but data on adults is limited.
Methods: This is a prospective, matched cohort, single center, pharmacokinetic study. For each adult patient who received vancomycin therapy in the ECMO group (with either centrifugal pump or roller pump), a control patient was matched by age ($\geq$ 60 years or $<$ 60 years), gender, and creatinine clearance (CL_{Cr}) in intensive care units. After vancomycin was administered for at least four doses, serial blood samples were drawn at 0.5 hours, 1 hour, 2 hours, 3 hours, 5 hours, 7 hours, 11 hours, 23 hours, 35 hours, and 47 hours post vancomycin infusion according to the dosing intervals. The serum concentration-time profile was fitted to a non-compartment model and a nonlinear mixed effect model to determine the PK parameters.
Results: Twenty-two critically ill adults without renal replacement therapy were enrolled. There were no significant differences between the ECMO group and the matched group in demographics, renal function, and PK parameters. However, vancomycin clearance in the roller pump group was significantly lower than that in the matched control (0.83 $\pm$ 0.43 mL/min/kg vs. 0.97 $\pm$ 0.43 mL/min/kg, $p = 0.002$).

Conflict of interest: The authors have no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.jfma.2015.05.017

Conclusion: Vancomycin clearance in patients receiving ECMO with a roller pump was significantly lower than that in the matched cohort. Vancomycin PK parameters in patients on ECMO with a centrifugal pump were comparable to those in the matched control group.

Introduction

Extracorporeal membrane oxygenation (ECMO) was initially used for neonates with respiratory failure,[1] and its use has expanded to cardiac or respiratory failure in adults.[2] Blood stream infection was the most common infection acquired during ECMO therapy.[3] With increased nosocomial bloodstream infections by methicillin-resistant *Staphylococcus aureus* (MRSA),[4] especially in this patient population,[5] vancomycin is frequently used to prevent or treat MRSA infections in patients receiving ECMO in our medical center.

ECMO can be viewed as an artificial heart and lung for respiratory and circulatory support, and can be used for a longer period than traditional cardiopulmonary bypass. Its clinical indications include cardiogenic shock, acute respiratory distress syndrome, organ donation, transplantation, and short-term bridge of operation. ECMO is composed of a blood pump, an oxygenator, a heater, and many other components including a monitor. ECMO circuits probably represent another pharmacokinetic (PK) compartment because they can sequester a significant amount of drug, and therefore increase the volume of distribution (V_d).[6] There are various methods such as venoarterial (VA) and venovenous (VV) modes to cannulate ECMO. VA ECMO is achieved by drawing blood from a vein, such as the jugular vein, passing the blood through the oxygenator, and pumping the blood into the aortic arch. The VV mode is similar to the VA mode, except that the blood is pumped back into a different vein. Because the VA mode lacks pulsatility, renal function is transiently altered.[7] Altered renal function is also found in the VV mode.[8] Dagan et al[9] found that drug disposition was altered because the oxygenator could sequester many medications such as vancomycin. In summary, ECMO may alter PK by decreasing drug elimination, increasing the V_d, and sequestering drugs in the ECMO circuits.[6]

In patients with normal renal function, the reported vancomycin V_d, clearance (CL), and half-life ($t_{1/2}$) are respectively 0.5—1 L/kg, 0.9—1.45 mL/min/kg, and 5—9 hours.[10—14] However, there is limited data on vancomycin PK in adult patients receiving ECMO. Previous studies on the PK of vancomycin in patients receiving ECMO are mostly limited to neonates, and the results are conflicting. Some studies reported a lower vancomycin CL, a larger V_d, and a longer $t_{1/2}$,[15—17] while other studies reported that ECMO did not affect the vancomycin PK.[18]

Despite the increasing use of vancomycin in adult patients receiving ECMO,[19] there is only one noncontrolled study that evaluated the effect of ECMO on vancomycin PK in adults.[17] The objective of this matched-cohort study was to determine the influence of ECMO on the PK of vancomycin in adults. Determination of an appropriate dosage regimen was also intended for these patients.

Methods

Patient eligibility

This prospective, matched-cohort study was approved by the research ethics committee of the National Taiwan University Hospital, Taipei, Taiwan. The patients on ECMO who received vancomycin treatment, were at least 18 years old were eligible for the study. The patients who used continuous renal replacement therapy, hemodialysis, plasmapheresis, had acute kidney injury [an increase in serum creatinine (S_{Cr}) of $\geq$ 0.3 mg/dL in 24 hours or a reduction in urine output with an output of $<$ 0.5 mL/kg/h for $>$ 6 hours], or suffered from severe burns over 30—40% of the body surface area were excluded from this study. These patients were recruited after informed consent was obtained from them or their representatives.

For each patient in the ECMO group, a control patient was matched by age ($\geq$ 60 years or $<$ 60 years), gender, and creatinine clearance (CL_{Cr}, mL/min/1.73 m^2) in intensive care units. The CL_{Cr} was matched by a difference of $<$ 20 mL/min/1.73 m^2 or a CL_{Cr} in the identical range group ($>$ 90 mL/min/1.73 m^2, 60—89 mL/min/1.73 m^2, 30—59 mL/min/1.73 m^2, and $<$ 30 mL/min/1.73 m^2). The CL_{Cr} was estimated using the Cockcroft and Gault method (CG method). If a patient's S_{Cr} was $<$ 0.8 mg/dL, it will be replaced by 0.8 mg/dL to avoid overestimation of the patient's renal function. For obese patients [(true body weight—ideal body weight)/ideal body weight $>$ 30%], the Salazar-Corcoran equation was used to estimate the CL_{Cr}.[20] The CL_{Cr} was normalized to a body surface area of 1.73 m^2. From December 2005 to December 2006, each group recruited 12 patients.

ECMO apparatus

The ECMO system was predominantly composed of a blood pump, a membrane oxygenator, a heater (ECMO-TEMP Unit, Zimmer Patient Care Division, Dover, OH, USA), arterial and venous cannulas, pump tubing, and other monitors. Two types of blood pumps were used for the ECMO group. One blood pump is the centrifugal pump (Biomedicus Pump Console 550, Medtronic Bio-medicus Inc., Eden Prairie, MN, USA) connected with a hollow fiber microporous membrane oxygenator (CBIV97R, Medtronic Inc., Anaheim, CA, USA), and the other type was a roller pump (Precision blood pump, COBE Cardiovascular, Inc., Arvada, CO, USA) connected with a silicone membrane oxygenator (Avecor I4500, Medtronic Inc., Anaheim, CA, USA). The priming fluid was 850 mL of normal saline for the centrifugal pump and 1500 mL of normal saline plus 500 mL of packed red blood