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O1160 Determination of optimal dosing and maintenance doses for continuous infusion of vancomycin in critically ill patients: population pharmacokinetic modelling and simulation

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Background: Despite extensive clinical use, only limited data is available regarding optimal loading and maintenance doses of vancomycin needed for rapidly achieving and maintaining adequate drug concentrations in critically-ill patients. Our aim was to develop a rational approach for optimized dosage of vancomycin given in continuous infusion that could easily be used in Intensive Care Units (ICU).

Materials/methods: Vancomycin pharmacokinetic (PK) data (total serum concentrations) were obtained from 55 ICU patients (Bach Mai hospital; >18 years; excluding renal replacement therapy) receiving a loading dose (60 to 120 min infusion) followed by continuous infusion for 6 days (median; interquartile range: 5-11) and for whom creatinine clearance was calculated (Cockroft-Gault equation). Population modeling and Monte Carlo simulations were performed using NONMEM (1000 simulated patients/dosage scenario) for a target of 20-30 mg/L (AUC = 480-720, covering MICs up to 1.5 mg/L [Clin Pharmacokinet. 2004;43:925-42] while minimizing nephrotoxicity [J Antimicrob Chemother. 2008 Jul;62(1):168-71).

Results: A two-compartment model with first-order elimination best fitted the PK data (central and peripheral V_d: 77.6 and 112 L, respectively [both corrected for a standard 70-kg individual]; total clearance: 3.21 L/h). Only the renal function was retained as covariate in the final model. Overall, simulation results showed that (i) a 25-mg/kg loading dose infused over 90 minutes was optimal to reach the target range; (ii) the maintenance dose had to be adjusted from 1 to 4.5 g/24h for patients with creatinine clearances spanning from <10 to 240 mL/min to obtain and maintain the serum concentration within the target range (see Table for results after 24h treatment [69 to 81% of patients within the target; most doses being larger than previously proposed for non-ICU [Int J Antimicrob Agents. 2013;41:439-46]).

Table. Percentage of simulated patients with vancomycin serum concentrations reported within the target range of 20-30 mg/L after 24h

CLCr (mL/min)	Maintenance dose (mg/day)										
	300	**500**	**750**	**1000**	**1500**	**2000**	**2500**	**3000**	**3500**	**4000**	**4500**
<10	*16.0%*	41.2%	69.0%	**74.1%**	37.5%	11.3%					
10-20	4.7%	*22.4%*	54.9%	**74.8%**	54.5%	19.4%	4.4%				
21-30		8.2%	*34.5%*	64.9%	**69.1%**	31.3%	8.9%	2.5%			
31-45			13.3%	*41.2%*	**77.4%**	50.6%	19.4%	4.9%	1.3%		
46-60				17.0%	*68.5%*	**71.5%**	36.9%	13.2%	3.3%	0.9%	
61-85					38.4%	***77.0%***	65.6%	32.7%	13.2%	3.9%	
86-110						51.1%	***79.0%***	65.3%	35.1%	14.7%	5.0%
111-130							63.5%	***81.2%***	63.1%	35.1%	15.2%
131-180							21.8%	*59.1%*	**77.4%**	71.0%	48.1%
181-240							0.9%	*9.7%*	37.3%	66.6%	**79.1%**

- CLCr, creatinine clearance
- Figures in bold: largest percentage of patients achieving the target range with the proposed maintenance dose
- Figures in italic: actual percentage of patients that would achieve the target range if using the doses proposed for non-ICU patients (Ampe et al. Int J Antimicrob Agents. 2013;41:439-46)

Conclusions: Larger loading and maintenance doses of vancomycin are needed to achieve desired target concentrations in ICU patients. A sizable proportion of patients may nevertheless show concentrations outside these targets, highlighting that vancomycin dosing schemes based on creatinine clearance may not be optimal in ICU patients for whom drug monitoring may still be necessary to rapidly correct for too low or too high vancomycin serum levels.