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Vancomycin Penetration of Uninfected Pleural Fluid Exudate after Continuous or Intermittent Infusion

Baudouin Byl,[1]* Frédérique Jacobs,[1] Pierre Wallemacq,[2] Camelia Rossi,[1] Philippe de Francquen,[3] Matteo Cappello,[3] Teresinha Leal,[2] and Jean-Pierre Thys[1]

Infectious Diseases Clinic[1] and Thoracic Surgery Department,[3] Erasme University Hospital, Université Libre de Bruxelles, and Clinical Chemistry Department, Saint-Luc University Hospital, Université Catholique de Louvain,[2] Brussels, Belgium

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Blood and pleural exudate samples were obtained from 16 patients receiving intermittent or continuous infusions of vancomycin after lung surgery. The areas under the concentration-time curves for blood and pleural exudates were identical for both administration schedules, while continuous infusion allowed the concentrations in pleural exudates to be more sustained (mean concentration, 12 mg/liter).

Vancomycin is a glycopeptide antibiotic used worldwide to treat infections caused by staphylococci and enterococci. The use of vancomycin continues to increase as resistant gram-positive cocci including methicillin-resistant *Staphylococcus aureus* (MRSA) strains and other β-lactam-resistant staphylococci and streptococci become more prevalent. While vancomycin resistance associated with vancomycin use was described in enterococci several years ago, in 1997, the first case of MRSA with intermediate resistance to vancomycin was described, rapidly followed by other reports (6, 8, 11, 12). Both the difficulty of treatment of severe infections caused by gram-positive bacteria and the threat of the emergence of resistance emphasize the need to optimize the use of glycopeptides. Vancomycin exhibits time-dependent killing that is maximized at concentrations of four to five times the MIC for the organism. In animal models, the most predictive parameter for vancomycin efficacy is the area under the concentration-time curve (AUC)/MIC ratio (4; M. Dudley, D. Griffith, E. Corcoran, et al., Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 2031, 1999). The continuous infusion of vancomycin has already been suggested as a mode of administration. Little is known, however, about the penetration into body fluids of vancomycin administered in this way.

The aim of the present study was to compare the penetration into uninfected pleural exudates of vancomycin administered as a conventional intermittent infusion and a continuous infusion.

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Sixteen patients (13 males, 3 females) underwent lobectomy or pneumectomy for bronchial cancer and had continuous pleural drainage postoperatively. The mean patient age was 59 years (range, 40 to 76 years), and the mean weight was 75 kg (range, 57 to 100 kg), for a mean lean body weight of 65 kg (range, 53 to 72 kg). All patients had normal renal and hepatic functions. None presented any clinical or laboratory signs of infection and had not received antibiotic treatment during the previous 7 days. The study received the approval of the Ethical Committee of Erasme Hospital. All patients gave written consent. Between days 2 and 4 after surgery, the patients were administered vancomycin (GlaxoSmithKline, Brussels, Belgium) at either 15 mg/kg of body weight twice a day as a 60-min infusion (8 patients) or 30 mg/kg as a continuous infusion after the administration of a loading dose of 500 mg over 30 min (8 patients). Blood and pleural fluid were sampled during the second day of vancomycin administration. In patients with continuous vancomycin administration, samples were collected every 4 h over 12 h. For patients with intermittent vancomycin administration, blood was collected just before administration and at 1, 2, 4, 6, 8, and 12 h afterwards. Pleural fluid that had accumulated in the chest drainage tube during the previous 30 min (for the first four samples) or 60 min (for the subsequent

TABLE 1. Blood and pleural fluid vancomycin concentration during intermittent and continuous infusion

Time after administration	Concn (mg/liter)			
	Intermittent infusion		Continuous infusion	
	Blood	Pleural fluid	Blood	Pleural fluid
0	4.1 ± 1.4	5.5 ± 2.0	14.0 ± 3.8	11.8 ± 2.7
30 min		5.8 ± 2.0		
1 h	48.3 ± 14.9	9.4 ± 3.0		
1 h 30 min		15.3 ± 3.7		
2 h	22.4 ± 5.2	19 ± 4.8		
4 h	14.4 ± 4.9	16 ± 4.5	14.0 ± 4.3	12.1 ± 2.9
6 h	10.3 ± 3.8	13 ± 3.6		
8 h	8.6 ± 3.3	9.8 ± 3.0	14.7 ± 4.3	13.0 ± 3.6
12 h	5.6 ± 2.1	6.6 ± 2.3	16.0 ± 4.5	13.7 ± 3.5
AUC_{0-12}	172 ± 40	145 ± 35	178 ± 52	152 ± 37
AUC_{0-12} for pleural fluid/AUC_{0-12} for blood		0.88 ± 0.07		0.86 ± 0.14

* Corresponding author. Mailing address: Infectious Diseases Clinic, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Phone: 32 2 5556746. Fax: 32 2 5553912. E-mail: baudouin.byl@ulb.ac.be.

TABLE 2. Pharmacokinetic parameters for vancomycin during intermittent administration[a]

Compartment	Creatinine clearance (ml/min)	Vamcomycin clearance		V (liters/kg)	k_{el} (h^{-1})	$t_{1/2\beta}$ (h)
		ml/min	ml/min/kg			
Blood	98 ± 27	113 ± 28	1.55 ± 0.48	0.83 ± 0.29	−0.12 ± 0.03	6.3 ± 1.9
Pleural fluid					−0.11 ± 0.03	6.4 ± 1.5

[a] The values are means ± SDs. V, volume of distribution; k_{el}, elimination rate constant; $t_{1/2\beta}$, elimination half-life.

samples) was collected just before vancomycin administration and at 30 min and 1, 1.5, 2.5, 3.5, 4.5, 6.5, 8.5, and 12.5 h afterwards. The blood contamination of the pleural fluid was expressed as a percentage by the ratio of the pleural fluid hemoglobin concentration and the blood hemoglobin concentration and was 3.2% ± 2.0% (mean ± standard deviation [SD]). The pleural fluid protein concentration was 32 ± 6 g/liter (mean ± SD), which represents 46.1% ± 7.6% of the blood protein concentration, suggesting the presence of a greater fraction of free vancomycin in the pleural fluid. Within 30 min the samples were stored at −20°C until assay. Vancomycin concentrations were obtained by fluorescence polarization immunoassay on a TDx analyzer (Abbott Diagnostics, Louvain-la-Neuve, Belgium). The limit of quantification was 2 μg/ml, and the intra-assay coefficient of variation was 2.5%. The AUCs from 0 to 12 h ($AUC_{0\text{-}12}$s) were calculated by use of the linear trapezoidal rule. The median $AUC_{0\text{-}12}$s obtained by the two regimens for both pleural fluid and plasma samples were compared by the Mann-Whitney test (Prism software for Windows, version 3.02; GraphPad Software, San Diego, Calif.). A one-compartment open model was used to estimate the pharmacokinetic parameters during intermittent infusion.

The serum and pleural fluid vancomycin concentrations and the $AUC_{0\text{-}12}$s for both groups of patients are reported in Table 1, and the pharmacokinetic parameters for intermittent administration are presented in Table 2. No significant difference in the $AUC_{0\text{-}12}$s for serum or pleural fluid was observed between the two modes of administration, with the P values for comparison of the median $AUC_{0\text{-}12}$s for blood and pleural fluid being 0.82 and 0.69, respectively. The AUC/MIC ratio is thus as favorable for continuous infusion as it is for intermittent infusion. However, as expected, the concentrations in pleural fluid were more sustained during continuous administration and reached a mean value of about 12 mg/liter. This value is only three times the breakpoint of vancomycin for vancomycin-susceptible microorganisms such as MRSA.

Comparison of intermittent and continuous infusion of vancomycin for determination of the levels of penetration into tissue or body fluid is rare. Continuous infusion of vancomycin allowed a mean concentration of 11 mg/liter to be reached in the cerebrospinal fluid of patients with meningitis (1). The level of penetration of vancomycin into tissue is usually lower than the levels of penetration of other antibiotic groups, and for some tissues, such as lung tissue, the level of penetration is below the MICs for susceptible staphylococci (5). Vancomycin is most commonly administered intermittently to take advantage of its relatively long half-life. This property and the report of a greater risk of phlebitis when it is administered as a continuous infusion (10) may explain the lack of enthusiasm for continuous infusion. Clinical data about the efficacy of continuous infusion of vancomycin remain rare. Several papers reported on the efficacy of continuous infusion for the treatment of meningitis, osteomyelitis, and other severe infections in uncontrolled studies (2, 3). The continuous infusion of vancomycin in patients with suspected or documented infections caused by gram-positive bacteria was associated with a serum bactericidal titer that always remained above 1/8, but this did not occur with conventional (intermittent) administration (9). In a retrospective study with critically ill patients, the continuous infusion of vancomycin was associated with a faster decrease in the leukocyte count and the clinical severity score, while no differences in mortality or morbidity were observed (7). Only one randomized study compared the efficacies of the two modes of vancomycin administration for miscellaneous infections including bacteremia and pneumonia (13). In the study described in this paper, no difference in the clinical efficacy was observed between the two modes of administration. While the AUCs for serum were similar, the targeted concentrations were more quickly reached in the continuous infusion arm of the study. Less variability in the daily dose infused was observed with continuous infusion, and the costs of vancomycin administration were reduced by 23%. Beyond these practical considerations, the eventual clinical benefit of continuous infusion is actually undetermined. Our data support the possibility that more sustained levels in body fluid are obtained by continuous infusion. These sustained antibiotic levels obtained by continuous infusion may contribute to better prognoses for deep-seated infections and to the prevention or reduction of the risk for the emergence of vancomycin resistance, although the best pharmacokinetic and pharmacodynamic markers of glycopeptides governing the emergence of resistance are not clearly established.

In conclusion, our study shows that the continuous infusion of vancomycin results in levels of penetration into pleural fluid similar to those achieved with intermittent administration, with levels in pleural fluid being more sustained, however. Further studies are needed to evaluate the eventual clinical benefit of this mode of administration.

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