Vancomycin dosing in hemodialysis patients

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Nefrología 2008; 28 **(6)** 607-612

SUMMARY

Vancomycin is widely used in haemodialysis (HD) patients for treating infections of vascular access due to St. Aureus. To avoid subtherapeutic levels it is important to know the adequate dosing in patients undergoing haemodialysis with high flux membranes. Objective: *The aim of this study was to evaluate whether HD patients treated with 1 g intravenous (IV) vancomycin reached optimum plasma levels.* Material and methods: *In a crossover design we studied 28 chronic HD patients, 3 times a week, treated with vancomycin between 15/2/2006 and 14/2/2007. Antibiotic was given at dose of 1 g during the last hour of dialysis session. Plasma levels of vancomycin were measured immediately before next HD (preHD1) and after (postHD1), and prior to the beginning of the second next session (preHD2). We evaluated age, sex, dry height, week Kt/V and the type of membrane used.* Results: *Of 28 patients, 5 were analysed 3 times, 2 were analysed twice and 9 were analysed once . There were 43 samples, 19 men (44.2%) and 24 women (55.8%), with a mean age of 70 ± 8,4 years. 1 g dose is equivalent to > 15 mg/kg in 31 patients (72.1%) and < 15 mg/kg in 12 (27.9%). The type of membrane used was high flux polyetersulfone (PES-AP) (44.2%), eval (7%), medium-low polyetersulfone (PES-BP) (32.5%) and polyacrylonitrile (16.3%). PreHD1 mean concentration results for the total population was 7.06 mg/ml, being 16.3% bellow optimum levels. There were not difference between patients treated with dose > 15 mg/kg (7.5 mg/ml) and < 15 mg/kg (6 m/ml). When the dose administered was > 15 mg/kg, 6.45% results were subtherapeutic, whereas if the dose was < 15 mg/kg, 41.67% values were bellow optimum levels (p < 0.05). With regard to the dialyzers used, the lowest concentrations were observed with PES-AP (5.95 mg/ml) and the highest values were observed with PES-BP (7.27 mg/ml) (p no significance). No patient using PES-BP* versus *31.58% patients using PES-AP showed suboptimum values (p = 0,07). All postHD1 and preHD2 results were in subtherapeutic range (mean values, dose > and < 15 mg/kg and all types of membrane).* Conclusions: *Based on the above results, the vancomycin dosing schedule of 1 g IV every 5-7 days is not recommended for patients undergoing haemodialysis with high flux membranes. Since there are not guidelines for handling this antibiotic in these patients our findings suggest that it may be necessary to monitorize predialysis plasma levels to avoid subtherapeutic values.*

Key words: *Vancomycin. Optimum levels. Haemodialysis. Dosing.*

RESUMEN

Dado el amplio uso de vancomicina en hemodiálisis (HD) es necesario adecuar la dosificación con las actuales membranas de diálisis, asegurando niveles óptimos. *Objetivo:* Valorar si, en HD, tras 1 gramo intravenoso (IV) los niveles plasmáticos de vancomicina se encuentran en rango terapéutico. *Material y métodos:* Estudio de cohorte transversal que incluye 28 pacientes en HD 3 veces/semana tratados con vancomicina entre el 15/2/2006 y el 14/2/2007. Se administró 1 gramo IV durante la última hora de HD, determinando niveles antes y después de la sesión siguiente (preHD1, postHD1) y antes de la 2ª sesión siguiente (preHD2). *Resultados:* De los 28 pacientes, 5 presentaban 3 determinaciones y 5 presentaban 2 y el resto 1. De las 43 muestras, 19 eran hombres (44,2%) y 24 mujeres (55,8%), con edad media 70 ± 8,4 años. La dosis de 1 gramo correspondía a > 15 mg/kg en 31 pacientes (72,1%) y < 15 mg/kg en 12 (27,9%). El 44,2% utilizaban polietersulfona de alta permeabilidad (PES-AP), 7% eval, 32,5% polietersulfona de media-baja permeabilidad (PES-BP) y 16,3% poliacrilonitrilo. El nivel medio preHD1 fue 7,06 mcg/ml, 7,5 mcg/ml para la dosis > 15 mg/kg y 6 mcg/ml para < 15 mg/kg (p < 0,05). El 16,3% presentó niveles por debajo del rango terapéutico, siendo 6,45% para una dosis > 15 mg/kg frente a 41,67% para la dosis < 15 mg/kg. Respecto a los dializadores, los niveles más bajos se observaron con PES-AP (5,95 mcg/ml) y los más elevados con PES-BP (7,27 mcg/ml) (p no significativa). Ningún paciente con PES-BP se encontró en rango infraterapéutico, frente a 31,58% con PES-AP (p = 0,07). Los valores postHD1 y preHD2 se encontraban en niveles subóptimos, tanto la media como los que recibían > 15 mg/kg y < 15 mg/kg, y en todos los dializadores. *Conclusiones:* La administración de 1 gramo IV de vancomicina cada 5-7 días no es adecuado para pacientes en HD, sobre todo cuando se utilizan membranas de alto flujo. Mientras no se actualizan las pautas de dosificación es necesario monitorizar los niveles prediálisis del fármaco para evitar concentraciones infraterapéuticas.

Palabras clave: Vancomicina. Niveles óptimos. Hemodiálisis. Dosificación.

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INTRODUCTION

Vancomycin is an antibiotic produced by *Streptomyces orientalis*, an actinomycete isolated from soil samples in Indonesia and India. Vancomycin is a glycopeptide with

Table I. Baseline sample description

	n	%	CI
Sex:			
Males	19	44.20%	(21.86; 66.53)
Age:			
< 65 years	11	25.60%	(0.0; 51.39)
65-74 years	23	53.50%	(33.11; 73.88)
> 75 years	9	20.90%	(0.0; 47.46)
Dose:			
> 15 mg/kg	31	72.10%	(56.31; 87.88)
< 15 mg/kg	12	27.90%	(2.52; 53.27)
Dialyzer:			
HP-PES	19	44.20%	(21.86; 66.53)
EVAL	3	7,00%	(0.0; 35.87)
LP-PES	14	32.50%	(7.96; 57.03)
PAN	7	16.30%	(0; 43.66)

CI: Confidence interval.
HP-PES: high-permeability polyethersulphone; LP-PES: middle-low-permeability polyethersulphone; PAN: polyacrylonitrile.

bactericidal action that acts by inhibiting peptidoglycan synthesis in the cell wall. It is poorly absorbed by the oral route, and is excreted in large amounts in feces. Following intravenous (IV) administration to subjects with normal kidney function, plasma protein binding is 10%-55%. Eighty percent of the drug is excreted unchanged by glomerular filtration, with a half-life of 6-8 hours. In patients with advanced renal failure (RF), half-life may be up to 150-250 hours, and plasma protein binding is 18%.[1] Despite its low molecular weight (1,449 kD), vancomycin is not removed by conventional hemodialysis (HD) with low flux membranes, such as cuprophan, but its removal is increased when high permeability filters, such as polysulphone, polyacrylonitrile, or polymethylmethacrylate, are used. Monitoring of vancomycin plasma levels allows for ensuring therapeutic levels (5-10 mcg/dL) and avoiding toxic levels.

Because of the high rate of infections by *Staphylococcus aureus* (St), often methicillin-resistant, and frequently related to the vascular access,[2] vancomycin is widely used in patients on HD. Moreover, dosing is simple according to the conventional administration regimen, since the drug is infused at the end of the dialysis session and no dose is required in the period between dialyses. Its use, however, does not always results in germ eradication, even in cases where antibiotic susceptibility tests show the organism to be susceptible to the drug.

A study was therefore undertaken to assess whether this conventional regimen consisting of administration of vancomycin 1,000 mg IV during the final hour of the HD session was effective for maintaining therapeutic levels of the drug.

MATERIALS AND METHODS

This was a quasi-experimental intervention study with no control group enrolling all HD patients treated with vancomycin from February 15, 2006 to February 14, 2007 regardless of treatment nature (therapeutic or prophylactic), age, and associated comorbidity. Patients who had received drug doses within the previous 30 days were excluded from the study. Vancomycin 1 g, diluted in 250 mL of saline, was infused in the venous line during the final hour of the HD session, and drug plasma levels were measured before and after the next session (pre-HD_1 and post-HD_1) and before the second next session (pre-HD_2). Optimum plasma levels were defined as 5-10 mcg/mL. Conventional HD with bicarbonate bath, with a blood flow of 300 mL/min and a dialysis fluid flow of 500 mL/min, was performed in all cases, and no special techniques (hemodiafiltration, on-line hemodialysis, hemofiltration) were used in any patient.

Drug levels were measured by a procedure of fluorescence polarization immunoassay (FPIA) using the AxSYM Vancomycin II® system (Abbott Laboratories).

Variables analyzed included age, sex, dry weight, dialyzer membrane and surface area, and weekly Kt/V (total Kt/V was used in patients with residual diuresis). The milligrams per kilogram of weight corresponding to the total 1,000 mg dose were calculated. Clinical histories and microbiological laboratory databases were reviewed to assess the reason for vancomycin administration (prophylactic vs therapeutic).

Data are given as mean and standard deviation for quantitative variables, and as percentage for qualitative variables. Ninety-five percent confidence intervals were calculated. Statistical tests used included a Chi-square test to compare qualitative variables within the groups in the pre-HD_1, post-HD_1, and pre-HD_2 phases, and the non-parametric tests of Mann-Whitney, Wilcoxon, median, and McNemar Chi-square for paired data for phase comparison.

RESULTS

Thirty-three patients, 28 undergoing HD for 240 min three times weekly and 5 on daily HD lasting 135 min. The latter group was excluded because of the small sample size. Among the 28 patients enrolled, 3 studies and 2 studies were performed in 5 patients each, and a single study was done in all other patients. A total of 43 studies were therefore performed. As above discussed, in patients where more than one study was done, the interval between vancomycin doses was longer than one month to prevent interference with data.

Among the 43 samples taken, 19 were from males (44.2%) and 24 from females (55.8%). Mean patient age was 70 years (CI: 67.5; 72.6). Patient age was older than 65 years in 74.4% of cases, and older than 75 in 20.9%. The 1000 mg dose corresponded to > 15 mg/kg of weight in 31 patients (72.1%) and to < 15 mg/kg in 12 patients (27.9%) (table I).

As regards dialyzers, polyethersulphone membranes 1.8 m^2 in surface with a ultrafiltration coefficient (KUF) of 72 mL/h/mmHg (HP-PES) were used in 44.2% of patients, 1.3

Table II. Pre-HD$_1$ vancomycin plasma levels

	n	Levels (mcg/mL)	p-value*	% subtherapeutic (CI)	p-value**
Total	43	7.05 (6.2; 7.91)		16.3 (5.25; 27.34)	
Dose:					
> 15 mg/kg	31	7.45 (6.37; 8.54)	NS	6.45 (0; 15.09)	< 0.05
< 15 mg/kg	12	6.01 (4.92; 7.11)		41.67 (13.77; 69.56)	
Age:					
< 65 years	11	8.43 (7.23; 9.63)	NS	0 (0; 0)	< 0.05
65-74 years	23	6.85 (5.54; 8.15)		13.04 (0; 26.8)	
> 75 years	9	5.89 (4.32; 7.45)		44.44 (11.97; 76.9)	
Dialyzer:					
HP-PES	19	5.945 (5.02; 6.87)	NS	31.58 (10.67; 52.48)	0.08
LP-PES	14	7.271 (6.18; 8.353)		0 (0; 0)	
PAN	7	7.112 (5.88; 8.336)		14.29 (0; 40.21)	

*Mann Whitney's test.
**Chi-square test.
CI: Confidence interval.
HP-PES: high-permeability polyethersulphone; LP-PES: middle-low-permeability polyethersulphone; PAN: polyacrylonitrile.

m^2 EVAL membranes with a KUF of 11.1 mL/h/mmHg (EVAL) in 7% of patients, 1.68 m^2 polyethersulphone membranes with a KUF of 20 mL/h/mmHg (LP-PES) in 32.5% of patients, and 1.4 m^2 polyacrylonitrile membranes with a KUF of 50 mL/h/mmHg (PAN) were used in 16.3% of patients.

Mean pre-HD$_1$ vancomycin plasma levels were 7.06 mcg/mL, with no sex differences. Higher levels were found among patients < 65 years, and lower levels were seen in patients aged > 75 years. Subtherapeutic levels were found in 16.3% of measurements (Table II). When patients receiving doses > 15 mg/kg and < 15 mg/kg of weight were compared, the values were 7.5 and 6.0 mcg/ml respectively, but the difference was not statistically significant. Subtherapeutic levels were seen in 6.45% of patients given > 15 mg/kg and in 41.67% of patients given < 15 mg/kg ($p < 0.05$). As regards the different dialyzers, EVAL was excluded because of the small sample size. The lowest levels were found in patients dialyzed with HP-PES (5.95 mcg/mL), and the highest values in those using LP-PES (7.27 mcg/ml) ($p < 0.05$), with slightly lower levels seen

Table III. Post-HD$_1$ vancomycin plasma levels

	n	Levels (mcg/mL) CI	p-value*	% subtherapeutic (CI)	p-value**
Total	43	4.43 (3.96; 4.91)		62.79 (48.34; 77.23)	
Dose:					
> 15 mg/kg	31	4.5 (3.95; 5.05)	NS	61.29 (44.14; 78.43)	NS
< 15 mg/kg	12	4.25 (3.28; 5.23)		66.67 (39.99; 93.34)	
Age:					
< 65 years	11	4.94 (4.35; 5.52)	NS	45.54 (16.1; 74.97)	NS
65-74 years	23	4.28 (3.54; 5.02)		69.57 (50.76; 88.37)	
> 75 years	9	4.2 (3.15; 5.26)		66.67 (35.87; 97.46)	
Dialyzer:					
HP-PES	19	4.04 (3.34; 4.74)	NS	68.42 (47.51; 89.32)	NS
LP-PES	14	4.45 (3.74; 5.17)		64.29 (39.19; 89.38)	
PAN	7	4.18 (3.52; 4.83)		71.43 (37.96; 100)	

*Mann Whitney's test.
**Chi-square test.
CI: Confidence interval.
HP-PES: high-permeability polyethersulphone; LP-PES: middle-low-permeability polyethersulphone; PAN: polyacrylonitrile.

Table IV. Pre-HD$_2$ vancomycin plasma levels

	n	Levels (mcg/mL)	p-value*	% subtherapeutic	p-value**
Total	35	4.27 (3.71; 4.83)		65.71 (49.98; 81.43)	
Dose:					
> 15 mg/kg	24	4.6 (4; 5.2)	NS	66.67 (47.81; 85.52)	NS
< 15 mg/kg	11	3.55 (2.42; 4.68)		63.64 (35.21; 92.06)	
Age:					
< 65 years	9	5.19 (4.3; 6.07)	NS	55.56 (23.09; 88.02)	NS
65-74 years	19	4.04 (3.21; 4.86)		63.16 (41.46; 84.85)	
> 75 years	7	3.72 (2.7; 4.74)		85.71 (59.78; 100.0)	
Dialyzer:					
HP-PES	18	3.69 (2.85; 4.53)	NS	66.67 (44.89; 88.44)	NS
LP-PES	10	4.73 (3.84; 5.61)		70 (41.59; 98.4)	
PAN	6	4.72 (4.09; 5.34)		66.67 (28.95; 100.0)	

*Mann Whitney's test.
**Chi-square test.
CI: Confidence interval.
HP-PES: high-permeability polyethersulphone; LP-PES: middle-low-permeability polyethersulphone; PAN: polyacrylonitrile.

for PAN (7.11 mcg/mL). No patient dialyzed with LP-PES was found subtherapeutic levels, while such levels were seen in almost one third of patients using HP-PES (31.58%) (p = 0.08).

An analysis of the post-HD$_1$ values (table III) showed that both the mean levels and those found in patients receiving > 15 mg/kg and < 15 mg/kg were subtherapeutic, regardless of the dialyzer used. As regards the percentage of patients, 2/3 had subtherapeutic levels. The same occurred with pre-HD$_2$ levels (table IV). Table V summarizes the pre-HD$_1$, post-HD$_1$, and pre-HD$_2$ data.

DISCUSSION

Vancomycin is an antibiotic widely used in HD units because of the high rate of infections, most of them related to the vascular access, caused by Gram-positive organisms, mainly *St. aureus*.[2] Vancomycin is the empiric treatment of choice for these patients, usually combined with gentamicin, with which it has a synergistic effect.

The standard vancomycin dose for RF patients on HD was 1 g or 30 mg/kg every 7-10 days. However, in recent years, introduction of new dialysis membranes with an increased permeability and use of more effective dialysis

Table V. Vancomycin plasma levels in preHD$_1$, postHD$_1$ and preHD$_2$ monitoring

	PreHD$_1$	PostHD$_1$	PreHD$_2$	p-value*
Total	7.05 (6.2; 7.91)	4.43 (3.96; 4.91)	4.27 (3.71; 4.83)	0.000
Dose:				
> 15 mg/kg	7.45 (6.37; 8.54)	4.5 (3.95; 5.05)	4.6 (4; 5.2)	0.000
< 15 mg/kg	6.01 (4.92; 7.11)	4.25 (3.28; 5.23)	3.55 (2.42; 4.68)	0.000
Age:				
< 65 years	8.43 (7.23; 9.63)	4.94 (4.35; 5.52)	5.19 (4.3; 6.07)	0.001
65-74 years	6.85 (5.54; 8.15)	4.28 (3.54; 5.02)	4.04 (3.21; 4.86)	0.018
> 75 years	5.89 (4.32; 7.45)	4.2 (3.15; 5.26)	3.72 (2.7; 4.74)	0.000
Dialyzer:				
HP-PES	5.945 (5.02; 6.87)	4.04 (3.34; 4.74)	3.69 (2.85; 4.53)	0.000
LP-PES	7.271 (6.18; 8.353)	4.45 (3.74; 5.17)	4.73 (3.84; 5.61)	0.001
PAN	7.112 (5.88; 8.336)	4.18 (3.52; 4.83)	4.72 (4.09; 5.34)	0.006

*Kendall's W test.
HP-PES: high-permeability polyethersulphone; LP-PES: middle-low-permeability polyethersulphone; PAN: polyacrylonitrile.

techniques with an increased clearance of substances, including drugs, has made this administration scheme inadequate. It is therefore important to ascertain whether the administered dose achieve plasma vancomycin concentrations within the therapeutic range (5-10 mcg/dL) in order to ensure adequate therapy, avoiding the side effects occurring at high levels and the lack of efficacy resulting from subtherapeutic levels.

In our study, 44 hours after a 1,000 mg vancomycin dose administered during the final hour of a HD session (before the next session), mean drug levels were 7.06 mcg/mL, and values fell to 4.44 mg/mL (37%) during the subsequent session. Similarly, 16% of patients initially had subtherapeutic levels, and the proportion increased to 62.8% at the end of the session. That is, almost two thirds of patients had no adequate levels after a HD session 48 hours after drug administration. These figures are lower than the 83% reported by the Bravo et al group,[3] though these authors studied patients on special techniques, on-line HD or AFB. If, in addition, the procedure use to measure antibiotic levels (FPIA) overestimates actual drug levels,[4] vancomycin concentrations would be lower, and the proportion of patients with subtherapeutic levels would be even higher.

In agreement with other authors that reported no differences in drug removal between different high-flux HD membranes,[5-7] we also found similar post-HD levels for the 3 membrane types used, although pre-HD_1 values were significantly lower in the group dialyzed with high-permeability polysulphone, which may be related to the proportion of drug cleared during antibiotic administration in the last hour of the previous session. In this regard, Scott et al[8] demonstrated that vancomycin administration during the final HD hour was associated to lower levels as compared to administration after dialysis in both patients using cellulose triacetate and cellulose acetate membranes. Foote et al[9] in turn reported a 46% decrease in drug levels during a HD session using high-permeability polysulphone. DeSoi et al also found that after IV administration of 1 g, 43% of the drug is removed during HD using cellulose triacetate and polysulphone membranes, 35% with polyacrylonitrile membranes, and only 6% with cuprophan membranes. The Torras et al group[10] similarly reported a vancomycin clearance of 9.7 mL/min in a group of patients dialyzed with cuprophan. However, vancomycin clearance increased to 58.4 mL/min when the same patient group was dialyzed with polyacrylonitrile. Quale et al also found post-HD vancomycin levels representing 63% of pre-HD levels in 6 patients on chronic HD with polyacrylonitrile membranes.[11] In a clinical review of several studies in patients on hemodialysis, Launay-Vacher et al[12] concluded that vancomycin is not significantly dialyzed when low-flux membranes such as cuprophan membranes are used, but is dialyzed when high-flux membranes such as those of polysulphone, polyacrylonitrile, or polymethylmethacrylate are used.

Although vancomycin concentrations have been reported to sharply decrease during the HD session, they subsequently increase at the end of the session for 3-6 hours due to a rebound effect. Such rebound is due to the release of the drug bound to plasma protein and is variable. For some authors it is approximately 16%,[13] while others report higher figures. Thus, Pollard et al[14] found a 36% rebound in patients treated with polysulphone membranes, DeSoi et al[5] a 19% rebound in patients using cellulose triacetate, polyacrylonitrile and polysulphone membranes, and Bravo et al[3] reported a 21% rebound when polyacrylonitrile and polysulphone membranes were used. No measurements were made in our study 2 hours after HD, but since concentrations could be 70% of pre-HD levels, they would be 4.95 mcg/mL, and therefore below the therapeutic range, as also confirmed by the levels found before the next session.

In agreement with other authors,[3] no correlation was found either in our study between vancomycin levels and Kt/V, although the Scott et al group[8] showed that in patients dialyzed with cellulose triacetate, decreased drug levels did correlate to t/V.

The inconvenience of a 1 g dose every 7-10 days in patients on special techniques has already been reported, as well as drug removal when high-flux membranes (polyacrylonitrile, polymethylmethacrylate, or polysulphone) are used.[12] Our study supports these data. Zoer et al[7] recommended a loading dose of vancomycin 1 g IV followed by 500 mg after each HD session, and the Barth et al group[15] proposed a loading dose of 20 mg/kg with the same maintenance dose.

Further studies are required to help reach a consensus on the most adequate administration scheme of vancomycin for patients with chronic RF on HD, adapted to the new dialysis techniques and membranes. Meanwhile, drug plasma levels should be monitored in these patients to avoid subtherapeutic concentrations.

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