Behavior of vancomycin with the new techniques in hemodialysis

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SUMMARY

When using high convection dialysis techniques it arouses the necessity of considering the suitability of the regular protocols when administrating drugs, such as vancomycin.

Objectives: *To confirm if the usual guideline of vancomycin is efficient in patients undergoing treatments with acetate free biofiltration (AFB) and haemodiafiltration on-line (on-line). To propose an alternative guideline of administration.*

Material and methods: *13 patients treated with AFB or On-line. 10 of them used filters of polysulfone and 3 of them of AN69. First part: 6 patients were administered 1 g iv during the last hour of dialysis. Second part: 7 patients were given a loading dose of 30 mg/kg iv with a reinforcement of 500 mg post-dialysis. The blood levels of the antibiotic were monitorized during the week following the administration.*

Outcomes: *During the first phase it was noticed a decrease of 41% in the serum level of vancomycin during dialysis, conditioning subtherapeutic levels in the 83% of the patients until the end of the study. As for the second phase, therapeutic non-toxic levels were maintained during the whole study. The existence of a post-dialysis rebound of the 21% was confirmed. A bigger clearance of vancomycin was obtained with the On-line technique rather than with AFB (176* vs *135 ml/min). We find a strong correlation between the decrease of the antibiotic and the volume ultrafiltrated with the On-line technique.*

Conclusions: *The usual guideline of vancomycin may not be enough with the new convective dialysis techniques. A guideline based on a loading dose of 30 mg/kg and a reinforcement of 500 mg at the end of each dialysis could be adequate. The antibiotic clearance with the On-line technique is probably made by convective transport.*

Key words: ***Vancomycin. Haemodiafiltration. On-line. AFB.***

COMPORTAMIENTO DE LA VANCOMICINA CON LAS NUEVAS TÉCNICAS DE DIÁLISIS

RESUMEN

Con el uso de técnicas de diálisis de alta convección surge la necesidad de plantearse la idoneidad de los protocolos habituales de administración de algunos fármacos, como la vancomicina.

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Objetivos: *Confirmar si la pauta habitual de vancomicina es eficaz en pacientes a tratamiento con biofiltración libre de acetato (AFB) y hemodiafiltración en línea (On-line). Proponer una pauta alternativa de administración.*

Materiales y métodos: *Trece pacientes a tratamiento con AFB u On-line. Diez utilizaban filtros de polisulfona y 3 de AN69. Primera parte: a 6 pacientes se les administró 1 g iv de vancomicina en la última hora de diálisis. Segunda parte: a 7 pacientes se les administró una dosis de ataque de 30 mg/kg iv durante las dos últimas horas de diálisis, con un refuerzo de 500 mg post-diálisis. Se hizo un seguimiento de los niveles sanguíneos del antibiótico durante la semana siguiente a la administración.*

Resultados: *En la primera fase se observó un descenso del 41% de los niveles séricos de vancomicina durante la diálisis, condicionando niveles subterapéuticos en el 83% de los pacientes hasta el final del estudio. Durante la segunda fase se consiguió mantener niveles terapéuticos y no tóxicos durante todo el estudio. Se confirmó la existencia de un rebote post-diálisis del 21%. Con la técnica de On-line se conseguía un mayor aclaramiento de vancomicina que con AFB (176* vs *135 ml/min). Encontramos una fuerte correlación entre el descenso del antibiótico y el volumen ultrafiltrado con la técnica de On-line.*

Conclusiones: *La pauta habitual de vancomicina puede resultar insuficiente en pacientes a tratamiento con On-line y AFB. Podría ser adecuada una pauta basada en una dosis de ataque de 30 mg/kg y un refuerzo de 500 mg al final de cada diálisis. Posiblemente el aclaramiento de este antibiótico con la técnica de On-line se produzca por transporte convectivo.*

Palabras clave: ***Vancomicina. Hemodiafiltración. On-line. AFB.***

INTRODUCTION

Vancomycin is a frequently used antibiotic used in dialysis for its efficacy in gram-positive infections.[1] It is a tricyclic glycopeptide with a molecular weight of 1148 Daltons, with a large distribution volume, similar to urea, and a binding to plasma proteins that ranges from 10-50%.

In people with normal renal function, 80-90% of the administered dose is cleared non-metabolized by glomerular filtration, with a mean clearance time of 5-8 hours. In individuals with advanced renal failure, its clearance time increases up to 150-250 hours[2,3].

Due to its molecular features, vancomycin is not cleared by conventional hemodialysis using low-efficiency filters. The usual dose when using this technique is 1000 mg post-hemodialysis weekly.[4]

Drug monitoring is aimed at assuring that therapeutic levels between 10-20 µg/mL are reached, avoiding peak levels higher than 40-50 µg/mL to prevent its toxicity.[5,6,7].

For the last decade, new dialysis techniques comprised in a group known as hemodiafiltration (HDF)[8,9], and characterized by increasing convection, have gained interest. Among them free biofiltration with acetate (ABF) and on-line hemodiafiltration stand out, in which the use of high-permeability membranes (polysulfone, polyacrilonitrile (PAN)) allows for performing hemodialysis and hemofiltration simultaneously.[10,11] The main advantage of increasing convective transportation is greater depuration of high and intermediate molecular weight solutes,[12] among which vancomycin would be included. Although a greater vancomycin clearance has been shown in patients on high-flow hemodialysis (HFHD) with high-permeability membranes[13-15], there are no studies that assess its clearance by HDF techniques. Thus, the question is raised whether usual vancomycin doses uses in conventional hemodialysis may be appropriate for use in patients dialyzed with «on-line» or ABF techniques.

Therefore, the aim of this study is to confirm whether the vancomycin administration schedule allows reaching therapeutic levels in patients dialyzed with ABF or «on-line» techniques. If this were not the case, we would try to propose an alternative administration schedule.

MATERIALS AND METHODS

Patients

Thirteen patients with chronic renal failure treated with hemodiafiltration for longer than 1 year were

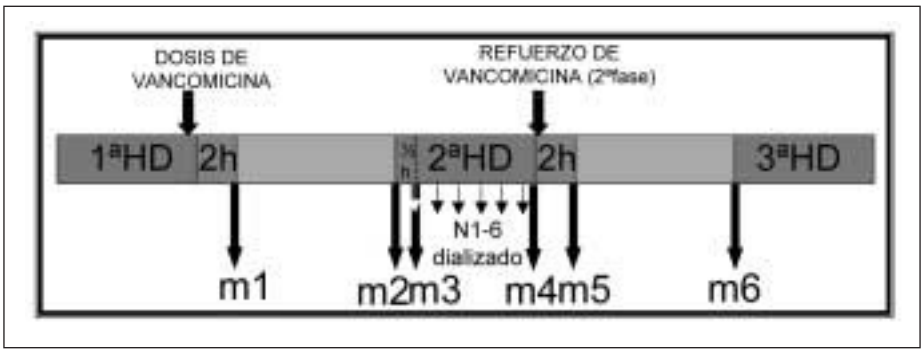

Fig. 1.—Vacomycin administration protocolos and samples collection.

included: 6 with «on-line» and 7 with ABF. The duration of the sessions was 3,5-4 h, with a Qb of 400 mL/min and Qd of 750 mL/min.

The membranes used were made of polysulfone (1.8m^2, KUF 40 mL/h/mmHg, KOA 800) in 10 patients and AN-69 (1.53m^2, KUF 46 ml/h/mmHg, KOA 750) en 3 patients. None of them was allergic or had received vancomycin treatment for the last 3 months.

Patients included in this study did not present signs of infection. All of them were informed about the procedures, objectives, and risks of the treatment, and signed an informed consent.

Study Protocol

The study was divided into two phases:

In both phases, the antibiotic was administered for the last hours of the first hemodialysis session of the week. The infusion was through the venous branch.

During the first phase, 6 patients (3 On-line and 3 ABF) were included. On thousand milligrams of vancomycin were administered during the last hour of the first hemodialysis session of the week.

In the second phase, 7 patients (3 On-line and 4 ABF) were studied. They received a loading dose of the antibiotic (2000 mg; approximately, 30 mg/kg) for the last two hours of hemodialysis and a 500 mg build-up dose post-hemodialysis in the following session (30% of the loading dose).

The scheme of the study is depicted in Figure 1:

The *first determination* of the antibiotic levels (mL) was done 2 hours after its administration, drawing blood from a peripheral vein. The next 3 determinations were done during the second session of the week:

– *2nd determination* (m2) prior to session beginning,

– *3^{d} determination* (m3) within 30 minutes of hemodialysis, and

– *4th determination* (m4) after ending dialysis.

La *fifth determination* (m5) was obtained 2 hours after the end of the second session. The *last determination* (m6) was prior to the third session of the week.

Besides, six 5 mL samples were obtained from the dialysis fluid at 30 min intervals during the second session.

Levels Determination

The determination was done by means of a polarized fluorescent immunoassay (FPIA) with a TDx analyzer (Abbott Científica SA, Madrid).

Data Analysis

Standard equations were used to estimate the dialysis clearance:

CL: R/AVC

Where R is recuperated vancomycin in the dialysis fluid, and AUC the area under the curve.

Due to the technical impossibility of retrieving large volumes, the amount of vancomycin in the dialysis fluid was calculated using the mean of the levels obtained in the 6 fluid samples multiplied by the volume used in each dialysis.

The statistics used for data analysis were: Mann-Whitney, U-Wilcoxon, T-Student and Spearman's correlation test.

RESULTS

The results from the first study phase are presented in Table I:

Table I. First phase results

Patient	Wight (kg)	Dose (mg/kg)	HD type	Time (min)	UF (L)	KT/V	% Decrease	% Rebound	% PreHD value	VANCO CL (mL/min)
1	51	19.6	O-L	210	16.6	1.43	52	20	60	199.7
2	57.9	17.3	AFB	240	8.2	1.38	55.8	38.9	74	210.2
3	74.5	13.42	O-L	240	18.4	1.35	38.9	11.7	70	124.5
4	57	17.5	AFB	210	9.5	1.37	24	16	76	86
5	80	12.5	AFB	240	7.6	1.46	31.8	8.4	75	97.6
6	67	14.9	O-L	210	18.7	1.47	46.8	21	78	153.3
	64.10	15.8 ± 3		225 ± 16	12.2 ± 5	1.41	41.5 ± 12	20.6 ± 12	72 ± 6	145 ± 50

VANCO CL: vacomycin clearance: R/AUC.

Mean weight of the 6 studied patients was 64.10 kg, and they received a mean vancomycin dose of 15.8 ± 3 mg/kg. A major ultrafiltration (UF) was performed with the on-line technique (about 16-19 L/session) by contrast to ABF (about 7-9 L/session). However, the Kt/V was similar (mean 1.41) in both techniques.

During the intermediate session of the week, a decrease in vancomycin serum levels of 41.5 ± 12% was observed. After two hours of dialysis ending, there was a rebound in serum levels that showed a 20.6 ± 12% increase. This meant that the antibiotic levels within 2 hours post-dialysis were 72 ± 6% of those at the beginning of dialysis.

The calculated vancomycin clearance was 145 ± 50 mL/min.

When observing the levels course along the week (Figure 2), we note that before the beginning of the second session there were therapeutic levels (> 5 mg/mL), but their decrease during dialysis determined subtherapeutic levels (< 5 mg/mL) in 83% of the patients. After the rebound two hours after hemodialysis, levels still are subtherapeutic and remain unchanged until the end of the study in 83% of the patients.

The results from the second study phase are summarized in Table II:

The load dose administered was 30.7 ± 3 mg/kg. The levels decrease and the calculated clearance during the second hemodialysis were 45.7 ± 7% and 162.1 ± 38 mL/min, respectively, slightly higher than those of the first phase.

During this phase, patients received a 500 mg build-up dose at the end of the second session, observing two hours after its administration a level increase of 13.2 ± 4 µg/mL. When comparing levels at the beginning of the 2^{d} and 3^{d} dialysis sessions, the increase is only of 2.9 ± 3 µg/mL.

In Figure 3 we may see how starting from therapeutic levels at the beginning of the second hemodialysis, after the decrease observed during this session 60% of the patients presented subtherapeutic levels (< 5 _g/mL). With the 500 mg build-up post-hemodialysis dose of vancomycin, the levels incre-

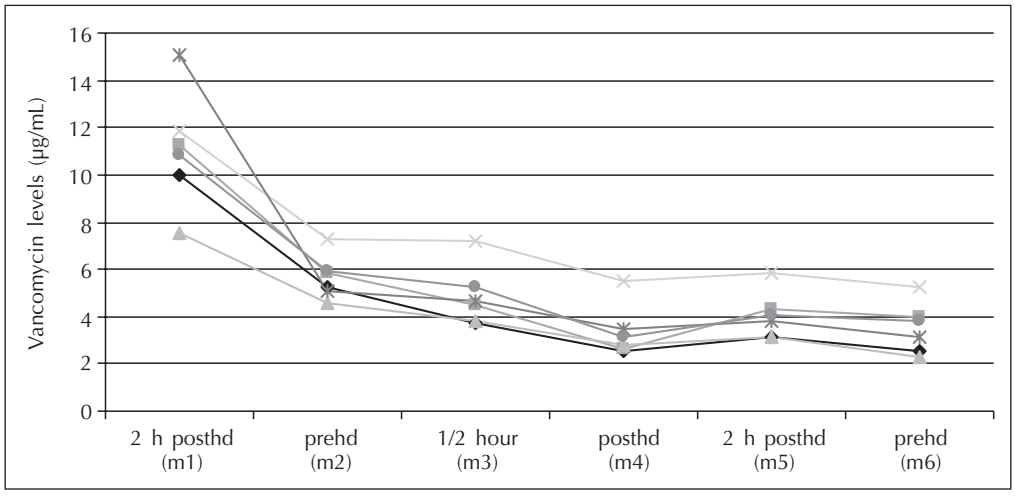

Fig. 2.—Levels progression during the firts phase.

Table II. Second phase results

Patient	Weight (kg)	Dose (mg/kg)	HD type	Time (min)	UF (L)	KT/V	% Decrease	Clearance (mL/min)	Increase after build-up	Increase between pre-HD levels
1	74.5	26.8	O-L	240	22.4	1.46	57.3	210.5	15.5	7.9
2	57	35.1	AFB	240	9.8	1.37	40	150.1	5.3	0.2
3	51	28.4	O-L	210	17.6	1.43	46.3	170	15.7	2.8
4	67.5	29.6	O-L	240	22.4	1.47	52.7	149	14.1	3.5
5	57.9	34.7	AFB	210	9.1	1.38	42.1	150	16.8	3.2
6	71.5	28	AFB	240	9.4	1.35	43.5	155	13.1	-1.2
7	80	31.2	AFB	240	8.2	1.46	37.5	100	11.5	2
	65 ± 9	30.7 ± 3		230 ± 16	14.1 ± 6	1.42	45.7 ± 7	162.1 ± 36	13.2 ± 4	2.9 ± 3

ase up to therapeutic ranges (between 10-15 _g/mL) for the remaining part of the study. No toxic levels (> 40 µg/mL) were observed throughout the study follow-up.

When comparing both phases (Table III), differences are observed only in administered doses (twice the dose in the second phase as compared to the first phase; 30.7 ± 3 mg/kg I 15.8 ± 3 mg/Kg) and in levels, which were significantly higher in the second phase and were kept in the non-toxic therapeutic range.

When comparing both techniques (Table IV), we notice significant differences in ultrafiltration volume (on-line 18.4 ± 4 L/session and ABF 8.8 ± 1 L/session; $p < 0.05$), and in vancomycin decrease (49.9 ± 6% *vs* 39.1 ± 9%) and clearance (176.6 ± 33 mL/m vs. 135 ± 43 mL/m, $p < 0.05$), which are significantly higher with the on-line technique. Although vancomycin levels are lower in patients with on-line treatment, the difference does not reach statistical significance; nor the Kt/V (1.43 *vs* 1.39).

An strong correlation was found between the decrease of antibiotic levels during dialysis and ultrafiltration volume during the session. This correlation was higher in on-line dialyzed patients and fitted a straight ascendant regression line (fig. 4).

DISCUSSION

Our study indicates that the usual vancomycin schedule may be insufficient in patients dialyzed with «on-line» or ABF techniques.

Forty-eight hours after the administration of 1000 mg of vancomycin, 83% of the patients presented subtherapeutic levels (< 5 µg/mL), after dialysis.

According to these results, and following the recommendations from other authors that demonstrated a greater vancomycin clearance by the use of HFHD with high-permeability membranes,[13-17] we designed an alternative administration schedule based upon a loading dose of 2000 mg (approximately 30 mg/kg), administered during the last two

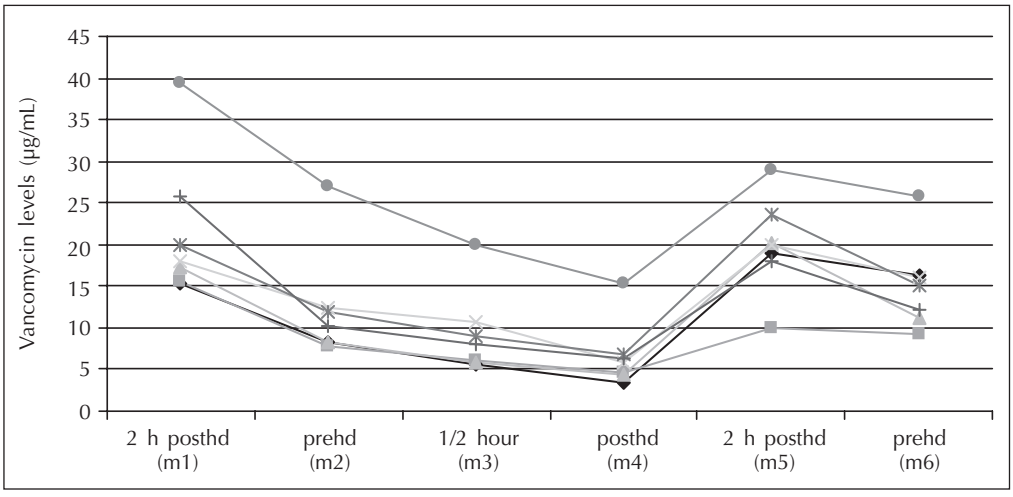

Fig. 3.—Levels progression during the second phase.

Table III. Comparison between phases

	Phase 1	Phase 2
Age (years)	64.2 ± 11	66.1 ± 9.8
Weight (kg)	64.5 ± 11	65.6 ± 10
Dose (mg/kg)	15.8 ± 3*	30.7 ± 3*
FRR (ml/min)	2.4 ± 5	2.1 ± 4
HD duration (min)	225 ± 16	231 ± 16
UF(L)	12.1 ± 5	14.1 ± 6
KT/V	1.41	1.42
Decrease (%)	41.5 ± 12	45.6 ± 7
Clearance (ml/min)	145 ± 50	162 ± 36
Peak 2 h post-infusion (m1) (µg/mL)	11.1 ± 2*	21.6 ± 8*
Level post-2nd HD (m4) (µg/mL)	3.3 ± 1*	6.7 ± 4*
Level post-2nd HD (m5) (µg/mL)	3.5 ± 1*	19.9 ± 5*&
Level pre-3d HD (m6) (µg/mL)	4 ± 1*	16.1 ± 5*

* $p < 0.05$ (Mann-Whitney, U-Willcoxon, *t*-Student).
& Peak level post-infusion of 500 mg of vancomycin within the last hemodialysis hour.

Table IV. Comparison of results with both techniques

	On-line	ABF
Age (years)	61.3 ± 12	69.3 ± 5
Weight (Kg)	64.2 ± 11	65.8 ± 11
FRR (mL/min)	2.3 ± 1	2.4 ± 1
Vancomycin Dose (mg/kg)	22.3 ± 7	25.2 ± 9
HD duration (min)	225	232
KT/V	1.43	1.39
UF (L)	18.4 ± *	8.8 ± 1*
Decrease (%)	49.9 ± *	39.1 ± 9*
Clearance (ml/min)	176 ± 33*	135 ± 43*
Rebound (%)	17.5 ± 5	17.7 ± 8
Level post-2nd HD (m4) (mg/mL)	3.2 ± 1	6.4 ± 4
Level post-2nd HD (m5) (mg/mL)	11.6 ± 9	13.4 ± 9
Level pre-3d HD (m6) (mg/mL)	8.6 ± 6	10.9 ± 8

dialysis hours, and a 500 mg postdialysis build-up dose in each session.

The levels were kept within the therapeutic range (10-25 µg/mL) throughout the study in the seven patients that received the new dose of the antibiotic.

Saunders measured 165 peak levels after the administration of 500-1500 mg IV in non-dialyzed patients, observing increases of 16.6 µg/mL within two hours of administration.[18] We found similar increases of 13.2 µg/mL after the 500 mg post-dialysis build-up dose in spite of the addition of the post-dialysis rebound.

We did not find at any time peak levels higher than 40 µg/mL that would be considered toxic.

It seems, therefore, that this could be an appropriate schedule based upon a loading dose of 30 mg/kg, administered within the last two hours of the session and reinforced with a 500 mg dose at the end of each dialysis, in patients dialyzed with hemodiafiltration techniques.

The short follow-up time of this study (1 week) forces the recommendation of monitoring vancomycin levels with prolonged treatments.

When doing determinations of plasma concentrations of the drug, the postdialysis samples underestimate real levels because of the postdialysis rebound. This phenomenon described with many drugs (cimetidine, gentamycin, and tobramycin)[19,20] and endogenous solutes (urea, creatinine)[21] occurs when the substance clearance from the vascular bed exceeds the redistribution capacity of the peripheral tissues.[22,23].

We did observe a rebound within two hours the end of the dialysis session of about 21%. At this time, the levels had recovered until representing 72% of the pre-dialysis ones.

Previous studies performed by other authors have shown this phenomenon with vancomycin.[15] Desoi *et al.* documented a 19% rebound with polysulfone, PAN and cellulose triacetate membranes.[24] Pollard *et al.* observed a 36% rebound in 11 patients dialyzed with HFHD with polysulfone.[16]

We should, therefore, recommend vancomycin monitoring by pre-dialysis determinations that although not representing true minimum values (since later on levels decrease because of dialysis) they do represent the lowest values during 90% of the interval between doses.[13]

By comparing both dialysis techniques (On-line and ABF), we observe a strong correlation between antibiotic decrease and ultrafiltration volume. This correlation, mainly due to on-line, may seem to indicate that possibly vancomycin clearance with this technique is mainly due to convective transportation.

Previous laboratory studies have suggested that convection is the main transportation system in vitamin B12 clearance (with a molecular weight similar to that of vancomycin, 1350 Da) with high-flow synthetic membranes.[25,26].

In our study, there was no correlation with Kt/V since it measures clearance of a low-molecular weight solute, such as urea, and essentially indicates diffusive transportation. We would highlight a study by Scott *et al.* that show a correlation between vancomycin decrease and Kt/V in patients dialyzed with cellulose triacetate. This leads them to hypothesize that clearance of this antibiotic with this type of membrane is essentially due to diffusion.[27] Previous studies had already shown that cellulose triacetate membrane is the only high-permeability membrane that clears high molecular weight solutes such as β2-microglobuline, essentially by diffusion.[28]

In our study we did not evaluate the possible contribution of membrane adsorption, especially AN-69,

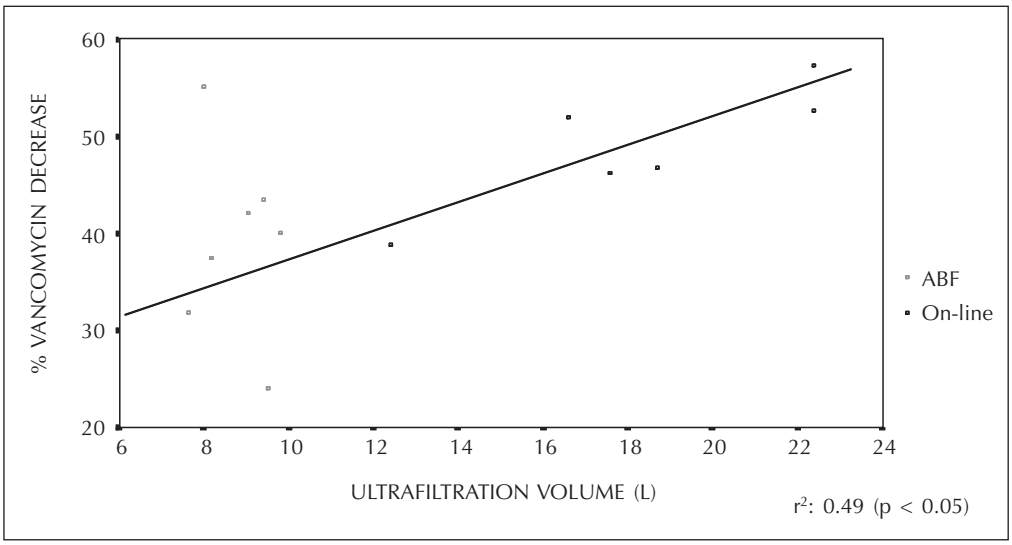

Fig. 4.—Correlation between vancomycin decrease and ultrafiltration volume.

on drug clearance. Other studies have shown the importance of this mechanism on clearance of some molecules such as â2-microglobulin, mainly by some synthetic membranes (hydrophobic) and, particularly, those with sulfone (PAN and PAMMA).[29]

We did not find differences with regards to vancomycin clearance between both membranes used (polysulfone and AN-69). Other authors such as Desio *et al.* have not find either differences in vancomycin kinetics comparing polysulfone, PAN and cellulose triacetate, indicating that membrane composition is not a determinant factor in vancomycin clearance during HFHD.[24]

A debatable issue of this study is the use of the FPIA assay since a cross-reactivity with the antibiotic by-products has been described so that real values are overestimated.[30] This fact, however, would support the observation that levels obtained with the conventional administration schedule are insufficient in patients dialyzed with HDF techniques (first study phase).

Audiometries were not performed in patients that received the highest vancomycin dose during the second phase, although we have been able to demonstrate levels lower than those considered being toxic. Besides, isolated ototoxicity seems to be extremely rare, so that systematic monitoring of peak levels of the drug has been questioned.[18,31]

Antibiotic administration in our study was done at the end of the session, during the last hour in the first phase, and during the last two hours during the second phase. Foote *et al.* have observed a significant clearance of the antibiotic administered during the last hours of dialysis using a polysulfone membrane, so that they recommend a 25mg/kg dose with that administration schedule.[17]

In this sense, both the conclusions obtained during the first study phase and the proposed schedule from the second phase are not applicable and need further studies if vancomycin were to be administered once the dialysis session would be completed.

We conclude our study indicating that the usual vancomycin administration schedule in conventional hemodialysis (15mg/kg within the last dialysis hour weekly) may be insufficient to keep the therapeutic levels in patients dialyzed with HDF techniques.

An alternative schedule could be based on a loading dose of 30 mg/kg administered during the last two hours of the dialysis session reinforced with a 500 mg build-up dose at the end of each dialysis. However, further studies assessing the efficacy and safety of this new schedule for prolonged treatments would be necessary. In the meanwhile, it is necessary to keep on monitoring vancomycin levels by means of pre-dialysis determinations.

Lastly, our study suggest that it is likely that the antibiotic clearance using on-line hemodiafiltration occurs mainly by convective transportation, although new studies will be again necessary to confirm this hypothesis.

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