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Study of Serum and Ultrafiltrate Vancomycin Levels in Patients Undergoing Predilution Online Hemodiafiltration

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Abstract

Aim: The aim of the study was to investigate the efficacy of vancomycin, when administered at a specific dose before the end of the dialysis session, in achieving therapeutic serum levels for the treatment of fistula infections or permanent venous catheter exit site infections. **Patients-Methods:** Sixteen hemodialyzed patients (6 men and 10 women), with a median age of 77 years (range 44 - 89), who were on predilution online hemodiafiltration, were studied. The diagnosis of infections was made using laboratory findings, clinical findings, and local clinical imaging. The dose of vancomycin given depended on the body weight of each patient (grouped). Vancomycin levels were measured both in serum (before and after the end of the dialysis session) and in the ultrafiltrate, which was collected in a specific barrel. In patients with residual renal function, urea and creatinine were determined in serum, as well as in urine from a 44-hour collection (to determine the patients' urea and creatinine clearances). Total protein and serum albumin levels were also determined (before and after the end of the dialysis session). **Results:** The patients were divided into 3 groups: Group A with 6 anuric patients, where the ultrafiltrate was collected only during vancomycin administration; Group B with 5 non-anuric patients with residual renal function (renal clearance from 0.865 to 6.45 ml/min), where again the ultrafiltrate was collected only during vancomycin administration; and Group C with 5 anuric patients, where the ultrafiltrate was collected throughout the whole dialysis session. In 34/64 serum samples which were taken before any dialysis session (after 44 or 68 hours of the previous vancomycin infusion), the serum vancomycin levels were subtherapeutic (<10 mg/L [where in 5 samples these were <5 mg/L]), while in 30/64 they were therapeutic (>10 mg/L). The

results also showed that the serum levels of vancomycin 44 hours after the infusion did not differ from those on the day after the long interval between dialysis sessions (Wednesday or Thursday) (p = NS). Also, in serum vancomycin levels at the end of any infusion from the second to the fifth, 9 samples were higher and 3 lower than the desired levels. In the patients with residual renal function, after 68 hours, the serum levels of vancomycin were not lower than those in anuric patients (p = NS), except for one with relatively increased renal clearance. The presence of hypoalbuminemia was found to be associated with lower serum levels of vancomycin (χ^2, $p < 0.05$) after its first administration (26/32 serum samples from patients with hypoalbuminemia had pre-session serum vancomycin levels < 10 mg/L, while in the group with normoalbuminemia 8/32 had levels < 10 mg/L). One patient with very low serum albumin levels (mean ± SD = 33.2 ± 0.4 g/L) among all patients had subtherapeutic vancomycin levels in all samples (from 3 to 5 mg/L). Comparing the removed amounts of vancomycin between the groups, a significantly higher amount was found in group C (315 ± 141 mg), compared to group A (212 ± 90 mg) and B (222 ± 118 mg), where the collection was limited only during the vancomycin infusion (p [A-C] < 0.002 and p [B-C] < 0.009). It is concluded that the levels of vancomycin achieved by its administration with a dosage that depends on body weight (not individually, but grouped, in a range of body weights) do not achieve therapeutic serum levels in about half of the samples, despite having a good clinical outcome. Vancomycin is lost throughout the entire course of the infusion (and not just during its infusion). Residual renal function should be considered when administering vancomycin, as should the presence of hypoalbuminemia, while a larger dose is not required at long intervals between the dialysis sessions.

Keywords

Predilution Online Hemodiafiltration, Vancomycin, Infection Exit Site Catheter, Fistula Infection, Hypoalbuminemia

1. Introduction

Vancomycin is a glycopeptide with a molecular weight of 1449 Da that kills Gram (+) microorganisms by inhibiting their cell wall synthesis. Its reported binding to proteins ranges from 10% - 60% (mainly to albumin and IgA globulins) [1]-[5]. Its distribution volume is 0.4 - 1.0 L/kgBW in patients with normal renal function and 0.72 - 0.9/L of body fluids in patients with end-stage renal disease (ESRD) [2] [4].

It can be administered to hemodialyzed patients, both during the session to save time for the patient and the staff (so part of its quantity is lost in the ultrafiltrate) [6], and after its end. In fact, the 1000 mg of vancomycin administered after the end of a conventional hemodialysis session should be increased to 1400 mg when it is administered during the last hour of the session, as first proposed by Ghouti-

Terki *et al.* [7]. Also, pharmacokinetic analysis showed that different parameters (type of dialyzer, dialysis method, blood supply to the filter, existence of residual renal function or hypoalbuminemia, instant of administration, etc.) interfere with its clearance. From the literature data, it does not appear that the removal of vancomycin by the polyethersulfone filters in predilution online hemodiafiltration (HDF), nor the amount of vancomycin lost during its administration during the dialysis session, parameters that were determined in the present study, have been particularly evaluated.

2. Patients Methods

2.1. Patients

The serum levels of vancomycin administered for infections of the exit site of hemodialysis catheter or fistula were studied in 16 patients on predilution online HDF. Six were men (37.5%) and 10 women (62.5%), with a median age of 77 years (range 44 - 89). The period of inclusion of patients in the study was from 06/03/2024 to 03/04/2025. Inclusion criteria were that patients were dialyzed 3 times a week, for at least 4-hour sessions, and were over 18 years of age. Patients positive for hepatitis B and C or HIV, those with a hematocrit below 28%, those known to have an allergy to vancomycin, those who were hemodynamically unstable, those who received vancomycin within the previous month of the study's beginning, or those with hearing loss were excluded from the study.

For each patient, age, sex, dry body weight, height, primary renal disease, vascular access, duration (hours) of dialysis/session, months on dialysis, and residual renal function (when present, GFR urea and creatinine were also determined) were recorded. Each patient's medications and the cause for vancomycin administration were also recorded.

Patients with infections of the vascular access (fistula) or the catheter exit site were studied, which were diagnosed by positive culture of material from the catheter exit site or fistula infection site with an obvious clinical picture of infection, with clinical diagnostic criteria (presence of fever, anorexia, local pain), episcopal (signs of inflammation of the catheter exit site or fistula), and laboratory (increased C-reactive protein [CRP], and white blood cells with polymorphonuclear type).

The study was approved by the Scientific Council of Komotini Hospital (1/2024, 29/02/2024) and was conducted in accordance with the Guidelines for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. Each patient gave written consent to participate in it, after being thoroughly informed before deciding to participate.

2.2. Study Protocol

Vancomycin was administered in doses according to the patients' body weight during the last 30 - 90 min of the dialysis session (for the convenience of patients and nurses, as is practiced in most dialysis units). The regimen suggested by Zelenitsky *et al.* was used also by Ghouti-Terki *et al.* More specifically, for patients

with a dry body weight < 70 kg, a loading dose of 1000 mg (infusion duration 60 min) was administered, followed by a maintenance dose of 500 mg/session (infusion duration 30 min). For patients with a body weight of 70 - 90 kg, the loading dose was 1250 mg, followed by a maintenance dose of 750 mg/session (infusion duration in both cases 60 min), and in patients weighing > 90 kg the loading dose was 1500 mg (infusion duration 90 min) and a maintenance dose of 1000 mg (infusion duration 60 min) [7] [8]. The duration of treatment of patients with vancomycin lasted depending on the patient's response, the type and severity of the infection, but in any case, for at least more than 5 dialysis sessions. The desired therapeutic concentration of vancomycin in serum was >10 mg/L, while 15 - 20 mg/L was considered absolutely desired [4]. For mild catheter exit site infections, concentrations as low as 5 mg/L were considered satisfactory.

The ultrafiltrate was collected in a specially constructed volumetric barrel, where the volume could be determined. After the end of the dialysis session and after stirring the ultrafiltrate with an electric stirrer for 10 min, a sample was taken for determination of vancomycin levels. In patients with catheters, blood samples were taken from the arterial limb, before and immediately after the end of the session, so that there was no impact of recirculation on serum vancomycin levels, which is increased in the sample from the venous limb of the catheter [9], while in those with arteriovenous anastomosis, samples were taken from the arterial fistula before and after the end of the session. In the blood samples taken, vancomycin levels were determined, as well as albumin and serum proteins (for patients with residual renal function, serum urea and creatinine were also determined once to determine their clearance).

2.3. Methods

All patients were on predilution online HDF (the substitution volume was 50% of the blood pump, which was 400 ml/min in all patients). Polyethersulfone (polynephron) filters (ElisioTM 21H Nipro, Japan, high flux) with a surface area of 2.1 m^2 were used, with a KoA of 1976 ml/min and a K_{UF} of 82 ml/h/mmHg. All were dialyzed with Nikkiso DBB EXA machines. In all patients, the composition of dialysate was: sodium 140 mmol/L, potassium 3 mmol/L, chlorine 106 mmol/L, bicarbonates 33 mmol/L, glucose 5.6 mmol/L, and magnesium 0.5 mmol/L. The dialysate flow rate in all patients was 500 ml/min. The duration of the dialysis session was 240 min for 14 patients and 265 min for two (**Table 1**).

All patients received low molecular weight heparin (vemiparin) as an anticoagulant before the beginning of the dialysis session, at doses ranging from 2500 - 3500 IU/session, depending on their body weight. The blood flow to the dialyzer for all patients was 400 ml/min with a negative pressure of <200 mmHg (*i.e.*, at least 0.8 - 1 m^2/200 ml/min of blood flow, meaning that at 400 ml/min of pump, a dialyzer of at least 2.0 m^2 is required, as it was used) [10].

Residual renal function was measured using creatinine and urea clearance in a 44-hour urine collection, dividing the sum of them by 2. Specifically, serum urea

Table 1. Basic characteristics of patients in each group and dose of vancomycin (loading and maintenance) (F = woman, M = man, AVF = arteriovenous fistula, CVC = central venous catheter).

Summary of clinical and other basic characteristics of the patients			
	Group A	Group B	Group C
Median age (range) Sex	77.5 (60 - 81) (4F/2M)	77 (44 - 89) (3F/2M)	80 (67 - 89) (3F/2M)
Vascular access	1 AVF/5 CVC	1 AVF/4 CVC	1 AVF/4 CVC
Months on dialysis	23.8 ± 11.4	49.2 ± 20.2	28.2 ± 19.6
Dialysis session duration (hours)	4.0 - 4.25	4.0	4.0
Dry weight (range) (kg)	79.2 ± 11.1	82.4 ± 13.1	65.6 ± 14.7
Weight gain between dialysis sessions (range) (mL)	(400 - 2700)	(440 - 3500)	(500 - 3000)
GFR [(Urea + Creatinine)]: 2 Mean ± SD (range)	0	2.63 ± 1.97 (0.865 - 6.45)	0
Vancomycin dose (loading)	1000 - 1250	1000 - 1500	1000 - 1250
Vancomycin dose (maintenance)	500 - 750	500 - 1000	500 - 1000
Outcome	Cure	Cure	Cure

and creatinine were measured in mmol/L, as well as their levels in samples of 44-hour urine collections. Clearances were determined according to the UV/P formula, where U = urine urea (or creatinine) concentration, V = urine volume in ml/min, and P = serum urea (or creatinine) concentration (in mmol/L). Hypoalbuminemia was present when pre-session serum albumin levels were <35 gr/L. To monitor the effectiveness of vancomycin, its serum levels were used before each session, while the amount removed was determined in the ultrafiltrate.

Vancomycin was determined by immunoturbidimetry, albumin by the colorimetric method, and urea and creatinine by the enzymatic method.

2.4. Statistical Analysis

The results are expressed as the arithmetic mean ± standard deviation (mean ± SD) or median and range, according to the normality of the distribution of each variable. Comparisons between groups were performed using Student's T-test and χ^2-test. Analysis was performed with the statistical software MedCalc (version 20.218). Significance levels of $p < 0.05$ (2-tailed) were considered statistically significant for all comparisons.

3. Results

Sixteen hemodialyzed patients with vascular access infections (catheter exit site [n = 13] or autologous arteriovenous fistula [n = 3]) were studied. The primary renal disease of the patients was hypertensive nephrosclerosis (n = 5), diabetic nephropathy (n = 3), cardio-renal syndrome (n = 2), glomerulonephritis (n = 1), multiple

myeloma (n = 1), and unknown (n = 4). The patients were divided into 3 groups, of which A had anuric patients (n = 6), where the ultrafiltrate was collected only during the vancomycin infusion (before the end of the session), B included patients with residual renal function, in whom the ultrafiltrate was collected again only during the vancomycin infusion (n = 5), and C included anuric patients in whom the ultrafiltrate was collected for the entire duration of the dialysis session (n = 5). The ultrafiltrate was collected in two ways (only during the vancomycin infusion or throughout the session) to see if the regimen was lost during the session (or only during the infusion time).

The diagnoses of the infections were made from the combination of positive culture of infected material and the clinical picture (n = 5), or from the obvious picture of infection, with clinical diagnostic criteria (presence of fever, anorexia, local pain), episcopal and laboratory findings (increased CRP, high white blood cells, and polymorphonuclear type) (n = 11). *Staphylococcus aureus* was isolated in 5 cases. The basic characteristics of the patients in each group and the dose of vancomycin (loading and maintenance) are shown in Table 1.

In 34/64 serum samples , which were taken before any dialysis session (after 44 or 68 hours of the previous vancomycin infusion), the serum levels of vancomycin were subtherapeutic (<10 mg/L), 5 of which were <5 mg/L, which, however, were therapeutic, as shown by the outcome of the patients (all were cured). Five patients with borderline body weight, *i.e.*, approximately 70 kg in Group A and 3 approximately in the middle of the range of weights of Group B (70 - 90 kg), had low vancomycin levels (<10 mg/L) in most blood samples. As for the higher levels that were found, before the beginning of each dialysis session, >10 mg/L were noted in Group A in 15/24 blood samples, in Group B 8/20, and in Group C 5/20 (total 28/64). This, as a result, shows that the serum vancomycin levels were not within the desired range in 50% of the samples after the infusion of vancomycin. Particularly elevated serum vancomycin levels (>25 mg/L) after infusion were found in a total of 17/64 patients. Regarding serum vancomycin levels after 3 days (*i.e.*, after 68 hours), no difference was found in comparison with those after 44 hours (χ^2, p = NS). When we saw the results of serum vancomycin levels at the end of any infusion from the second infusion to the fifth, 9 samples were higher than the desired levels and 3 lower than desired also (Figure 1).

The results showed that serum vancomycin levels after 44 hours (after a 2-day interval) did not differ from those after 68 hours (3-day interval) (p = NS). Also, those with residual renal function, after 68 hours, did not have lower vancomycin levels compared to anuric patients (p = NS), except for one woman with relatively increased urea and creatinine clearance. More specifically, the patient with the largest residual renal function had vancomycin levels of 4 mg/L 68 hours after the first dose and 5 mg/L 44 hours after the second dose. And since the dose was administered according to body weight (grouped), if the drug was somehow lost outside the dialysis session, its levels should be lower in the serum in the long interval between sessions, which is not confirmed by our results (Figure 1, Figure 2).

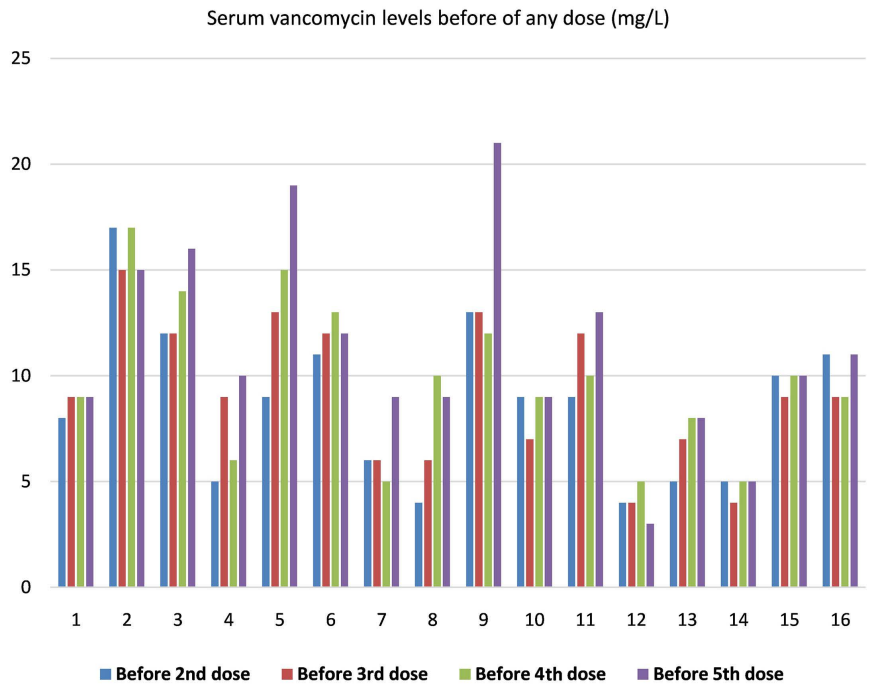

Figure 1. Contains the serum vancomycin levels before each infusion of the drug.

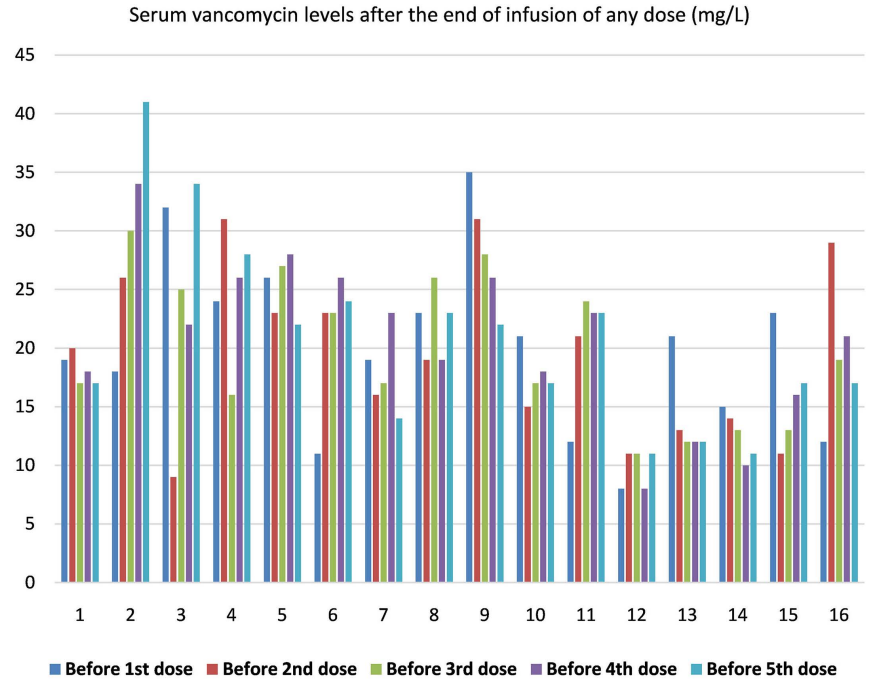

Figure 2. Contains the serum vancomycin levels after the end of each infusion in all patients.

When comparing the amounts of vancomycin removed between the groups, a significantly larger removal was found in the group in whom the entire ultrafiltrate was collected (Group C, 315 ± 141 mg), compared to groups A (212 ± 90 mg) and B (222 ± 118 mg), where the collection was limited only to the duration of the

vancomycin infusion (p [A-C] < 0.002 and p [B-C] < 0.009).

Table 2. Relationship between serum albumin and serum vancomycin levels.

						Serum vancomycin levels (mg/L)			
Patients	Weight	GFR	Load dose	Maintenance dose	Serum albumin (mean ± SD) (gr/L)	1	2	3	4
With hypoalbuminemia									
1	68	1.8	1000	500	35.0 ± 1.0	6	6	5	9
2	80	6.45	1250	750	34.0 ± 0.7	4	6	10	9
3	55	0	1000	500	30.8 ± 0.4	4	4	5	3
4	69	0.865	1000	500	30.6 ± 1.0	9	7	9	9
5	80	0	1250	750	34.2 ± 0.8	5	7	8	8
6	90.5	0	1250	750	33.2 ± 0.4	5	4	5	5
7	49.5	0.387	1000	500	31.2 ± 6.4	10	9	10	10
8	61	0	1000	500	34.4 ± 0.4	11	9	9	11
						6.8 ± 2.6	6.5 ± 1.8	7.6 ± 2.1	8.0 ± 2.5
With normal serum albumin									
1	95	1.625	1250	750	40.0 ± 0.5	13	13	12	21
2	93	0	1250	750	43.3 ± 0.8	12	12	14	16
3	64	0	1000	500	37.2 ± 3.9	8	9	9	9
4	94	0	1250	750	37.3 ± 1.9	9	13	15	19
5	78	0	1250	750	37.5 ± 0.5	17	15	17	15
6	76	0	1250	750	35.8 ± 0.7	11	12	13	12
7	70	0	1000	500	41.0 ± 0.9	5	9	6	10
8	100	2.39	1500	1000	38.6 ± 0.8	8	12	10	13
Mean ± SD						10.4 ± 3.5	11.9 ± 1.9	12.0 ± 3.3	14.5 ± 3.9
p						=NS	<0.05	<0.05	<0.05

Serum vancomycin levels were measured after 44 hours (before the beginning of the next dialysis session) to determine whether they were somehow related to the presence of hypoalbuminemia (because in hypoalbuminemia there is more unbound vancomycin to albumin and, obviously, a greater amount of it can be lost through the dialyzer). Based on this separation, two groups of 8 patients each were created (the hypoalbuminemic group with a mean serum albumin of 33.0 ± 4.5 g/L versus 38.6 ± 0.8 g/L in the group without hypoalbuminemia). It was found after the first administration that serum vancomycin levels were significantly lower in patients with hypoalbuminemia in all infusions except the first dose given [1st dose = 6.8 ± 2.6 vs 10.4 ± 3.5, p = NS, 2nd dose = 6.5 ± 1.8 vs 11.9 ± 1.9, p < 0.05, 3rd dose 7.6 ± 2.1 vs 12.0 ± 3.3, p < 0.05, and 4th dose = 8.0 ± 2.5 vs 14.5 ± 3.9, p < 0.05] (Table 2). Furthermore, in 26/32 measurements of hypoalbuminemic patients, serum vancomycin levels before the beginning of the dialysis session were found

to be <10 mg/L, levels which were considered safe for treating our patients' infections, while in the group without hypoalbuminemia, 8/32 had levels < 10 mg/L. However, it is worth noting that after the end of the session (and after the end of the vancomycin administrations), only two patients (one once and the other twice) had vancomycin levels < 10 mg/L, where the second one had the most severe hypoalbuminemia among all.

4. Discussion

Dialyzed patients are at increased risk of infections, which are the second most common cause of death among them [11]. Vancomycin is often used to treat infections caused by Gram (+) organisms, such as various types of Staphylococci (aureus and epidermidis) [12].

Vancomycin is normally mainly (80% - 90%) eliminated by the kidneys [13]; but in hemodialyzed patients, its renal clearance is usually absent. It is obvious that this is achieved by glomerular filtration, considering that it is protein-bound and that its tubular secretion also contributes to creatinine clearance, which is equivalent to 20% of its blood concentration [14] [15].

Due to the inherent difficulties in estimating the AUC (antibiotic area under the curve)/MIC (minimum inhibitory concentration) ratio, which is not easy to determine in clinical practice, the Infectious Diseases Society of America (ISDA), the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists have proposed monitoring serum vancomycin levels (trough levels) for adjusting the dosage of antibacterial therapy, due to their good correlation with AUC/MIC and the recommendation that serum vancomycin levels be maintained between 15 and 20 mg/L, avoiding levels below 10 mg/L [4], which has been found to lead to better clinical outcomes [16].

The desired maximum and minimum levels have traditionally ranged from 30 - 40 mg/L and 5 - 10 mg/L, respectively. However, Geraci's recommendation for a trough therapeutic concentration is not based on prospective clinical trial data, where the total reference vancomycin concentration of 5 - 10 mg/L is likely to be lower than the desired total vancomycin exposure for many types of infections [17]. Others have recommended minimum therapeutic serum vancomycin levels of 5 - 20 mg/L, although it is believed that microbe resistance to the drug develops when vancomycin levels are <10 mg/L [18]. Our patient's serum vancomycin levels were, in a large percentage (%) sample, below 10 mg/L; however, our patients had infections of the catheter exit site or of the fistula, and for this reason, perhaps the clinical picture improved for all and they were treated successfully.

These observations led to guidelines, which recommend maintaining a minimum serum vancomycin trough level of 10 mg/L to avoid the development of drug resistance and a concentration of 15 - 20 mg/L to optimize drug penetration into tissues and the best response in patients with severe staphylococcal infections [4], guidelines that are also agreed with by others [19], while some recommend different target trough levels, with the most common being 5 - 10 mg/L or 10 - 15 mg/L

[20].

There may also be no ideal dosing regimen for vancomycin, given that its pharmacokinetics show great variability between individuals and that this is exacerbated by various factors related to clearance (dialysis method, blood supply to the dialyzer, dialysis session duration, provided Kt/V), possibly from the volume of the substitution fluid in online HDF, the degree of hyperhydration [increase in the distribution space], ultrafiltration [21], the presence of hypoalbuminemia, residual renal function, etc. The fact that our patient with the best residual renal function had vancomycin levels of 4 mg/L 68 hours after the first dose and 5 mg/L 44 hours after the second dose indicates that those with diuresis and some residual renal function are very likely to not easily achieve therapeutic levels of vancomycin.

The binding of vancomycin to proteins is a determining factor in its pharmacokinetic and pharmacodynamic behavior. The unbound or free fraction of the drug, which is biologically active, is available for passive diffusion and binding to the sites of action. Changes in binding proteins are of clinical importance in certain patient groups, such as the critically ill, where hypoalbuminemia (which increases the concentration of unbound drug, leading to an increase in its clearance) is often observed [22], as we noted in this study. And of course, hemodialyzed patients often experience hypoalbuminemia, which highlights the need to control its levels in the serum to obtain adequate levels for vancomycin therapy [21]. In our study, it was shown that those who had hypoalbuminemia clearly had subtherapeutic vancomycin levels (<10 mg/L) more often, apparently because this played a role in the amount of vancomycin that was removed through the dialyzer and, of course, of serum levels ($p < 0.05$). This is confirmed by the fact that one patient with severe hypoalbuminemia had serum vancomycin levels <10 mg/L (especially in 5 samples that had, before the beginning of the dialysis session, serum levels <5 mg/L), which indicates that she lost vancomycin during the dialysis session because a large part of it was unbound to albumin and free to be removed through the dialyzer.

According to the literature, the most important factor affecting the reduction of serum vancomycin levels in hemodialyzed patients is the type of membrane [23]. Thus, the typical dose of vancomycin for patients on conventional hemodialysis (low flux dialyzers) was 1000 mg or 30 mg/kgBW every 7 - 10 days, where its levels decrease slightly during the dialysis session and do not need supplementary administration of the drug [1] [24]. However, in recent years, the introduction of new dialysis membranes with increased permeability (high flux and medium cut off membranes) and the use of more effective toxin clearance techniques have made this dosing inadequate.

However, in addition to the type of membrane (low or high flux), the kind of dialysis with the same filter also affects the dose of vancomycin (high flux hemodialysis or pre- or post-dilution online HDF). In high flux hemodialysis, it was found that increased loading doses are required (25 - 35 mg/kgBW), followed by maintenance doses of 7.5 - 15 mg/kgBW to achieve therapeutic levels [25],

regardless of whether they are administered during or after the end of the dialysis session, and an additional dose of 500 mg in the long interval between sessions, which achieves therapeutic levels in >90% of patients [26], which did not seem to be necessary in our patients and is not logical, since without removal through the kidneys (in anuric patients, of whom 11 were among the 16), the drug cannot be removed, nor can it be metabolized. A regimen that used 1000 mg as a loading dose and 500 mg as a maintenance dose in high flux hemodialysis was not therapeutically ideal [27].

Thus, Ghouti-Terki *et al.* studied 20 hemodialyzed patients (18 with high flux hemodialysis and 2 with postdilution online HDF), who were taking vancomycin in the last hour of the dialysis session. The loading dose, which depended on body weight, was 1000 mg if it was <70 kg, 1250 mg if it was between 70 and 90 kg, and 1500 mg if the body weight was >90 kg (administration protocol that we also used), while the maintenance dose depended on the serum vancomycin levels. The dialyzers they used were high flux (polysulfone polymethylacrylates and polyether polymers), the blood flow was >280 ml/min, the dialysate flow was 500 - 800 ml/min, and the substitution fluid was administered at a dose of 90 - 100 ml/min. The study showed that the serum concentrations achieved suboptimal drug levels in over a third of patients. However, their opinion was based on the study of only 2 patients under postdilution online HDF, so no firm conclusion could be drawn regarding a potentially increased clearance [7]. We found even lower serum vancomycin levels with the same dosing regimen, suggesting that this should not be followed in predilution online HDF, perhaps due to the large exchange volumes or other causes (dialyzer type) that we did not investigate. The fact that in our patients the collection of all ultrafiltrate (Group B), a greater amount of vancomycin was found compared to the groups where it was collected only during drug administration (Groups A and C) means that it is lost by the method or the filter. However, nowadays it is not known how much this contributes (method and type of filter), which makes it difficult to choose the appropriate dosage, when there is currently no bibliographic data, even for the newer methods (online), nor for most high flux filters.

It may also play a role whether vancomycin is administered during or after the end of the dialysis session. Many dialysis units infused vancomycin during the session, provided that the prescribed dose takes into account the loss of the drug during the session, which is approximately 20% - 40% of an infused vancomycin dose [9] [28], something with which we agree, since the removed amount of vancomycin per session was 212 ± 90 mg in group A, 222 ± 118 mg in group B, and 315 ± 141 mg in group C. Also, in the collection of the total ultrafiltrate, the loss of vancomycin was higher than the loss only during the vancomycin infusion, which means the drug is removed during the entire dialysis session for some reasons (*i.e.*, hypoalbuminemia). Thus, an accepted practice in many units is to infuse the vancomycin dose in the last hour of the session, when low flux filters are used, without changing its dosage [6] [29]. Whereas when it comes to higher

permeability dialyzers (high flux), the amount of vancomycin removed must be considered. This is because this can lead to subtherapeutic concentrations of the drug in the serum, which may not be noticed, due to the rare monitoring of drug levels in these patients. For this reason, some in these cases recommend higher doses (e.g., 25 mg/kgBW) [30], a fact supported by others, who recommend administering a 30% higher dose [25]. And this as a guideline may be wrong, because as shown in this study, 34/64 samples of the serum vancomycin levels of our patients before the beginning of each dialysis session were <10 mg/L (of which 5 were <5 mg/L), while others with the same dose had supratherapeutic serum levels. Accordingly, Nyman *et al.* found that administering 1500 mg of vancomycin intravenously during the last hour of high flux hemodialysis provides serum vancomycin concentrations like a 1000 mg dose of vancomycin administered immediately after the end of the hemodialysis session [9]. On the other hand, Taylor and Allon, by administering a loading dose of 20 mg/kgBW and a maintenance dose of 1000 mg during the last hour of high flux hemodialysis, with polysulfone dialyzers, achieved satisfactory vancomycin levels in their patients [23]. Our results clearly show that in predilution online HDF, the dosing regimen of Ghouti-Terki *et al.* that we followed [7], does not ensure therapeutic levels of vancomycin in more than 50% of serum samples of our patients. The cause of the high percentage of serum samples of our patients with low vancomycin levels may be explained by the vancomycin dose and the way it was administered (in patient groups based on body weight). Since the serum levels of vancomycin immediately after the end of the vancomycin infusion in our study were in 3 patients below the desired levels, it seems that it is difficult to achieve the desired blood vancomycin levels with the dosage regimen used. Therefore, it would perhaps be preferable to determine the dose of vancomycin based on individual body weight only and not the dose based on the body weight range of a group of patients. The reason this happens is that the weight range classifies patients into groups, and those at the extremes of the range either receive smaller doses or larger ones, but not those that are appropriate for them, while sometimes even for 1 kg in body weight, they may be classified in one group or the other (with a different dose of medication).

HDF is essentially a combination of hemodialysis and hemofiltration using the physical principles of both diffusion and convection. Low molecular weight molecules are effectively cleared by diffusion [21]. However, convection is less dependent on molecular weight, and therefore the clearance of large molecules is increased in HDF compared to conventional hemodialysis. Jager et al. concluded that larger molecules (defined as >500 Da), such as vancomycin, are likely to be cleared more by online HDF compared to high flux hemodialysis [21]. Of course, it should not be overlooked that the type of membrane also plays a role in the amount of vancomycin removed during online HDF [31]. The fact that a greater amount of vancomycin was lost in ultrafiltrate in the group where it was collected throughout the session may indicate that vancomycin is also lost during the session (not only during the infusion), apparently because there is a free (non-albumin bound)

fraction, which would mean a higher excreted amount in patients with hypoalbuminemia.

Rodríguez *et al.* studied 11 anuric dialyzed patients and compared the clearance of vancomycin with high flux hemodialysis and postdilution online HDF, with the drug administered at a loading dose of 1000 mg and a maintenance dose of 500 mg during the last 45 min of each dialysis session. They found higher clearance with online HDF ($p = 0.012$) and therefore recommended increased loading doses with this dialysis method and avoiding the administration of vancomycin during the session [32]. In fact, they found a 63% clearance of vancomycin with postdilution online HDF [32]. For this reason, Foote *et al.*, to replace the drug lost when administered during the last hour of the session, recommend a loading dose of 25 mg/kgBW [30]. In contrast, Bravo *et al.* found that a loading dose of 30 mg/kgBW intravenously, with an additional 500 mg administered after each dialysis session, resulted in therapeutic and non-toxic levels of vancomycin throughout the study with postdilution online HDF [33].

The administration of vancomycin during predilution online HDF, at a dose of 15 mg/kgBW during the last hour of the dialysis session (approximately the dose we used), does not achieve therapeutic levels in the blood (with a Polyesterpolymer filter, surface area 1.8 m^2 and with 40 L of substitution volume). The researchers found a clearance of vancomycin of 74.6 ± 20.9 ml/min and a decrease in its concentration by 50.8% ± 4.1% [34]. In our own study, with predilution online HDF, we found significant variability in the amount of vancomycin removed (4.40% - 142%), without being able to explain this, perhaps due to the small number of patients included.

The fact that there are not yet enough studies of vancomycin administration in patients undergoing online HDF (there are two others in addition to ours with a small number of patients), and we do not yet know what happens with regard to vancomycin loss with the different high flux filters that exist, and the knowledge that the low flux membranes do not allow the removal of vancomycin through their fibers, makes it logical for any staphylococcal infection in patients undergoing dialysis with high flux filters (mainly online HDF) to switch temporarily to conventional hemodialysis, to ensure better drug blood levels in a larger percentage of blood samples.

It is concluded that: 1) vancomycin doses based on a range of patient body weights may not be able to achieve safe serum vancomycin levels in all patients, 2) vancomycin administered during the dialysis session is lost during the infusion to a significant amount (depending on serum albumin levels), 3) residual renal function must be taken into account for vancomycin dosage, 4) during the dialysis session, regardless of vancomycin administration, the drug is removed, 5) a higher dose of vancomycin is not required during the long intervals between hemodialysis sessions, and 6) the determination of vancomycin levels in the blood could be a guide in diagnosing the adequacy or otherwise of the administered drug dose.

Limitations: 1) The number of patients was small per group, 2) the admini-

stration of the drug was according to a range of body weight values and not according to the individual weight of each patient, and 3) the use of one type of high flux dialyzer (polyethersulfone), while the clearance of vancomycin may differ compared to other types of high flux filters.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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