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Comparison of the Effects of Three Haemodialysis Membranes on Vancomycin Disposition

J. ALWAKEEL,* T. A. NAJJAR,** M. J. AL-YAMANI,** S. HURAIB,* A. AL-HAIDER,*** H. ABU-AISHA*

Departments of *Medicine; **Clinical Pharmacy; ***Pharmacology; College of Medicine, King Khalid University Hospital; College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

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Polysulfone (PSF) and polyacrylonitrile (PAN) were recently introduced haemodialysis (HD) membranes. The effect of each on vancomycin disposition was compared with cuprophan (SCE) in 12 chronic HD patients who received 14 infusions. Vancomycin (1 g) was infused over 1 hour, followed by three 4-hour HD sessions over 5 days, beginning 1 hour after the end of infusion. The intradialytic clearances of vancomycin were 73, 54 and 15 ml/min for PSF, PAN and SCE, respectively. At the end of the third HD session, vancomycin concentration dropped to subtherapeutic level (<7.5 μg/ml) only in patients dialysed with PSF and PAN. The corresponding elimination half-lives ($t_{1/2}\beta$) were 61, 60 and 86 hours for the three membranes, respectively. According to these findings, vancomycin should be given every three HD sessions for PSF and PAN. The dosage interval should be extended up to every 5 HD sessions for patients on SCE. The peak (mean±S.D.) obtained one hour after the end of infusion was 34.2±11.4 μg/ml, which is within the therapeutic range.

Introduction

Vancomycin is commonly used during haemodialysis (HD) for the treatment of serious staphylococcal infections, particularly against methicillin-resistant strains [1, 2]. Several investigators have studied the influence of HD on the elimination of vancomycin [3, 4, 5]. They found that the amount removed was not significant, and a single dose appeared to be adequate for a minimum of one week. Recently, the interest in using more biocompatible membranes such as polysulfone (PSF) and polyacrylonitrile (PAN) has increased [6]. These membranes are thought to be more permeable, particularly for the intermediate size molecules such as vancomycin. Because of that, it has become prudent to reexamine the impact of these changes on the dialysability of vancomycin. Recently, the permeability of the two membranes was evaluated during single HD sessions in a small number of patients [7, 8]. In this study, the effect of each on vancomycin disposition was studied during single and multiple HD sessions. The aim was to estimate the dosage interval of vancomycin during chronic HD with each membrane.

VSP, Utrecht
Akadémiai Kiadó, Budapest

Material and methods

Twelve patients with end-stage renal disease (ESRD) were involved in this study. They were on regular haemodialysis consisting of three 4-hour sessions per week. The study was approved by the hospital investigation review board and informed consent was obtained from each patient. Vancomycin (1 g) was infused over 1 hour, followed by three HD sessions, separated by 2–3 days. The first session started one hour after the end of infusion. During each session, blood samples from the arterial side were collected at 0, 0.25, 2 and 4 hours. The venous site was also sampled at the end of each session and used to calculate the clearance of vancomycin. Some of the patients were studied twice separated by a minimum of 3 weeks to end up with 14 vancomycin infusions. On the other hand, some of the patients had only two sessions after vancomycin infusion to end up with 35 HD sessions.

The flow rates to the dialysis machine were adjusted to 200 ml/min for blood and 500 ml/min for dialysate. The membranes studied were polysulfone (F-60, Fresenius), polyacrylonitrile (Hospal. AN69) and cuprophan. The surface areas (SA) were 1.25, 0.8 and 1.2 m^2, respectively, for the three membranes. The three HD sessions for eight of the 14 infusions were carried out with fixed membrane.

Vancomycin was measured by fluorescence polarization immunoassay (TD_x machines, Abbott, USA). The coefficient of variation between and within the runs is ±4%. Each sample was done as single measurements.

Data analysis

The following formula was used to calculate vancomycin clearance (CL_{vanc}).

$$CL_{vanc} = [(A - V)/A]\ [Q_b - (1 - HCT)]$$

where Q_b is blood flow, HCT is haematocrit concentration and A and V are arterial and venous concentrations, respectively.

Linear regression analysis was used to obtain the line of the best fit and to calculate the elimination half-lives of vancomycin. The mid-arterial vancomycin concentrations for the three consecutive HD sessions were the data used to estimate the elimination half-life ($t_{1/2}\beta$) postinfusion. Statistical analysis was performed using the unpaired Student *t*-test. A probability of ≤ 0.05 is considered statistically significant.

Results

The results were obtained from a total of 35 HD sessions and 14 infusions. Table 1 contains the results of clearance, half-life and the amount removed for the three membranes. Because the time elapsed between vancomy-

Table 1
Vancomycin pharmacokinetic parameters calculated from 35 HD sessions. Group A stands for sessions performed one hour after the end of infusion and Group B for sessions performed 2 and 5 days postinfusion. N is the number of HD sessions

Paremeter	PSF	PAN	SCE
Group A			
N	4	8	2
Clearance (ml/min)	76 ±18	55 ±18	15 ±17
Half-life (h)	3.6± 0.09	4.9± 1.5	5.6± 0.24
Removed (%)	50 ± 3.5	41 ± 8.9	31 ± 0.1
Group B			
N	8	7	6
Clearance (ml/min)	71 ±17	52 ± 6.7	15 ± 4.7
Half-life (h)	4.56± 1.3	5.9± 1.9	35.2±25.9
Removed (%)	44 ±15	36 ±15	5.4± 5.2

Table 2
Maximum (one hour after the end of infusion) and minimum (end of the third HD session) vancomycin concentrations (μg/ml) and the corresponding elimination half-life (h) for the three membranes. N is the number of patients undergoing HD with a particular membrane

	Vancomycin concentration		Half-life ($t_{1/2}\beta$)	N
	maximum	minimum		
PSF	30.1± 9.3	4.6±1.4	61±13.6	4
PAN	40.5±16.2	6.5±3.5	60±24.0	2
SCE	29.2± 6.2	13.1±0.9	86±11.9	2

cin infusion and HD is critical, the results of the initial HD sessions were reported separately. The main findings in this Table are the following: the newer membranes PSF and PAN were more efficient than SCE in removing vancomycin, being 3–5 times for clearance. The differences between the two groups were statistically significant for the initial (Group A) and subsequent HD sessions (Group B). The differences between PSF and PAN were within a narrow range and usually in favour of PSF. The time interval between vancomycin infusion and the first HD session had no significant effect on the parameters determined for PSF and PAN. However, for SCE, the amount removed during the initial HD sessions was about three times higher than that obtained after the

subsequent HD sessions (Fig. 1). The plasma concentration–time profile of vancomycin for selected initial and subsequent HD sessions are shown in Fig. 1.

Vancomycin levels one hour after the end of infusion (maximum) and at the end of the third HD session (minimum) were determined for each membrane (Table 2). The level dropped to a subtherapeutic concentration (<7.5 μg/ml) [9] only in patients dialysed with PSF and PAN. The elimination half-lives ($t_{1/2}\beta$) were about 60 hours for PSF and PAN and 86 hours for SCE. The mean±S.D. concentration one hour after the end of 14 infusions was 34.2±11.4 μg/ml (range 17–53).

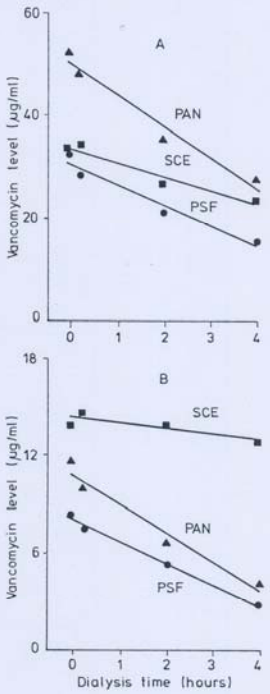

Fig. 1. Plasma vancomycin level during haemodialysis sessions with polysulfone (PSF), polyacrylonitrile (PAN) and cuprophan (SCE). Group A: HD sessions one hour after the end of infusion; Group B: 2 and 5 days postinfusion

Discussion

Vancomycin is currently administered as a single dose every 1–2 weeks to patients undergoing chronic HD. This is mainly applied to dialysis performed with membranes such as SCE and cellulose acetate, which has very poor permeability to vancomycin. The clearance of those membranes to vancomycin which has been reported by others and in agrement with the findings of this study, did not exceed 15 ml/min [7, 8]. The newer membranes (PSF, PAN), however, had a greater permeability to vancomycin as it was also reported in previous studies [7, 8, 10]. The clearance values obtained with each membrane exceeded that of SCE by more than 30%. The arterio-venous (A-V) difference was the method used to calculate the clearance of vancomycin, which is poorly correlated to the amount removed during chronic HD. Because of that, an increase of 30% in clearance has been suggested as the minimum required to cause changes in the dosing interval [11]. The differences in clearance between PSF and PAN indicates that similar dosage intervals can be used for the two membranes.

The impact of the high clearance of PSF and PAN in the dosing regimen of vancomycin was studied during chronic HD. The concentration at one hour after the end of infusion (maximum) and at end of the third HD session (minimum) were compared for each membrane. The concentration was reduced to a subtherapeutic level (i.e. <0.5 μg/ml) only in the users of PSF and PAN. This corresponds to elimination half-lives of about 60 hours compared to 85 hours in the patients who used SCE. Based on these findings, vancomycin should be given every three HD session for patients using PSF, PAN. The patients who used SCE may require four to five HD sessions before the next dose. In other words, the dosage interval should be either 5 or 10 days if vancomycin was infused prior to HD session, or 7 or 12 days if infused after the HD session, respectively, for the two groups of membranes.

The distribution of vancomycin in patients varies according to renal function [9]. While it is one hour in normal patients, it takes several hours in patients with ESRD [12]. Because distribution may influence the efficiency of dialysis, the parameters determined during the initial HD session were compared with those of the subsequent sessions. The effect was not statistically significant for PSF and PAN. However, the amount removed (%) during the initial HD sessions was higher (31% vs 5.4%) for SCE. Although the reason is not clear, it can be related to the poor efficiency of SCE.

The mean concentration one hour after the end of vancomycin infusion (peak) was 34.2±11.2 μg/ml. The interindividual variability was wide, being about threefold. The peaks reported in the literature vary according to dose, duration of infusion and sampling time. Generally, the concentrations obtained here are fairly close to the values reported in earlier studies for similar dosing regimens [10]. Therefore, it seems that this dose is adequate, since most patients will get a peak above the minimum therapeutic level (20 μg/ml) and far below the toxic (80 μg/ml) concentration.