 removal of vancomycin by high-flux hemodialysis membranes

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levels of vancomycin in serum are traditionally believed to be unaffected by hemodialysis. By both in vivo and in vitro techniques, the effects of a newer, more permeable dialyzer membrane on vancomycin concentrations were investigated. Six patients who were receiving vancomycin and undergoing maintenance hemodialysis with polyacrylonitrile dialyzer membranes had postdialysis levels in serum that were 63% of predialysis levels; the intradialytic half-life was 5.7 h. Vancomycin concentrations in serum exiting the dialyzer were 68% of those simultaneously entering the dialyzer at the beginning of dialysis. When polyacrylonitrile and conventional cellulose membranes were perfused in vitro with a recirculating solution of vancomycin, vancomycin concentrations fell to 39 and 91%, respectively, of the original concentration. The vancomycin concentration in the ultrafiltrate collected from the polyacrylonitrile membranes was only 24% of the original predialysis concentration. A significant decrease in the serum vancomycin concentration may occur during hemodialysis with newer high-flux dialyzer membranes. It appears that vancomycin binds to polyacrylonitrile membranes; this binding does not require the presence of protein and is affected by the pH of the perfusate.

Vancomycin is a glycopeptide antimicrobial agent which has been available for over 30 years for the treatment of serious infections by gram-positive organisms. Because of increasing resistance of bacteria (e.g., staphylococci) to beta-lactam antibiotics, the importance of vancomycin has grown. Vancomycin is largely eliminated by glomerular filtration, and guidelines regarding its dosing in patients with renal impairment have been established (6, 7, 10, 11, 16). Traditionally, the recommended dosage for anuric patients has been 1 g every 7 to 10 days (7, 10, 16). Intermittent hemodialysis has been said to have little effect on serum vancomycin concentrations (7, 10, 16). In these reports, however, hemodialysis was performed with conventional cellulose membranes (7, 11, 16). More recently, dialyzer membranes which are more permeable to solutes with molecular masses of greater than 500 Da have become available. These more efficient, high-flux dialyzers, in combination with increased blood flow rates, have allowed hemodialysis time to be decreased. Recent reports suggest that hemodialysis with these newer membranes may significantly alter vancomycin concentrations (3, 5, 9), although the mechanism of vancomycin removal is unknown. Filtration of vancomycin, binding of vancomycin (e.g., to the membrane surface), or precipitation of vancomycin (e.g., with heparin saturated on the membrane), alone or in combination, may account for the loss of vancomycin. Sulfonated polyacrylonitrile dialyzers are frequently used at our institution for hemodialysis; however, vancomycin pharmacokinetics have been reported in detail for very few patients dialyzed with this membrane (5). The purpose of this investigation was to further define the influence of polyacrylonitrile membranes on vancomycin concentrations during the dialytic period. In addition, we investigated the mechanism of vancomycin loss with in vitro studies utilizing this membrane.

MATERIALS AND METHODS

Clinical investigation. Patients undergoing maintenance hemodialysis with hollow-fiber 1.7-m² sulfonated polyacrylonitrile dialyzers (Filtral 16; Hospal Industrie, Lyon, France) who had received vancomycin prior to dialysis (but no other concomitant antibiotic therapy) were studied. Simultaneous serum samples were collected from the arterial (dialyzer inflow) and venous (dialyzer outflow) ports at the beginning and immediately following the completion of dialysis. The average period between the collection of samples at the beginning and end of hemodialysis was 3.5 h. The indicated blood flow rate was 500 ml/min, and the dialysate flow rate was 500 ml/min. With the assumption of first-order elimination, the intradialytic half-life was calculated by $t_{1/2} = 0.693/k$, where $k = \ln(C_{eNd}/C_{beg})/t$, $C_{eNd}$ and $C_{beg}$ are the vancomycin concentrations at the end and beginning of the dialytic period, respectively, and $t$ is the time between collection of samples.

In vitro investigation. A comparison between the polyacrylonitrile and conventional cellulose (surface area, 1.3 m²) membranes on vancomycin concentrations was made with an in vitro model. A saline solution containing approximately 80 µg of vancomycin per ml underwent two serial single-pass perfusions through the dialyzer. The pH of the saline perfusate was adjusted with sodium hydroxide and hydrochloric acid; perfusate solutions with pHs of 3.5, 7.1, and 10 were employed. In addition, to assess the effect of protein binding on the disposition of vancomycin, fresh frozen plasma was used as the perfusate in one experiment. Samples were collected before and after each passage through the dialyzer. Following the second passage, the solution was perfused through the membrane in a recirculating manner for 90 min, and a final sample was collected. Ultrafiltrate was collected from the polyacrylonitrile membranes following the recirculation for 90 min (no ultrafiltrate was present after the first- and second-pass experiments). No ultrafiltrate was available from the cellulose membranes. Vancomycin clearance was calculated by $CL = Q \times (C_v - C_u)$.
C_v/C_i), where Q is the flow rate through the dialyzer (150 ml/min) and C_i and C_v are the inflow and outflow solution vancomycin concentrations, respectively.

Vancomycin concentrations were determined by a standard disk diffusion bioassay using Bacillus subtilis (8); all specimens were tested in duplicate. The microbiological assay has been reported to correlate well with other vancomycin assay methods (12). We performed both the microbiological assay and the fluorescence polarization assay on nine of the clinical samples with vancomycin concentrations of 4 to 10 μg/ml. Results from the microbiological assay were within 11% ± 8% of the fluorescence polarization assay results. The mean intrarun and intrarun coefficients of variation for these samples were 8.5% and 7.2%, respectively. Both of these values are similar to those reported elsewhere (12) concerning the precision of the bioassay method. The average linear correlation coefficient was 0.996 (range, 0.991 to 1.0) in our bioassay determinations. Between vancomycin concentrations of 5 and 80 μg/ml, the linear correlation coefficient (concerning the relationship between the diameter of the zone of inhibition and the logarithm of concentration) has been reported to be ≥0.98 (12). Statistical analysis included Student’s t test for paired and unpaired data, and results are reported as means ± standard deviations.

## RESULTS

Five patients who had received vancomycin prior to their day of hemodialysis had simultaneous arterial and venous samples from the dialyzer obtained at the beginning and end of dialysis; one patient had only pre- and postarterial levels obtained (Table 1). The vancomycin concentration in serum exiting the dialyzer was 68% ± 14% of that entering the dialyzer (8.9 ± 4.3 versus 13 ± 5.9 μg/ml, P = 0.013) at the beginning of dialysis. Similarly, at the end of the dialysis period, the venous vancomycin concentration was 67% ± 8.3% of the arterial concentration (8.2 ± 3.8 versus 5.6 ± 3.2 μg/ml, P = 0.005). Postdialysis vancomycin concentrations were 63% ± 11% of the predialysis concentrations (P = 0.018). The intradialytic half-life was 5.7 ± 1.9 h. Because the period between collection of vancomycin samples (3.5 h) was less than the intradialytic half-life, the calculation of the intradialytic half-life should be interpreted with caution. The indicated blood flow rate, based on blood pump velocity, does not accurately reflect the actual blood flow rate when flows in excess of about 300 ml/min are used (15). Because there are no simple reliable techniques for accurately determining high blood flow rates during rapid hemodialysis, vancomycin clearances could not be accurately determined by the arterial-venous method.

With the in vitro model with normal saline (pH = 7.1) as the perfusate, the vancomycin concentrations following the first and second passes through a cellulose membrane were 97% ± 4.5% and 90% ± 9.5% of the original concentrations, respectively. In comparison, the concentrations following two serial passes through polyacrylonitrile membranes were 55% ± 4.9% and 51% ± 0.78% (P ≤ 0.03 compared with cellulose values) of the original concentrations, respectively. Following 90 min of continuous recirculation through cellulose and polyacrylonitrile membranes, the vancomycin concentrations were 91% ± 6.8% and 41% ± 0.21% of the original concentrations, respectively (P = 0.06). The concentration of vancomycin in the ultrafiltrate from the polyacrylonitrile membrane was 24% ± 1.5% of the original concentration. Only 11.9% of the amount of vancomycin removed during the 90 min of recirculation could be accounted for in the ultrafiltrate. The clearance of vancomycin following a single pass through the cellulose membrane was 4.2 ± 6.8 ml/min and 63 ± 7.4 ml/min for the polyacrylonitrile membrane (P = 0.014). When fresh frozen plasma was used as the solution, only 31 and 32% of the original vancomycin concentration were found following a single passage and following recirculation for 90 min, respectively, through a polyacrylonitrile membrane. Therefore, vancomycin loss was slightly enhanced when protein was present in the perfusate.

The influence of changes in pH on the removal of vancomycin by polyacrylonitrile membranes was also investigated with the in vitro model. The vancomycin concentrations following a single pass through the membrane in solutions with pHs of 3.5 and 10 were 53% ± 15% and 65% ± 5.8% of the original concentrations, respectively. Following recirculation for 90 min, the vancomycin concentrations were 20% ± 0.5% and 42% ± 11% of the original concentrations in solutions with pHs of 3.5 and 10, respectively. The concentration of vancomycin in the ultrafiltrate was 47% ± 8.1% of the original concentration for the solution with a pH of 10, compared with 16% ± 3.8% for the solution with a pH of 3.5 (P = 0.04).

## DISCUSSION

Serum vancomycin concentrations are relatively unaffected by conventional dialyzers (7, 10, 16). Following a single 1-g dose in anuric patients, peak values decline rapidly (over hours) to 10 to 20 μg/ml; the concentration then slowly declines to 3 to 7 μg/ml over the next 7 to 14 days (7). With increasing blood flow rates and newer, more permeable membranes, hemodialysis may reduce vancomycin concentrations (3, 5, 9). We found that vancomycin levels decreased 37% over a single hemodialytic period by using polyacrylonitrile membranes. The clinical significance of decreasing a vancomycin level from approximately 12 to 7 μg/ml, as we observed, is unknown. However, with weekly dosing of vancomycin and thrice-weekly hemodialysis, it is likely that some patients may go for periods of time with suboptimal vancomycin concentrations. Maintaining a mean concentration of 15 μg/ml, recommended by Moellering et al. as a safe and therapeutic level (10, 11), may not be reliably predicted during high-flux hemodialysis (3).

With the vancomycin molecular mass of 1,448 Da (13), it might be expected that significant convective removal of vancomycin would occur during ultrafiltration with highly permeable membranes. With our in vitro studies, we found only small concentrations in the ultrafiltrate; the large amount of lost vancomycin was apparently bound to the membrane. Polyacrylonitrile membranes carry a negative
surface charge. At an acidic pH, vancomycin carries a net positive charge, becomes neutral at approximately a pH of 7, and has a net negative charge at an alkaline pH (13). We found that at an acidic pH very little vancomycin appeared in the ultrafiltrate, whereas at a higher pH significantly more was able to cross the membrane. It should be noted that we employed extremes of pH, clearly outside the physiologic range. These extremes were chosen to help define the mechanism of vancomycin removal by the membrane. It has been postulated that membrane polarization and deposition of protein allows for increasing trapping of drugs (doxycycline and gentamicin) and an overflow of drug into the filtrate (14). Since normal saline was used in our in vitro experiments, the presence of protein was not necessary for the removal of vancomycin by polyacrylonitrile membranes. However, the presence of protein did appear to enhance the removal of vancomycin.

Heparin is commonly used in hemodialysis to prevent thrombogenesis and may saturate dialyzer membranes. When present in high concentrations together, heparin and vancomycin may precipitate, leading to reduced vancomycin bioactivity (1). Heparin does not appear to be involved in the reduction of bioactive vancomycin that we observed, however, since significant clearance of vancomycin across the dialyzer occurred prior to the administration of heparin in our patients. Also, our in vitro studies did not employ heparin.

Significant vancomycin removal has also been noted with use of polysulfone (9) and polyacrylonitrile membranes (3, 5). Supplementary vancomycin doses following each dialytic period with a high-flux membrane may be necessary to ensure appropriate antibiotic concentrations (2). In addition, intermittent dosing (versus continuous infusion) of antibiotics may be important for penetration into nonvascular areas (4). Frequent vancomycin administration may allow sporadic peak levels and improve diffusion into infected areas (e.g., fibrin loci). Since a rebound in vancomycin concentrations may occur after the completion of high-flux hemodialysis (4), it remains to be determined whether supplemental vancomycin doses following hemodialysis will affect the clinical outcome of the patient. Our results do not provide a basis for dosing recommendations for patients on high-flux hemodialysis, and further investigation will be necessary to determine the clinical significance and proper management of these findings.

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REFERENCES