Vancomycin mass transfer characteristics of high-flux cellulosic dialysers

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Abstract

Background. In comparison to conventional haemodialysis membranes, highly permeable membranes allow a broader spectrum of solute removal, including enhanced elimination of vancomycin (1448 Daltons). However, the mass transfer characteristics of vancomycin removal by highly permeable membranes have not been adequately assessed. An understanding of vancomycin’s predominant dialytic mass transfer mechanism under a given set of operating conditions, including dialyser type and flow rates, may permit more accurate dosing of the drug.

Methods. We performed a mass transfer analysis of vancomycin removal by a high-flux dialyser, cellulose triacetate (CT). In a cross-over fashion with a 3-week washout between treatments, eight subjects received vancomycin 1000 mg (1) during the last hour of CT haemodialysis; or (2) after dialysis. Serial urea and vancomycin serum concentrations were used to assess dialytic removal.

Results. Dialysis removed 26.2% (mean; range 16–44%) of the administered vancomycin dose. While vancomycin removal and (Kt/V)urea were directly correlated (r = 0.88; P < 0.005), no correlation was observed between vancomycin removal and weight-normalized ultrafiltration rate.

Conclusions. These findings suggest that for the CT dialyser and dialysis operating conditions employed in this study, vancomycin clearance was primarily mediated by diffusion. As such, these data challenge the general concept that convection is primarily responsible for the removal of solutes in the same molecular weight class as vancomycin during high-flux dialysis.

Key words: convection; diffusion; haemodialyser; pharmacokinetics; vancomycin

Introduction

The molecular weight (MW) spectrum of solutes eliminated by most haemodialysis (HD) membranes, particularly those made of cuprophan, is limited in comparison to the size range of molecules removed by glomerular filtration [1]. However, both conventional and more permeable (high-efficiency and high-flux) membranes are capable of efficiently removing low-molecular weight (less than 150 Daltons) nitrogenous waste products. Several recent studies [2–4] have demonstrated a direct correlation between removal of these small solutes and outcome in chronic HD patients dialysed with membranes of varying permeability. Cuprophan’s restrictive pore structure, however, permits only marginal clearance of substances much larger than 500 Daltons (Da) [5]. The increasing use of membranes having higher permeability than cuprophan has extended the MW range of dialytic solute removal. In the ongoing NIH study [6] evaluating HD adequacy and outcome, the differential removal of β₂-microglobulin (MW 11800 Da) by membranes of varying permeability is one factor being assessed. This will provide useful information regarding the removal of larger molecules and the potential clinical benefit to end-stage renal disease (ESRD) patients.

Another solute whose removal is critically dependent on membrane permeability is vancomycin (MW 1448 Da), widely used in the ESRD population for the treatment of Gram-positive bacterial infections. Several previous investigations have determined vancomycin clearances and other pharmacokinetic parameters for dialysers of varying flux [7–14]. However, these studies have been performed with a lack of consideration of the predominant mass transfer mechanism (diffusion or convection) mediating the drug’s removal during treatment. In addition, only one prior study [15] has attempted to assess vancomycin removal when the entire amount of drug was administered during the last hour of HD, a common administration protocol in many American HD centres. Although previous in vitro data suggest that convection is primar-
ily responsible for dialytic removal of solutes approxi-
mately the size of vancomycin [16–18], corroborative
clinical data are lacking.

The present study is an in vivo characterization of
vancomycin removal by a highly permeable cellulosic
membrane, cellulose triacetate (CT). In a series of
chronic HD patients, we correlated vancomycin
removal with various dialytic operating parameters in
an attempt to obtain fundamental mass transfer
information. Our data indicate that vancomycin
removal during high-flux cellulosic dialysis is mediated
primarily by diffusion.

Subjects and methods

Patients

Eight subjects from the Adult Outpatient Hemodialysis Unit
at the Indiana University Medical Center were enrolled in
this trial. All patients were receiving chronic haemodialysis
on a thrice-weekly basis and were free of acute intercurrent
illness. Patients with a known sensitivity to vancomycin,
those who had received the drug within a month prior to
study initiation, and those with a post-dialysis weight of less
than 40 kg were excluded. The study protocol was approved
by the Indiana University–Purdue University Institutional
Review Board and the Purdue University Human Subjects
Committee.

Haemodialysis regimen

For the study, no changes were made in the patients’ therapy
prescription. Patients were treated with cellulose triacetate
(CT 190, Baxter Healthcare Co. McGaw Park, IL) dialysers.
New (non-reprocessed) dialysers were used in all cases. The
membrane surface area of this dialyser is 1.9 m², while the
membrane thickness is 15 μm. Based on the manufacturer’s
in vitro data obtained from experiments using an aqueous
test solution, the dialyser’s performance characteristics
include: ultrafiltration coefficient (Kuf) of 36 ml/h/mmHg;
urea clearance (at a blood flow rate of 200 ml/min)
192 ml/min; and vitamin B12 clearance (at a blood flow rate
of 200 ml/min) 137 ml/min [19]. Bicarbonate dialysate and
dialysis machines having ultrafiltration control capability
were used exclusively. Intradialytic ultrafiltration was based
solely on the fluid removal required for the attainment of
each patient’s estimated dry weight. Information obtained
during each dialysis treatment included pre- and post-dialysis
weights, dialysate flow rate, blood flow rate, treatment dura-
tion, and ultrafiltration rate both for the entire treatment
and the last hour of treatment. In addition, changes in any
of the flow rates were recorded. In phase I, subjects received
a 1-g intravenous dose of vancomycin infused during the last
hour of dialysis. This vancomycin administration time was
employed because the accepted practice at many American
haemodialysis centres is to infuse vancomycin during the last
hour of haemodialysis treatment. In phase II, a 1-g dose
of vancomycin was infused intravenously over 60 min, but
occurred after the completion of a regularly scheduled
haemodialysis session (control). A washout period of at least
3 weeks between the two phases occurred for all patients.

Blood samples for serum vancomycin determination were
obtained at zero (pre-infusion), and at 15, 30, 60, 90, 120,
and 180 min after the start of the vancomycin infusion.

Solute concentration determinations

Serum vancomycin concentrations were assayed by use of
an Enzyme Multiplied Immunoassay Technique (EMIT),
which has interassay and intra-assay coefficients of variation
of less than 7% (Syva Co., Palo Alto, CA). Samples for the
determination of blood urea nitrogen (BUN) concentration
were obtained immediately before and within 5 min after the
completion of dialysis in phase I. These data were used to
calculate the normalized (single-pool) dose of dialysis,
(Kt/V)urea, by the second-generation Daugirdas formula for
each patient [20].

Data analysis

Log-trapezoidal area under the curve (AUC) data derived
from the two study arms were compared using paired t
tests for repeated measures. Statistical significance was considered
to be P<0.05 for all comparisons. The fraction of vancomy-
cin removed by the CT 190 dialysis study arm was calculated
using the following equation:

\[
\text{Fraction of dose removed} = 1 - \frac{\text{AUC}_{\text{CT dialysis study arm 0–44 h}}}{\text{AUC}_{\text{no dialysis study arm 0–44 h}}}
\]  

(1)

Results

All eight subjects (mean age 51.4±9.2 y; mean±SD)
completed the trial. No adverse effects were noted in the
study. The mean ultrafiltrate volume in the final
hour of dialysis was 0.8 l. Dialysis operating conditions
were not changed throughout the entire dialysis session
(blood flow rate = 423±55 ml/min, dialysate flow rate
= 500 ml/min, and treatment time = 3.5±0.4 h).
Based on these mean treatment parameters, diffusion
is expected to have accounted for almost all urea
removal [21]. Therefore, the (Kt/V)urea of 1.52±0.14
was a reflection of diffusive solute removal during the
dialysis session in its entirety as well as during the last
hour when the vancomycin was administered. All
subjects had been on HD for more than 2 years prior
to study participation and had no residual renal
function.

The mean serum concentration vs time profile is
displayed in Figure 1. Serum concentrations during the
CT dialysis phase were consistently lower than the
control phase. Area under the curve (AUC) calcula-
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Fig. 1. Vancomycin serum concentrations achieved when infused during CT 190 dialysis and after dialysis.

Fig. 2. Vancomycin removal vs small-solute clearance.

Fig. 3. Vancomycin removal vs normalized ultrafiltration rate.

Only a small fraction (mean = 8.2%) of the total vancomycin removal. This estimate provided additional evidence that diffusion primarily mediated vancomycin removal. Of note, this analysis neglects the effect of the simultaneous presence of diffusion on convective solute removal. Therefore, this estimate of convective solute removal represents a theoretical maximum value.

Treatment time and membrane surface area are two additional factors that may influence convective solute removal to a greater extent than diffusive solute removal [26,27]. In this study, treatment time was similar between subjects, as vancomycin dialytic clearance was studied only during the final hour of dialysis for all subjects. Because CT 190 dialysers were used exclusively, dialyser surface area was the same for all subjects. Therefore, the effect of time and/or surface area on solute removal could not be evaluated in this study.

Discussion

Other than conventional small solutes, such as urea and creatinine (MW less than 120 Da), $\beta_2$M is the only other uraemic solute whose $\text{in vivo}$ removal by high-flux dialysers has been extensively studied. Several studies have demonstrated that transmembrane $\beta_2$M removal during high-flux dialysis is significantly reduced by convection [28–30]. Cellulose triacetate dialysers represent the exception to this general finding as some previous investigations involving these dialysers have demonstrated diffusion is the predominant removal mechanism [31,32]. To assess this latter finding, our group recently quantified the $\beta_2$M diffusion characteristics of CT and another high permeability membrane, sulphonated polyacrylonitrile (PAN) [33,34]. Providing an explanation for the above clinical studies [31,32], our analysis showed that the $\beta_2$M membrane diffusivity for CT was more than fivefold greater than that for PAN ($3.25 \times 10^{-7}$ cm$^2$/s vs $0.60 \times 10^{-7}$ cm$^2$/s respectively). These $\text{in vitro}$ data suggest that CT is a relatively good diffusion medium for solutes even as large as $\beta_2$M. Recent work also has demonstrated that adsorption is a prominent $\beta_2$M removal mechanism for certain synthetic (hydrophobic) membranes, par-
Therefore, we attempted to correlate high-flux generation rate in urea kinetic modelling, were the intradialytic administration of the entire vancomycin group. The amount of vancomycin infused and its removal by high-flux dialysers. In addition, only removal could not be correlated with dialyser surface area, which was the same (1.9 m²) for the entire patient group. The amount of vancomycin infused and its elimination to the relatively hydrophilic CT membrane is limited [34].

For high-flux dialysis, the in vivo removal of solutes having MW between the two extremes of the low-MW nitrogenous waste products and β₂M is poorly characterized. Vancomycin is a clinically relevant solute whose MW falls in this intermediate range. Laboratory studies have suggested convective transport is primarily responsible for the removal of vitamin B₁₂, a solute having a MW (1350 Da) similar to that of vancomycin, by conventional [16,17] and synthetic high-flux [37,38] membranes. However, clinical confirmation of these data has been lacking and the extensive protein binding of vitamin B₁₂ does not allow it to be a practical marker for clearance studies.

The ability to perform detailed mass transfer analyses for vancomycin stems from a number of the drug's characteristics. First, the drug is commonly used in the ESRD population and assays for serum concentration determinations are widely available. Second, vancomycin is minimally protein-bound in patients with renal failure [39] and available to be dialysed. Finally, the drug's volume of distribution is well characterized [40] and although it has a slightly larger range, it approximates that of urea.

An understanding of vancomycin's predominant dialytic mass transfer mechanism under a given set of operating conditions, including dialyser type and flow rates, may permit more accurate dosing of the drug to ESRD patients. However, there is a lack of information pertaining to the mass transfer characteristics of vancomycin removal by high-flux dialysers. In addition, only one previous study [15] has quantified the effect of intradialytic administration of the entire vancomycin dose on its simultaneous removal during high-flux dialysis. Therefore, we attempted to correlate high-flux cellulosic removal of intradialytically administered vancomycin with dialysis-operating parameters that may have influenced drug elimination. For the operating conditions employed in the study, convective transport is expected to have contributed minimally (i.e. only approximately 5%) to total urea removal [21]. Therefore, quantifying urea removal by (Kt/V)area determinations provided a general estimate of diffusive solute removal. Our data exhibited a significant direct correlation between vancomycin removal and (Kt/V)area, suggesting that diffusion was primarily responsible for the drug's elimination by CT dialysers (Figure 2). This finding was corroborated by our estimate that at least 92% of the total vancomycin elimination was due to diffusion (Table 1).

Diffusive solute removal is a function of transmembrane concentration gradient. Dialysis parameters that tend to enhance these gradients are high dialysate and blood flow rates and low membrane thickness [41]. On the other hand, as solute molecular size increases, treatment time, ultrafiltration rate, and dialyser surface area become increasingly important determinants of solute removal [16,17,26,27]. During the study, the time during which vancomycin removal occurred was the same as the infusion period, the final hour of dialysis in all patients. Therefore the independent effect of time could not be analysed. In addition, no attempt was made to augment specifically the convective renal removal of vancomycin by employing an ultrafiltration rate greater than that required for attainment of dry weight post-dialysis. Previous studies have demonstrated that, relative to high-flux dialysis, β₂M removal is enhanced by the use of haemodiafiltration, which involves the purposeful use of a total ultrafiltration rate which greatly exceeds the net ultrafiltration requirement of the patient [21,30,42]. Finally, drug removal could not be correlated with dialyser surface area, which was the same (1.9 m²) for the entire patient group. The amount of vancomycin infused and its infusion rate, the latter of which is analogous to generation rate in urea kinetic modelling, were the same in all patients (1000 mg/h), regardless of patient size or volume of distribution. This potential problem,

### Table 1. Calculation of vancomycin removal by diffusion and convection

<table>
<thead>
<tr>
<th>Subj. no.</th>
<th>Midpoint (30') Serum conc. (mg/l)</th>
<th>Total vancomycin removed (mg)</th>
<th>Ultrafiltrate production in final hour (l)</th>
<th>Vancomycin (mg) removed by convection* (% of total removal)</th>
<th>Vancomycin (mg) removed by diffusion (% of total removal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.9</td>
<td>346</td>
<td>0.3</td>
<td>9.1 (2.6%)</td>
<td>336.9 (97.4%)</td>
</tr>
<tr>
<td>2</td>
<td>48.9</td>
<td>444</td>
<td>0.5</td>
<td>19.6 (4.4%)</td>
<td>424.4 (95.6%)</td>
</tr>
<tr>
<td>3</td>
<td>29.1</td>
<td>189</td>
<td>1.0</td>
<td>23.3 (12.3%)</td>
<td>165.7 (87.7%)</td>
</tr>
<tr>
<td>4</td>
<td>50.0</td>
<td>341</td>
<td>1.3</td>
<td>52.0 (15.2%)</td>
<td>289.0 (84.8%)</td>
</tr>
<tr>
<td>5</td>
<td>31.3</td>
<td>209</td>
<td>1.1</td>
<td>27.5 (13.2%)</td>
<td>181.5 (86.8%)</td>
</tr>
<tr>
<td>6</td>
<td>19.2</td>
<td>182</td>
<td>1.5</td>
<td>23.0 (12.6%)</td>
<td>159.0 (87.4%)</td>
</tr>
<tr>
<td>7</td>
<td>30.5</td>
<td>159</td>
<td>0.5</td>
<td>12.2 (0.7%)</td>
<td>146.8 (92.3%)</td>
</tr>
<tr>
<td>8</td>
<td>36.8</td>
<td>230</td>
<td>0.2</td>
<td>5.9 (2.6%)</td>
<td>224.1 (97.4%)</td>
</tr>
<tr>
<td>Mean</td>
<td>35.5</td>
<td>262.5 mg</td>
<td>0.8</td>
<td>21.6 (8.2%)</td>
<td>240.9 (91.8%)</td>
</tr>
</tbody>
</table>

*Calculated as: (30 min (midpt) conc) × (SC) × (ultrafiltrate production) = estimate of mg removed (theoretical maximum) via convection during last hour of dialysis.

The sieving coefficient (0.8) used in calculations of convective clearance was derived from literature value for high-permeability membranes [32–31].
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However, was circumvented by correlating vancomycin removal with urea clearance that had been normalized to urea distribution volume. When mean ultrafiltration rates, both over the entire treatment and only during the vancomycin infusion period, were normalized in a similar manner, no significant correlation with vancomycin elimination was observed (Figure 3). These results provided additional evidence that convection did not assume a significant role in vancomycin removal by the CT membrane in this patient group.

A relationship between solute removal and outcome in chronic haemodialysis patients has only been established for small solutes [2–4]. However, recent data suggest that the retention of solutes in the middle molecule range may play a major role in uremia. Using uraemic ultrafiltrate, Anderstam et al. [41] have isolated a solute, having a molecular weight (1000–5000 Daltons) similar to that of vancomycin, which inhibits ingestive behaviour in rats. These recent data confirm the importance of understanding the removal mechanisms for solutes of this size during high-flux dialysis.

The potential limitations associated with our experimental design and analysis must be considered for proper interpretation of these results. Our attempted correlation of vancomycin removal with factors potentially influencing convective solute removal may have been enhanced if dialysers of varying surface area and variable treatment times had been utilized. In addition, a similar analysis with different high-flux dialysers would have made our analysis more comprehensive. The relatively small thickness of CT (15 μm) is one feature which distinguishes this membrane from synthetic high-flux membranes, which have thicknesses of 25 μm or more [5]. Because membrane diffusivity is inversely proportional to membrane thickness [43], diffusion may not assume the same prominent role in middle-molecule removal by the synthetic membranes. This possibility will need to be assessed in future investigations. A second potential shortcoming of this study concerns our evaluation of vancomycin removal only during the last hour of dialysis. By this time period, the adsorbed protein layer (secondary membrane) was most probably fully developed, acting as an additional barrier to mass transfer. However, secondary membrane formation has been shown to cause a significant reduction in the transmembrane removal of low-molecular-weight proteins by synthetic membranes [44] but is expected to have little effect on the removal of these compounds by CT [21,34]. In addition, we assumed that vancomycin removal occurred exclusively in a transmembrane manner. Although a previous study has shown that sulphonated (anionic) PAN can remove cationic aminoglycosides by adsorption [45], electrostatic adsorptive interactions between vancomycin and uncharged CT would have been unlikely. We cannot exclude definitely the possibility that vancomycin removal by CT was achieved by non-specific (hydrophobic) adsorption. However, the low lipophilicity of vancomycin [46], the relatively small adsorption potential of CT [34], and the presumed full development of the secondary membrane before the vancomycin removal period, make this latter possibility very unlikely. Finally, we did not explore the possibility that backfiltration or backdiffusion [21,47] influenced the net removal of vancomycin. However, the clinical relevance of these phenomena has not yet been determined. In addition, previous analyses [21,48] suggest that backfiltration would have been negligible at the mean ultrafiltration rate (0.8 l/h) during the last hour of our study.

A final point of emphasis is that this study was performed with new (non-reused) dialysers. Prior investigations have shown that peracetic acid-based reprocessing results in a significant decrement in β2M removal by some high-flux dialysers [42,49]. Conversely, two recent studies have reported enhanced β2M removal by high-flux polysulphone dialysers during bleach-based reprocessing [50,51]. In a similar manner, vancomycin removal may be influenced by reuse techniques. Therefore, significantly different results may have been observed in this study if patients had been treated with reprocessed dialysers.

While the purpose of this study was to determine the mass transfer characteristics of vancomycin, we do not advocate indiscriminate use of the drug. The recent increase of vancomycin-resistant pathogens has led to recommendations for stricter vancomycin administration guidelines [52]. However, vancomycin is frequently used in ESRD patients and knowledge of its mass transfer mechanisms is important to provide optimal care of patients receiving high-flux HD.

In summary, our findings suggest that for the specific conditions of high-flux cellullosic dialysis, quantitative increases in diffusive small-solute removal (e.g. {Kt/V}_{urea} or urea reduction ratio) lead to a proportionally similar enhancement of vancomycin removal when the drug is infused during dialysis. Therefore, these data challenge the general concept that convective transfer is primarily responsible for the dialytic removal of solutes in the same molecular weight class as vancomycin. Future studies are required to determine the applicability of these findings to other high-flux membranes. In addition, future work should characterize the relative importance of diffusive and convective mass transfer of solutes in vancomycin’s size range during haemodiafiltration.

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