Comparison of the new polyethersulfone high-flux membrane DIAPES\textsuperscript{®} HF800 with conventional high-flux membranes during on-line haemodiafiltration

Walter Samtleben\textsuperscript{1}, Christina Dengler\textsuperscript{1}, Birgit Reinhardt\textsuperscript{2}, Annekatrin Nothdurft\textsuperscript{2} and Horst-Dieter Lemke\textsuperscript{2}

\textsuperscript{1}Department of Nephrology, University Hospital Munich-Grosshadern, Munich and \textsuperscript{2}Membrana Research, Obernburg, Germany

Abstract

Background. Current modalities of renal replacement therapy allow only a limited removal of larger, possibly toxic molecules, which accumulate in uraemia. Recently, a haemodiafilter has been made available with the new, high-flux, polyethersulfone-based membrane DIAPES\textsuperscript{®} HF800. We performed a study to compare DIAPES\textsuperscript{®} HF800 with two conventional high-flux membranes in on-line haemodiafiltration (HDF), with respect to the removal properties for the two marker proteins, $\beta_2$-microglobulin ($\beta_2$m, 11.8 kDa) and albumin (66.5 kDa).

Methods. In a prospective, controlled study 10 stable end-stage renal disease patients were randomly allocated to 30 sessions of post-dilutional on-line HDF with three types of steam-sterilized membranes: DIAPES\textsuperscript{®} HF800, polysulfone and polyamide. Blood flow rate was 250 ml/min and treatment time was 240 min. Pre-treatment $\beta_2$m and albumin plasma concentrations did not differ between the three groups. The concentration of the two proteins was determined before and after treatment in plasma as well as in the continuously collected haemodiafiltrate.

Results. Tolerance of all treatments was very good, without any side-effects for all filters. The mean plasma reduction rate of $\beta_2$m was 77 $\pm$ 1\% for DIAPES\textsuperscript{®} HF800 and polysulfone whereas it was 71 $\pm$ 1\% for polyamide ($P < 0.05$). The mean $\beta_2$m amount removed and found in the haemodiafiltrate per session was 230 $\pm$ 14 mg for DIAPES\textsuperscript{®} HF800, 186 $\pm$ 13 mg for polysulfone and 147 $\pm$ 13 mg for polyamide ($P < 0.05$ between each pair of membranes). The same ranking was obtained for albumin removed and found in haemodiafiltrate per session for the three membranes: 5.7 $\pm$ 0.4, 3.5 $\pm$ 0.4 and 1.0 $\pm$ 0.4 g, respectively. Although DIAPES\textsuperscript{®} HF800 showed the highest value for albumin in haemodiafiltrate the mean post-treatment plasma albumin was higher after the treatment with DIAPES\textsuperscript{®} HF800 compared with the other membranes ($P < 0.05$).

Conclusions. On-line HDF has shown to achieve plasma reduction rates for $\beta_2$m of up to 77\% for the DIAPES\textsuperscript{®} HF800 membrane and for polysulfone. The amounts of $\beta_2$m and albumin in haemodiafiltrate were much higher for DIAPES\textsuperscript{®} HF800 than for the other two membranes indicating a greater permeability for molecules up to a molecular weight of 66.5 kDa. This could, at least theoretically, offer the advantage also to remove uraemic toxins in the molecular weight range of albumin or of albumin-bound toxins. The future must show whether this will counterbalance the loss of albumin.

Keywords: albumin; $\beta_2$-microglobulin; haemodiafiltration; high-flux membrane; polyethersulfone; post-dilution

Introduction

The introduction of a newly developed, highly permeable haemodialysis (HD) membrane arises interest in today’s nephrological community. The question is often considered as to whether a membrane with higher permeability may fulfil an improved balance between a higher removal of uraemic toxins in the molecular weight range from urea to small proteins such as $\beta_2$-microglobulin ($\beta_2$m) and a clinically tolerable albumin loss. In recent years, the choice of membranes of either synthetically modified cellulose or synthetic membranes has expanded to a large extent. In parallel, a trend towards treatment modes with higher plasma reduction rates has recently been
Comparison of DIAPES® HF800 and conventional high-flux membranes during HDF

Table 1. Characteristics of treatment parameters

<table>
<thead>
<tr>
<th></th>
<th>DIAPES® HF800</th>
<th>Polysulfone</th>
<th>Polyamide S®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane manufacturer</td>
<td>Membrana</td>
<td>Fresenius</td>
<td>Gambro®</td>
</tr>
<tr>
<td>Haemodiafilter</td>
<td>BLS819SD</td>
<td>HF800S</td>
<td>Polyflux® 17S</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Bellco</td>
<td>Fresenius</td>
<td>Gambro</td>
</tr>
<tr>
<td>Membrane surface area</td>
<td>1.8 m²</td>
<td>1.8 m²</td>
<td>1.7 m²</td>
</tr>
<tr>
<td>Number of patients</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Treatment time (min)</td>
<td>240 ± 0</td>
<td>240 ± 0</td>
<td>240 ± 0</td>
</tr>
<tr>
<td>Qs (ml/min)</td>
<td>250 ± 0</td>
<td>250 ± 0</td>
<td>250 ± 0</td>
</tr>
<tr>
<td>Qd (l/4 h)</td>
<td>123.6 ± 0.5</td>
<td>123.3 ± 0.7</td>
<td>123.6 ± 0.7</td>
</tr>
<tr>
<td>UF volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Weight loss) (l/4 h)</td>
<td>3.38 ± 0.48</td>
<td>3.10 ± 0.72</td>
<td>3.35 ± 0.71</td>
</tr>
<tr>
<td>Substitution fluid volume (l/4 h)</td>
<td>14.6 ± 0.5</td>
<td>14.9 ± 0.7</td>
<td>14.7 ± 0.7</td>
</tr>
</tbody>
</table>

*One drop-out.*

witnessed [1,2]. The reason for such a trend may be derived from a revived interest in the field of uraemic toxins. Apart from being small, dialysable molecular substances, uraemic toxins may be bound to plasma proteins such as albumin or can be proteins itself, like β2m (11.8 kDa). The removal of plasma proteins up to the 66.5 kDa range of albumin has been investigated by several authors employing different membranes and dialysis modalities [3–5]. The factors involved in the removal of low molecular weight proteins depend not only on membrane permeability, but also on the transmembrane pressure applied during treatment [6] and on patient specific variables.

Recently, DIAPES® HF800, a highly permeable membrane made of polyethersulfone (PES) has been developed. DIAPES® HF800 exhibits an increased hydraulic permeability compared with conventional high-flux membranes. This leads to an in vitro ultrafiltration rate of 80 ml/h × mmHg for DIAPES® HF800 in the BLS819SD haemodiafilter (Bellco) compared with 55 ml/h × mmHg for the polysulfone membrane in the Hemoflow® HF800S (Fresenius Medical Care). In this study, we evaluated the removal of β2m and albumin in patients undergoing post-dilutional on-line haemodiafiltration (HDF) using DIAPES® HF800 in comparison with two other synthetic membranes.

Subjects and methods

Patients

The study was prospective, randomized and cross-over in nature and the study protocol was approved by the local ethics committee. Ten chronic uraemic patients on a regular thrice weekly HD programme were enrolled after giving informed consent [seven males, three females; aged 51 ± 13 years (range 33–70 years); 42 ± 37 months on dialysis (range 5–118 months)]. The patients were randomly treated once with DIAPES® HF800 (Membrana GmbH, Wuppertal, Germany; BLS819SD, 1.8 m², steam-sterilized, Bellco S.p.A., Mirandola, Italy), and once with polyamide (Polyflux® 17S, Gambro, Lund, Sweden) and polysulfone (Hemoflow® HF800S, Fresenius Medical Care, Bad Homburg, Germany), respectively, in a 4-h post-dilutional on-line HDF regime (Gambro AK100 Ultra monitor). Treatments under investigation were once a week after the long dialysis-free interval. Details of the HDF treatment parameters and of the haemodiafilters are listed in Table 1. One patient had to be admitted to the hospital after the second study treatment for reasons, which were not related to the study. As a consequence, one treatment with DIAPES® HF800 could not be performed.

Determination of albumin and β2m

In order to study the removal of β2m and albumin with the haemodiafiltrate, a T-connector was introduced into the effluent haemodiafiltrate line allowing continuous collection of haemodiafiltrate at a flow rate of 1 ml/min into a separate beaker during the entire duration of the treatment (Figure 1). Samples were drawn from this haemodiafiltrate pool after each hour of treatment. Before sampling, the pool was mixed well by a magnetic stirrer.

The mass of solute transferred to the haemofiltrate after a given time t was calculated from:

\[
\text{mass of solute} = Q_{out} \times t \times c_t
\]

where \(Q_{out}\) is the outlet haemofiltrate flow rate, consisting of the dialysate flow rate \(Q_{dial/in}\), the substitution fluid flow rate \(Q_{sub}\), and the net ultrafiltration flow rate \(Q_{UF}\) as shown in Figure 1. \(c_t\) is the concentration of the solute in the cumulated haemodiafiltrate pool after time t.

The plasma levels of β2m and albumin were measured directly before (pre, \(t = 0\)) and after (post, \(t = 240\) min) the treatment. β2m and albumin in haemodiafiltrate and in plasma were measured by laser nephelometry (BN 100 Analyzer, Dade-Behring Marburg GmbH, Marburg, Germany) using ‘N Latex β2-microglobulin’ and ‘N Antiserum to human albumin’ (Dade-Behring Marburg GmbH), respectively. The β2m post-haemodiafilter concentration was corrected for haemoconcentration according to Bergstrom and Wehle [7].

Statistics

Differences between parameters were tested by multivariate ANOVA and Duncan’s multiple range test. A \(P\) value of <0.05 was considered significant. Results are given as mean of all treatments ± SEM.
Results

The absolute amount of $\beta_2m$ and of albumin detectable at the end of the treatment in the cumulative haemodiafiltrate pool as well as the pre- and post-treatment plasma values for albumin are shown in Table 2. Both total $\beta_2m$ and total albumin found in the haemodiafiltrate decreased in the sequence DIAPES® HF800 > polysulfone > polyamide. There was a significant difference for both, $\beta_2m$ and albumin in the haemodiafiltrate between the three membranes. All other data, especially the respective pre-treatment values, showed no significant differences between the three membranes.

While the DIAPES® HF800 haemodiafilter reduced the plasma $\beta_2m$ level by 77 ± 1% of the pre-dialysis value (identical to the reduction with polysulfone), polyamide achieved only a reduction rate of 71 ± 1% ($P < 0.05$) as shown in Figure 2.

The amount of $\beta_2m$ in haemodiafiltrate corresponded with the amount of albumin in haemodiafiltrate. All membranes showed an increase of the albumin concentration in haemodiafiltrate during the last 2 h of treatment.

Pre-dialysis plasma albumin values and ultrafiltration volumes were comparable for the three membranes, the latter despite the fact that in all cases the ultrafiltration rates were set individually in order to achieve the patients’ dry weights (see Table 1). Although DIAPES® HF800 showed the highest albumin loss into haemodiafiltrate, interestingly, the post-dialysis plasma albumin level after the DIAPES® HF800 treatments was significantly higher compared with the other two haemodiafilters (Table 2).

Discussion

Treatments with DIAPES® HF800 used in the HDF mode were tolerated very well without any side-effects and did not differ in this regard from those with established membranes. Average blood pressure was slightly increased before and normalized during treatments in all three groups as expected. Blood and
haemodiafiltrate flow rates, ultrafiltration and infusion volumes, pre-treatment $\beta_2m$ and albumin concentrations were not significantly different between the three membranes under investigation. Therefore, these factors did neither influence the removal of $\beta_2m$ nor of albumin during treatment.

In conventional HD with high-flux polysulfone and a blood flow of 300 ml/min a $\beta_2m$ plasma reduction rate of $\sim$50\% has been reported whereas on-line HDF in post-dilution mode with 100 ml/min substitution fluid resulted in a reduction rate of 73\% [8]. With a substitution rate of 120 ml/min and a blood flow of 350 ml/min $\beta_2m$ plasma reduction rate could not be raised further [8]. In our study, a higher $\beta_2m$ plasma reduction rate was observed for both DIAPES® HF800 and polysulfone with a substitution fluid flow rate of only 60 ml/min and a blood flow of only 250 ml/min. In another report on conventional HDF (22 ml/min substitution flow rate, 402 ml/min blood flow rate) and for online HDF (120 ml/min, 434 ml/min) using polysulfone as well as AN69® membranes a removal rate of $\beta_2m$ from plasma of 56 and 71\% was observed, respectively [2]. On the contrary, as shown recently, CAPD patients with normal albumin, lose more albumin into dialysate compared with hypoalbuminaemic patients. Reduction of plasma albumin was only observed in those patients having a reduced protein catabolic rate even without overt inflammation [13].

In our HDF study, albumin loss was lowest with polyamide (1.0 ± 0.7 g/session), intermediate with polysulfone (3.5 ± 1.4 g/session) and highest with the DIAPES® HF800 membrane (5.7 ± 1.4 g/session). To operate the HDF process under stable conditions during the entire session in all patients, we choose a blood flow rate of 250 ml/min and limited the filtration/substitution volume to 60 ml/min. If the membranes, however, will be used at higher blood flow rates and substitution volumes albumin loss will presumably increase.

A previous study from an Italian group with two different PMMA membrane-based filters, even in HD mode, which is prone to a reduced loss of albumin compared with HDF, revealed a higher loss of albumin compared with the three filters we have examined (Filtryzer BK-P, 5.9 g/session; BK-F, 7.4 g/session, Toray, Tokyo, Japan) [4]. In another study with the Filtryzer BK-F, the dialyser with the highest loss of albumin reported to date, after 6 months of HD the plasma albumin level returned to 3.7 ± 0.2 g/dl after an initial drop. In parallel, renal anaemia improved [5]. It was hypothesized that enhanced removal of some compounds of higher molecular weight (probably having a molecular weight of $\sim$40 kDa), exerting an inhibitory effect on erythroid progenitors, could be responsible [14].

Our study shows that with the three membranes DIAPES® HF800, polysulfone and polyamide, $\beta_2m$ removal into haemodiafiltrate was directly related to albumin loss (Table 2). Thus, a higher loss of albumin...
seems to be unavoidable to remove more effectively certain uraemic toxins, e.g. proteins with a molecular weight higher than $\beta_\text{m}$ [5]. In our study, a loss of albumin with DIAPES® HF800 higher than with the two other membranes was not associated with a decrease of post-treatment albumin concentration. Provided a sufficient dietary protein intake, a loss of 6 g albumin/treatment in patients free of symptoms of inflammation can probably be tolerated as it will be compensated by enhanced albumin synthesis. However, these questions need to be addressed in a separate, long-term study [15].

Taking into account the two aspects of excellent low molecular weight clearances and the high permeability for low molecular weight proteins (indicated by the high $\beta_\text{m}$ in haemodiafiltrate), a general conclusion regarding serum albumin levels, treatment conditions and patient’s risk cannot be made at the present time. Although, DIAPES® HF800 in HDF mode appears to offer a valuable alternative to conventional membranes long-term experience with this new membrane is needed to show whether its higher removal capacity for low molecular weight proteins is associated with additional clinical benefit.

Conflict of interest statement. B. Reinhardt, A. Northdurft and H.-D. Lemke were at the time of the study employed by Membrana GmbH, the manufacturer of DIAPES® HF800.

References

7. Bergstrom J, Wehle B. No change in corrected $\beta_\text{m}$-microglobulin concentration after Cuprophan hemodialysis. Lancet 1987; 1: 628–629

Received for publication: 18.11.02
Accepted in revised form: 13.6.03