Removal of Plasma Porphyrins with High-Flux Hemodialysis in Porphyria Cutanea Tarda Associated with End-Stage Renal Disease

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ABSTRACT
Plasma porphyrin levels are markedly increased in patients with porphyria cutanea tarda (PCT) associated with end-stage renal disease. Conventional hemodialysis (CHD) with lower blood flow rates (<250 mL/min) and cuprophan or cellulose acetate membranes is ineffective in removing significant amounts of porphyrins in this condition. Changes in plasma porphyrin levels and porphyrin clearances during hemodialysis with higher blood flow rates and more-permeable, high-efficiency cellulose acetate and high-flux polysulfone dialyzers were evaluated in a chronic hemodialysis patient with PCT and markedly elevated plasma porphyrins. The polysulfone membrane achieved significantly better fractional porphyrin removal ($P = 0.02$) and porphyrin clearances ($P < 0.01$) than did the high-efficiency cellulose acetate membrane. After conversion from maintenance CHD with a standard cellulose acetate dialyzer to a 4-wk period of high-flux hemodialysis (HFHD) with a polysulfone dialyzer, predialysis plasma porphyrins fell by 37%. After returning to CHD, plasma porphyrins returned to the higher prestudy levels. These observations suggest that HFHD with more permeable membranes and higher blood flow rates removes porphyrins more effectively than does CHD. HFHD may be a useful adjunct to other measures used in treating dialysis patients with PCT.

Key Words: High-flux hemodialysis, porphyrins, porphyria cutanea tarda

Porphyria cutanea tarda (PCT) occurs in some patients with end-stage renal disease and is associated with increased levels of plasma porphyrins and cutaneous photosensitivity (1,2). Recent reviews have described in detail the characteristic blistering, depigmented skin lesions, biochemical abnormalities, and pathogenesis of PCT, as well as other bullous dermatoses with little or no increase in plasma porphyrins that are observed in dialysis patients (1–5).

Photosensitivity in PCT results from an accumulation of light-reactive porphyrins in plasma and skin. The excess porphyrins originate from the liver because of a deficiency of uroporphyrinogen decarboxylase, an enzyme of the heme biosynthetic pathway that is subject to inactivation by iron. Reducing hepatic iron content by phlebotomy or other methods lowers plasma porphyrins and is associated with clinical improvement (6–8). Unfortunately, repeated phlebotomies may not be a realistic option for some hemodialysis patients with PCT because of the anemia associated with chronic renal failure. Although erythropoietin administration can mobilize hepatic iron stores and support phlebotomies in such patients (9), a complete remission may require several months. Therefore, adjunctive therapies to remove porphyrins from dialysis patients with PCT would be useful.

Efforts to lower plasma porphyrin levels with hemodialysis with conventional cuprophan and cellulose acetate membranes have been unsuccessful. The few published reports that examine porphyrin removal have shown no significant differences in predialysis and postdialysis plasma porphyrin concentrations. Although porphyrins have occasionally been detected in dialysate, the amounts removed are small and of little clinical significance (1,2,10,11).

Dialysis with more-permeable membranes has somewhat greater potential for removing porphyrins.
Garcia-Parilla et al. (12) reported a 40% reduction in plasma porphyrin levels in a patient with PCT during a single 5-h conventional dialysis session with the acrylonitrile RP6-HP dialyzer (Rhône Poulenc, Paris, France). However, total plasma porphyrins remained high despite continued use of this dialyzer.

The following report describes our efforts to lower porphyrin levels in a chronic hemodialysis patient with PCT by using dialyzers with more-permeable membranes and blood flow rates higher than those routinely used during conventional hemodialysis (CHD). The purposes of our study were (1) to determine if high-flux hemodialysis (HFHD) can achieve better removal of porphyrins than does CHD; and (2) to compare porphyrin clearances of currently available high-efficiency and high-flux membranes.

METHODS

Clearance Studies

Fractional porphyrin removal and total porphyrin clearance were studied during HFHD with a Drake-Willock 480 machine with volumetric ultrafiltration control (Abthin Drake Willock, Portland, OR). Blood flow rate was 300 mL/min, and dialysate flow was 500 mL/min. Dialyzers used for the porphyrin clearance studies were the CDAK Duoflux (CD Medical Inc., Miami Lakes, FL) and Fresenius F-60 (Fresenius UAS, Concord, CA). The Baxter CA-90 dialyzer (Baxter Healthcare Corp., Deerfield, IL) was used for the patient’s routine maintenance CHD (Table 1). Porphyrin clearances were measured during isovobemic dialysis (i.e., no net ultrafiltration) in a darkened room with no exposure to fluorescent light. Simultaneous arterial and venous blood line and dialysate samples were collected in duplicate in shielded containers and were analyzed for total porphyrin content by fluorescence spectroscopy as previously described (12). Four clearance measurements were made with the high-efficiency and high-flux dialyzers during two separate dialysis sessions. Samples were taken during the first 30 min of dialysis. Porphyrin clearance was calculated by the standard formula:

$$C = \frac{(A - V) \cdot Q_h}{A}$$

where C is porphyrin clearance in milliliters per minute, A is arterial blood line porphyrin concentration, V is venous blood line porphyrin concentration, and \(Q_h\) is blood flow rate in milliliters per minute.

Maintenance Dialysis Study

After the porphyrin clearance studies, which were carried out at the end of a 4-month observation period on CHD, the patient was converted from maintenance CHD (CA-90 dialyzer; 4 h, 3 times/wk; \(Q_h\), 225 mL/min) to a HFHD regimen (F-60; 4 h, 3 times/week; \(Q_h\), 300 to 350 mL/min) with ultrafiltration to remove only the interval weight gain. HFHD was performed for 4 wk with twice-weekly measurements of predialysis plasma porphyrins. Plasma porphyrins were monitored for 4 wk after the patient returned to CHD. Data are expressed as mean ± SE and were analyzed by the paired t test unless noted otherwise. P values < 0.05 were considered significant.

RESULTS

Figure 1 demonstrates the measured porphyrin clearances and fractional porphyrin removal, expressed as the percentage of the A − V difference divided by the arterial line infow porphyrin concentration. The polysulfone F-60 provided substantially better porphyrin clearance than did the cellulose acetate Duoflux (27.98 ± 2.87 versus 12.65 ± 1.46 mL/min; P < 0.002). The F-60 dialyzer also achieved approximately twice the fractional porphyrin removal of that obtained with the Duoflux (9.91 ± 0.98 versus 4.31 ± 0.45%; P = 0.02). The mean total porphyrin concentration measured in the dialysate collected from four separate HFHD sessions with the F-60 dialyzer was 5.9 ± 0.63 μg/dL.

Conversion from maintenance CHD to a 4-wk trial of maintenance HFHD with a polysulfone membrane was associated with a substantial decrease in the patient’s plasma porphyrin levels. The baseline predialysis porphyrin level declined from 202 μg/dL during CHD to 128 μg/dL by the end of the trial of HFHD (Figure 2). This decrement represented a 37% reduction in the plasma porphyrin concentration and was evident by the third week of HFHD. Four weeks after resuming CHD, plasma porphyrins had returned to the baseline pre-HFHD level of 209 μg/dL. When all predialysis plasma porphyrin levels are combined for

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**TABLE 1. Characteristics of high-efficiency and conventional dialyzers**

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Surface Area (m²)</th>
<th>Ultrafiltration Coefficient (mL/h/mm Hg)</th>
<th>Clearance of Vitamin B12a (mL/min at QB300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duoflux</td>
<td>1.5</td>
<td>15</td>
<td>88</td>
</tr>
<tr>
<td>F-60</td>
<td>1.25</td>
<td>40</td>
<td>134</td>
</tr>
<tr>
<td>CA-90</td>
<td>0.9</td>
<td>4.3</td>
<td>42</td>
</tr>
</tbody>
</table>

*In vitro data supplied by manufacturer.*

*b In vivo data supplied by manufacturer.*
Porphyrin Removal (%)

Figure 1. Total porphyrin clearance and fractional porphyrin removal. Fractional removal is expressed as the percentage of the A − V difference divided by the arterial line inflow porphyrin concentration. The high-flux polysulfone F-60 dialyzer achieved significantly higher porphyrin clearances than did the high-efficiency cellulose acetate Duoflux (27.98 ± 2.87 versus 12.65 ± 2.46 mL/min; " P < 0.002). The F-60 also provided significantly better fractional porphyrin removal than did the Duoflux (9.91 ± 0.98 versus 4.31 ± 0.45%; " P = 0.02).

Figure 2. Maintenance dialysis study: Predialysis plasma porphyrin concentration as a function of dialysis method. Baseline porphyrin levels declined 37% from 202 μg/dL during CHD to 126 μg/dL after 3 wk of HFHD. Four weeks after resuming CHD, porphyrin levels returned to baseline (209 μg/dL).

the two periods of CHD and were compared with levels during HFHD (Figure 3), the mean porphyrin level during HFHD is significantly lower than the mean porphyrin level during CHD (166 ± 7 versus 186 ± 5 μg/dL; P = 0.02 by unpaired t test).

DISCUSSION

PCT is recognized as a cause of cutaneous photosensitivity in some CHD patients (1–4). The condition is caused by inactivation of hepatic uroporphyrinogen decarboxylase by iron overload or an inherited partial deficiency of uroporphyrinogen decarboxylase. Other factors such as ethanol, estrogens, and drugs or toxins that stimulate hepatic heme biosynthesis may contribute in some patients. Azotemia, aluminum intoxication, and exposure to plasticizers in blood tubing have been suggested as inducers of PCT in predisposed individuals (4,13).

Successful management of PCT often requires additional measures beyond the avoidance of recognized stimulating factors. Because excess hepatic iron is the major cause of uroporphyrinogen decarboxylase inhibition in most cases, efforts to remove iron are of major importance. Periodic phlebotomy and i.v. deferoxamine therapy are effective in inducing clinical remissions by depleting iron stores and restoring uroporphyrinogen decarboxylase activity (6,8). Although some porphyrins in plasma are removed by phlebotomy, the amounts are small and of
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Figure 3. Combined results of predialysis plasma porphyrin levels for CHD versus HFHD. The mean plasma porphyrin level during HFHD was 166 ± 7 μg/dL compared with 186 ± 5 μg/dL while on CHD. P = 0.02 by unpaired t test.

little consequence. Alternative therapies such as chloroquine, which enhances the solubility of porphyrins and facilitates their excretion into the urine (14,15), and oral sorbents to remove porphyrins via the gastrointestinal tract have also been tried but have produced disappointing results in patients with renal failure (12,13).

The anemia associated with chronic renal failure has made the treatment of PCT in dialysis patients difficult because it precludes repeated phlebotomies, which may be required in patients with large tissue burdens of iron and porphyrins. Although small-volume (50 to 100 mL) phlebotomies carried out 1 to 2 times weekly over 1 yr are effective in inducing remission of skin lesions and lowering plasma porphyrin levels (6), the cumulative blood losses are substantial and can maintain a degree of anemia that may not be well tolerated by many dialysis patients. Correcting anemia with erythropoietin in order to deplete excess hepatic iron stores is an encouraging treatment strategy recently developed by Anderson et al. (9).

Rapid and substantial removal of porphyrins by extracorporeal techniques would be a useful adjunct to erythropoietin therapy and phlebotomy especially in patients with severe debilitating skin lesions and very high plasma porphyrin levels. Unfortunately, hemodialysis with conventional cuprophan and cellulose acetate dialyzers is ineffective in removing porphyrins. Most reported cases demonstrate no meaningful reduction in plasma porphyrin levels and only trivial amounts of porphyrins detectable in dialysate (1,10,16,17). Charcoal hemoperfusion is also ineffective in removing porphyrins (18). Plasmapheresis and plasma exchange, however, have demonstrated limited success in removing porphyrins. Allen et al. (19) reported reductions in plasma porphyrin levels ranging from 33 to 99% in five patients with cutaneous hepatic porphyria who underwent between 9 and 22 plasmapheresis sessions. In one chronic dialysis patient with PCT, Disler et al. (7) demonstrated an 80% reduction in plasma porphyrin levels after two sessions of plasma exchange with a hollow fiber cellulose acetate plasma separator. Remission of skin lesions occurred despite a rebound rise in plasma porphyrin levels after the last treatment.

Given the inadequacy of conventional dialysis in removing porphyrins and the limitations of plasma exchange, such as expense and risk of infection, it would seem reasonable to consider whether newer, more-permeable high-efficiency and high-flux membranes combined with higher blood flow rates during dialysis might accomplish better porphyrin removal than what has been reported previously with CHD. With standard hemodialysis with ethylenvinyl alcohol (EVAL) and polyacrylonitrile (PAN) membranes, Kusano and Asano noted a 12.5% reduction in plasma porphyrin levels with EVAL and a 16.5% reduction with PAN dialyzers along with fractional porphyrin removals of 19.2% with EVAL and 20.5% with PAN (20). Additional studies with the same membranes have shown a correlation between serum aluminum and porphyrin levels, but no relationship could be shown between plasma porphyrins and iron stores (21).

Our experience supports the utility of high-flux membranes for dialysis in patients with PCT. The F60 dialyzer achieved a fractional total porphyrin removal of approximately 10% and measured clearances of 27 mL/min (Figure 1). The significantly higher ultrafiltration capability of the F-60 may have provided more-convective porphyrin removal at the inflow end of the dialyzer where transmembrane
pressures favor ultrafiltration. Our results were obtained during isovolumic dialysis. If ultrafiltration were incorporated into the dialysis procedure (high-flux hemodialfiltration), additional convective removal of porphyrins would be expected to provide even better fractional porphyrin removal and clearances. Previous reports examining the use of high-flux dialyzers in patients with PCT do not give sufficient technical details to assess which factors could account for the higher fractional porphyrin removal and dialysance noted in these studies (12,20). Differences in dialyzer surface area, amount of ultrafiltration, blood and dialysate flow rates, and duration of the dialysis session could account for the discrepancies between our measured porphyrin removal and that of Garcia-Parilla et al. (12) and Kusano and Asano (20).

Although uroporphyrin (the predominant porphyrin in the plasma of patients with PCT) is a relatively water-soluble, small, middle-molecular-weight substance, it is unclear why hemodialysis fails to remove it and other porphyrins in patients with PCT. The discrepant observations regarding porphyrin clearances with conventional and high-flux dialyzers suggest that specific membrane characteristics may account for the better porphyrin removal seen with high-flux dialyzers. The larger pore size of high-flux polysulfone membranes may facilitate the passage of porphyrins across the membrane to a greater degree than what is achievable with conventional smaller-pore membranes. Whether polysulfone and conventional membranes differ in their ability to bind porphyrins or whether membrane binding significantly affects porphyrin clearance is a matter of speculation requiring additional study.

Plasma porphyrin levels decreased by 37% in our patient after only 3 wk of high-flux dialysis with the F-60 polysulfone dialyzer. With the resumption of CHD with a cellulose acetate dialyzer, plasma porphyrins returned to prestudy levels in excess of 200 μg/dL (Figure 2). The reduction in plasma porphyrins during the 4-wk of HFHD, however, was not sufficient to produce a clinical remission in our patient presumably because excess porphyrins continued to become available from tissue stores as well as from continued production in the liver.

A longer period of HFHD with the polysulfone dialyzer might have provided additional porphyrin removal. From measured dialysate porphyrin concentrations obtained during our clearance study, we calculate that approximately 6.2 mg of porphyrin could be removed during a typical 3½-h HFHD session with the F-60 dialyzer. Assuming that the typical patient with PCT accumulates a tissue porphyrin burden of 1.0 to 2.0 g (22), one HFHD session could remove 0.3 to 0.6% of the total porphyrin burden. At this rate, it would take approximately 1 yr for our method of HFHD to remove the total hepatic porphyrin content, provided there is no ongoing formation of porphyrins. Further studies are required to determine whether HFHD, perhaps with large amounts of ultrafiltration (i.e., hemodiafiltration) could accomplish more rapid removal of porphyrins during active PCT.

In summary, we have shown in a patient with hemodialysis-associated PCT that HFHD with a polysulfone high-flux dialyzer can achieve better porphyrin removal than can standard hemodialysis with conventional membranes and lower blood flow rates. Our finding of reduced porphyrin clearance with the CDAK-DuoFlow dialyzer suggests that high-efficiency hemodialysis would not be as effective an alternative as high-flux dialysis for removing excess porphyrins. Although the long-term significance of our findings remains to be determined, it is likely that HFHD with a polysulfone dialyzer will be a useful adjunct to erythropoietin therapy in patients with this potentially debilitating and life-threatening condition.

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