Vitamin B6 supplementation can improve peripheral polyneuropathy in patients with chronic renal failure on high-flux haemodialysis and human recombinant erythropoietin

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Abstract

Background. High-flux haemodialysis (HD) has recently been vigorously promoted as a novel standard, and it can indeed efficiently reduce the occurrence of most uraemic symptoms due to middle molecular toxins and/or underdialysis. However, some symptoms remain problematical, particularly peripheral polyneuropathy (PPN). One of the possible reasons for this is that the patients may have low concentrations of some nutrients, e.g. vitamin B6, necessary for normal peripheral neuron function.

Methods. Predialysis serum pyridoxal-5′-phosphate (P5P) level was determined in 36 chronic HD patients who were undergoing high-flux HD and receiving human recombinant erythropoietin. Among them, 26 patients suffered from PPN. Prior to supplementation, these 26 patients were examined and their neurological symptoms were ranked according to our PPN symptom score. Vitamin B6 (60 mg/day) was randomly prescribed to 14 of them, and vitamin B12 (500 µg/day) was prescribed to the others. After 4 weeks, all the patients were re-examined.

Results. We found that predialysis serum P5P levels of HD patients with PPN were not significantly lower than those of matched HD patients without PPN. Nonetheless, it was demonstrated that supplementation with vitamin B6 for 4 weeks significantly increased the predialysis level of P5P and dramatically attenuated PPN symptoms compared with initial symptoms. No improvement was observed in response to vitamin B12 supplementation.

Conclusion. This result suggests that although vitamin B6 deficiency could not be demonstrated in patients with chronic renal failure on high-flux HD, vitamin B6 supplementation was effective in improving PPN symptoms of various aetiologies, possibly because of vitamin B6 resistance to PPN in these patients.

Keywords: high-flux haemodialysis; human recombinant erythropoietin; peripheral polyneuropathy; vitamin B6

Introduction

In the early years of haemodialysis (HD), patients on standard HD treatment commonly suffered from uraemic peripheral polyneuropathy (PPN), e.g. restless leg syndrome and burning foot syndrome. It was assumed that this was because of underdialysis and/or poor clearance of uraemic toxins of middle to high molecular weights [1,2]. In fact, more effective removal of middle-sized and larger molecules by haemodiafiltration did prevent the worsening of uraemic PPN during standard HD treatment [1]. Recently, high-flux HD has supplanted regular HD as the standard treatment, and yields better clearance of not only low-molecular-weight solutes but also middle-sized molecules [3,4]. However, the incidence of PPN does not seem to have been lowered as a result. This may be explained by the fact that not only pure uraemic PPN, but also a variety of other aetiological factors, i.e. diabetic PPN, dialysis-related amyloidosis, or arteriosclerotic obliteration, may cause or aggravate numbness of the extremities in chronic HD patients [5,6]. Additionally, another possible explanation may be a depletion of thus far unrecognized members of B-complex vitamins [7]. Among these, vitamin B6 is metabolized to the active molecule, pyridoxal-5′-phosphate (P5P), which influences amino acids, protein and lipid metabolism [8–11]. Removal of P5P by standard HD has been extensively studied but with contradictory results [12–22]. Kasama et al. [23] reported that high-flux HD depletes vitamin B6 at a rate possibly great enough to cause vitamin B6 deficiency. Furthermore, administration of human recombinant erythropoietin (rHuEpo), which has dramatically improved haematopoiesis in patients with chronic renal failure, may contribute to vitamin B6 deficiency. Thus, indirect
Evidence has shown that much more vitamin B<sub>6</sub> is consumed by haemoglobin synthesis during rHuEpo treatment in HD patients, and this may contribute to vitamin B<sub>6</sub> deficiency [21,24]. In the present study, we examined whether alterations in vitamin B<sub>6</sub> metabolism have any impact on symptoms of PPN in chronic renal failure patients receiving high-flux HD and rHuEpo treatment.

Subjects and methods

Table 1 summarizes the demographic profile of the patients receiving chronic high-flux HD and rHuEpo treatment in this study. Patients were selected from the Kidney Disease Center of Saitama Medical College and its affiliated dialysis clinics. For inclusion in the study, the patients must have been on HD for at least 3 months with a constant HD prescription (Kt/V > 1.1) using high-flux, high-performance dialysers, and treated with rHuEpo (Epopin; Sankyo, Tokyo, Japan) 4500–9000 U/wk to maintain a haematocrit between 28 and 33%. Patients who met inclusion criteria were enrolled in the study if they complained of PPN symptoms in the lower extremities and wished to take medication. Patients with clinically or angiographically identified arteriosclerotic obliteration, megaloblastic anaemia, any systemic illness causing malnutrition and/or poor appetite, or those taking water-soluble vitamin supplements were excluded from the analysis. Informed consent was obtained from all patients prior to participation in the study.

The hollow-fibre dialysis membranes used in this study were FB-150F (Nipro, Osaka, Japan) (triacetate, 1.5 m<sup>2</sup>, ultrafiltration rate (UFR) 39.72 ml/mmHg/h, vitamin B<sub>12</sub> clearance 140 ml/min), TFW15 (Teijin-Gambro, Tokyo, Japan) (triacetate, 1.5 m<sup>2</sup>, UFR 22 ml/mmHg/h, vitamin B<sub>12</sub> clearance 140 ml/min), PS-1.6N (Fresenius-Kawasaki, Tokyo, Japan) (polysulphone, 1.6 m<sup>2</sup>, UFR 37.4 ml/mmHg/h, vitamin B<sub>12</sub> clearance 128 ml/min), and FLX-15GW (Nikkiso, Tokyo, Japan) (polyether polymer alloy, 1.5 m<sup>2</sup>, UFR 39 ml/mmHg/h, vitamin B<sub>12</sub> clearance 150 ml/min). None was reused. Standard HD modalities in our unit are as follows: dialysis duration, 4 h; blood flow rate, 200 ml/min; and dialysate flow rate, 500 ml/min. Routine heparinization was carried out as anticoagulation to keep activated coagulation time at 150 s.

All patients were examined and ranked according to the PPN symptom score by HO and KM when they complained of PPN symptoms in the lower extremities. The scoring scheme was as follows:

0, no symptoms;
1, loss of sensation and/or slight numbness;
2, moderate numbness and/or restlessness;
3, burning and/or soreness; and
4, pain.

The involvement of large myelinated sensory fibres in uraemic neuropathy has been demonstrated using electrophysiological tests [25], but in this study the results of such tests were not included because the PPN symptoms evaluated in this study, typically in a stocking and glove distribution, are derived mostly from small sensory fibres [25]. Predialysis blood samples were obtained at the first session of the week to determine routine laboratory data as well as to see the peak serum level of P5P before and during the supplementation. P5P was measured by SRL service (Kawagoe, Japan) using high-performance liquid chromatography [26], the normal range being 4.0–40.0 ng/ml. The patients studied were divided randomly into two groups, one of which received the vitamin B<sub>6</sub> supplement (60 mg/day) (G-VB<sub>6</sub>, n = 14) and the other was given the vitamin B<sub>12</sub> supplement (500 µg/day) (G-VB<sub>12</sub>, n = 12). Vitamin B<sub>12</sub> was used because it is also considered to be a neurotrophic vitamin. Patients were blinded as to which medication they received. The doses of vitamin B<sub>6</sub> and vitamin B<sub>12</sub> were chosen based on recommendations for HD patients treated with isoniazid (INH) and for patients with uraemic and diabetic PPN respectively [27,28]. Four weeks later they were re-examined by HO and KM.

Ten control patients (G-Cont) receiving high-flux HD and rHuEpo treatment but without PPN symptoms were selected and evaluated. Data are shown as mean ± SE. Data were analysed using analysis of variance; changes in PPN symptom scores were evaluated with a non-parametric statistical analysis, the Mann–Whitney U-test. P < 0.05 was required for significance.

Results

Table 1 shows the demographic data of each group; there were no significant differences between these groups. Notably, there was a tendency for predialysis level of P5P to be lower in G-VB<sub>6</sub> and G-VB<sub>12</sub> than in G-Cont, but this failed to reach statistical significance. Figures 1 and 2 show the changes in PPN scores during 4 weeks of supplementation with vitamin B<sub>6</sub> and vitamin B<sub>12</sub>, respectively. It was demonstrated that supplementation with vitamin B<sub>6</sub> but not with vitamin B<sub>12</sub> significantly reduced the PPN symptoms in chronic renal failure patients with high-flux HD and rHuEpo treatment (Figures 1, 2). Of interest, PPN symptoms of diabetes mellitus (DM) patients in G-VB<sub>6</sub> were also improved similarly to the ones of chronic glomerulonephritis (CGN) patients (Figure 1).

Discussion

Deficiency of vitamin B<sub>6</sub> in humans leads to seborrhoea-like lesions, cheilosis and glossitis, depressed lymphocyte counts, hypochromic anaemia and loss of the ability to convert tryptophan to nicotinic acid, and PPN [9–11]. Vitamin B<sub>6</sub> is rapidly converted by the body into P5P and pyridosamine phosphate, which function as coenzymes and play an essential role in amino acid metabolism [9–11]. Good sources of vitamin B<sub>6</sub> in the diet include avocado, carrots, spinach, peas, potatoes, milk, cheese, eggs, fish, meat, and wheat [11]. Because of such a wide availability of the vitamin, it is difficult to induce clinical signs and symptoms of vitamin B<sub>6</sub> deficiency by dietary restriction. However, biochemical abnormalities indicative of subclinical vitamin B<sub>6</sub> deficiency have been reported in certain groups of persons including uraemic patients [8,13]. Vitamin B<sub>6</sub> deficiency-related PPN was characterized by symmetrical numbness in a stocking and glove distribution, more severe in the feet than in the hands [9,11]. The similarity between the clinical picture of INH-induced PPN and vitamin B<sub>6</sub> deficiency had been noted. The examination of vitamin B<sub>6</sub> metabolism in patients...
### Table 1. Demographic data of the patients in this study

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Gender (M/F)</th>
<th>Age (years)</th>
<th>Duration of HD (years)</th>
<th>Disease</th>
<th>Dialyser</th>
<th>Kt/V</th>
<th>Predialysis Cr (mg/dl)</th>
<th>Predialysis β2-MG (mg/dl)</th>
<th>Predialysis PSP (ng/ml) pretreatment</th>
<th>Predialysis PSP (ng/ml) on-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VB₆</td>
<td>14</td>
<td>6/8</td>
<td>59 ± 5</td>
<td>4.6 ± 1.1</td>
<td>CGN(8)</td>
<td>FB-150F(8) TFW15(3) PSL6N(2) FLX-15GW(1)</td>
<td>1.3 ± 0.1</td>
<td>11.0 ± 1.2</td>
<td>32.7 ± 2.6</td>
<td>5.9 ± 0.8</td>
<td>29.7 ± 5.3</td>
</tr>
<tr>
<td>VB₁₂</td>
<td>12</td>
<td>6/6</td>
<td>60 ± 4</td>
<td>5.8 ± 1.2</td>
<td>CGN(7)</td>
<td>FB-150F(7) TFW15(2) PSL6N(1) FLX-15GW(2) FB-150F(5)</td>
<td>1.2 ± 0.0</td>
<td>10.1 ± 0.9</td>
<td>29.9 ± 4.0</td>
<td>5.4 ± 1.0</td>
<td>5.5 ± 1.0</td>
</tr>
<tr>
<td>Cont</td>
<td>10</td>
<td>6/4</td>
<td>53 ± 5</td>
<td>3.4 ± 1.0</td>
<td>CGN(6)</td>
<td>FB-150F(5) TFW15(2) PSL6N(0) FLX-15GW(3)</td>
<td>1.2 ± 0.0</td>
<td>13.3 ± 2.0</td>
<td>36.8 ± 3.3</td>
<td>7.2 ± 0.8</td>
<td>7.1 ± 1.0</td>
</tr>
</tbody>
</table>

VB₆, vitamin B₆ supplement; VB₁₂, vitamin B₁₂ supplement; HD, haemodialysis; CGN chronic glomerulonephritis; DM, diabetes mellitus; Cr, creatinine; β₂-MG, β₂-microglobulin; PSP, pyridoxal-5'-phosphate.

Taking INH revealed that INH-induced PPN is due to a vitamin B₆ deficiency or a competitive inhibition of its action mediated by the formation of pyridoxal isonicotinyl hydrazone [11].

There is also a great similarity between vitamin B₆ deficiency-related PPN and PPN in chronic HD patients. For that reason, we carried out the present study. Vitamin B₆ levels in HD patients have been extensively studied, but the results are divergent and confusing [12–23, 29]. Among them, Descombes et al. [29] and Kasama et al. [23] demonstrated increased clearance of PSP by high-flux HD (173 ± 90 ml/min), and showed that PSP levels were lower in patients on high-flux HD than on standard HD. In fact, in this study, the predialysis PSP level of 7.1 ± 0.8 ng/ml was lowered to the post-dialysis level of 3.7 ± 0.4 ng/ml by high-flux HD in G-Cont. Additionally, Mydlik et al. [21,24] showed that erythrocyte vitamin B₆ is consumed by the haemoglobin synthesis to a much greater extent during rHuEpo treatment in HD patients. Therefore, the current preferred prescription for HD, i.e. high-flux HD and rHuEpo administration, may result in vitamin B₆ deficiency more frequently than hitherto suspected. However, in this study, the predialysis levels of serum PSP prior to the supplementation in G-VB₆, G-VB₁₂, and G-Cont, which were presumed to be peak concentrations, were not significantly different, and stayed within the normal range.

Nonetheless, vitamin B₆ supplementation increased the predialysis level of PSP significantly and did improve PPN symptoms of these patients. This observation suggests the notion that perhaps even patients on high-flux HD and rHuepo treatment are in danger of vitamin B₆ resistance to PPN. This issue has been discussed previously with respect to folic acid resistance to hyperhomocysteaemia in patients with chronic renal failure [30,31]. It is difficult to explain why some patients suffered from vitamin B₆ resistance, but others did not.

As discussed earlier, the aetiology of PPN in chronic HD patients is complex, and it seems unlikely that
vitamin B₆ resistance is a primary cause. We consider it likely to be an important factor aggravating PPN caused by other mechanisms. Thus, the degree of improvement of PPN symptoms resulting from vitamin B₆ supplementation was variable among the patients, and considerable improvement was observed even in DM patients possibly suffering from diabetic PPN (Figure 1). Vitamin B₆ deficiency induces a pure axonal neuropathy, and it probably needs more than 4 weeks for the symptoms to improve with vitamin B₆ supplementation. [9,11]. However, in this study, PPN symptoms improved with vitamin B₆ supplementation within 4 weeks, which suggests that PPN in these patients was partially aggravated by vitamin B₆ resistance. There is no data to account for such vitamin resistance in chronic renal failure patients. Uraemic toxins that are not efficiently removed by current high-flux HD may be associated with the phenomenon. Although, from the point of view of the middle molecule theory [2], uraemic PPN underdialysis seems less likely in our study patients because of their relatively low levels of β₂-microglobulin, we cannot exclude the possibility that some of them may have derived benefits from more extensive HD as well as vitamin B₆ supplementation. Care must be exercised when evaluating patients on high-flux HD because vitamin B₆ resistance can contribute not only to PPN, but also to nausea, vomiting, anorexia, anaemia, and altered immune responses, which themselves can be misinterpreted as underdialysis [7,23]. At present, it remains unclear whether more extensive HD improves vitamin B₆ resistance or induces vitamin B₆ deficiency. This is the first report in which vitamin B₆ supplementation was demonstrated to improve PPN symptoms in patients on high-flux HD and rHuEpo treatment. Recently we have also found that PPN in CAPD patients can be efficiently improved following vitamin B₆ supplementation (data not shown). This suggests that vitamin B₆ resistance also exists in CAPD patients, consistent with a report by Ross et al. [8]. Since giving vitamin B₆ to all HD patients adds to the cost of care in end-stage renal disease, the cost-benefit ratio of the routine prescription of vitamin B₆ supplementation to prevent PPN needs to be evaluated in a larger study.

References


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