Effect of Vitamin B₆ Supplementation on Plasma Oxalate and Oxalate Removal Rate in Hemodialysis Patients

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ABSTRACT

Whether pyridoxine (B₆) supplements decrease plasma oxalate concentrations in patients on maintenance dialysis is unresolved. The effect of two dose levels of B₆, 0.59 mmol/day (100 mg/day) over 6 months and 4.43 mmol (750 mg) after each dialysis treatment for 4 wk, on plasma oxalate and oxalate removal rate (dialysis plus urinary excretion) was studied in patients on maintenance hemodialysis. In both studies, a control group unsupplemented with B₆, who remained on their regular diet, was also studied. The vitamin B₆ status of the patients was assessed by the erythrocyte glutamate pyruvate transaminase activity and index before and during supplementation. No decrease in plasma oxalate or oxalate removal rate was found in either study. The plasma oxalate and oxalate removal rates of the unsupplemented hemodialysis patients were not different from those receiving B₆ either before or after supplementation. These studies demonstrate that high-dose B₆ supplementation does not decrease plasma oxalate concentration in a population of hemodialysis patients.

Key Words: Oxalate synthesis, oxalosis, primary hyperoxaluria, B₆ deficiency, ESRD

Several studies have clearly demonstrated that plasma oxalate concentrations are substantially increased in patients on maintenance dialysis (1–6). Calcium oxalate crystals have been found in a variety of tissues in these patients (7–12). Crystal-Induced complications including renal stone disease (7,8), complete heart block (9), osteoarthritis (10), bilateral visual loss, and retinopathy (11) have been observed. In addition, oxalate concentrations similar to those found in patients with ESRD (30 μmol/L) suppressed replication and migration of human endothelial cells in tissue culture (12).

Deficiency of vitamin B₆ has been described in uremia (13,14). B₆ deficiency is reported to increase oxalate synthesis in animals and humans (15–17). In B₆-deficient rats, Sharma et al. (18) found hyperoxaluria and enhanced hepatic activities of the oxalate-biosynthesizing enzymes, glycocolate oxidase and glycocolate dehydrogenase, as well as increased in vitro oxalate uptake by rat intestines from these animals. B₆ supplements given to non-B₆-deficient subjects with primary hyperoxaluria Type I are postulated to decrease oxalate synthesis by increasing the transaminase activity responsible for the conversion of glyoxylate, the immediate precursor of oxalate, to glycine (19). This reduction is observed in only some patients with Type I, and the reason for the variable response to B₆ supplementation has not been elucidated.

Studies of patients on maintenance dialysis have reported substantial decreases in plasma oxalate when subjects were administered large supplements (3.55 to 4.73 mmol/day) of pyridoxine (20,21), whereas other investigators found no effect when patients received 0.59 mmol/day over 4 months (22). In two of the above studies, the B₆ status of the patients was not determined (20,21) whereas none of the above studies contained a control group unsupplemented with B₆, which we believe is essential because plasma oxalate levels may change over time. Furthermore, the effect of B₆ supplementation on oxalate removal in these patients has not been investigated. A significant decrease in plasma oxalate should result in a decreased oxalate removal rate on dialysis, which would further confirm the efficacy of B₆ supplementation.

We studied the effect of pyridoxine supplementation on plasma oxalate, oxalate removal rate, and vitamin B₆ status of patients on maintenance hemodialysis (HD).

METHODS

Two separate studies were carried out in which patients on HD were supplemented with vitamin B₆.
All patients were studied with their informed consent. Only patients who were clinically stable were recruited for these studies. Any patient who had a history of nephrolithiasis before going on dialysis was excluded. Patients on dialysis were prescribed a diet low in oxalate containing 1.2 g of protein/kg body wt. All of our HD patients are prescribed a multivitamin that contains ascorbate and pyridoxine (B6). Patients enrolled in the studies continued to take these supplements throughout the study period. The study populations and their dialysis regimens are summarized on Table 1. In the first study, nine patients, randomly selected, received B6, 0.59 mm/day (100 mg/day), over 6 months and eight control patients remained on their regular diet. Patients on pyridoxine were provided with 100 mg of B6 tablets and were requested to take one tablet daily. Patients supplemented with B6 were studied at the following interdialytic intervals: five patients after 2 days and two patients after 3 days at every stage of the study, two patients were studied at baseline after a 3-day interval, and all further sample collections were made after a 2-day interval. Four control patients were studied after a 2-day interval and one was studied after a 3-day interval at every stage of the study. Three patients were studied at baseline after a 3-day interval, whereas all further collections were made after a 2-day interval. Plasma, dialysate, and urinary oxalates from nonanuric patients were determined once before supplementation and after 1, 2, and 6 months of supplementation. Plasma ascorbate was determined at the 6-month stage of the study. Erythrocyte glutamate pyruvate transaminase (EGPT) activity, basal and stimulated, was also determined at each stage as a measure of the adequacy of B6 stores. Cinnamon and Beaton (23) have shown that EGPT activity is a sensitive and specific indicator of vitamin B6 status in humans. In a second study, eight patients, randomly selected, received 4.43 mmol (750 mg) of pyridoxine (one 500-mg and one 250-mg tablet) administered by the nursing staff after each dialysis treatment over 4 wk. Ten patients who remained on their regular diet were studied as a control group. This study was carried out 18 months after the 100-mg study described above. Nine patients who took part in the latter study also volunteered for the 750-mg B6 study and were randomly distributed between the two groups, control and experimental. Four B6-supplemented patients were studied after a 2-day interdialytic interval and four were studied after a 3-day interval at both stages of the study. Six controls were studied after a 2-day interval and two patients after a 3-day interval on both occasions. Two controls were studied at baseline after a 2-day interval and at the end of the study after a 3-day interval. Plasma, dialysate, and urinary oxalates as well as EGPT ac-

### Table 1. Study populations and dialysis regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>No. in Study</th>
<th>Sex</th>
<th>Age Range</th>
<th>Months on Dialysis</th>
<th>No. of Dialysis Sessions/wk</th>
<th>Dialysate Bath</th>
<th>Types of Dialyzer</th>
<th>Mean Duration of Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg Controls</td>
<td>8</td>
<td>4 4</td>
<td>51–83 (66)</td>
<td>66 ± 17</td>
<td>3</td>
<td>Bicarbonate (5) Cellulose Acetate (3)</td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td>Experimental</td>
<td>9</td>
<td>4 5</td>
<td>35–73 (55)</td>
<td>35 ± 19</td>
<td>3*</td>
<td>Bicarbonate (9)</td>
<td>Cellulose Acetate (4) Cuprophane (4)</td>
<td>3.8</td>
</tr>
<tr>
<td>750 mg Control</td>
<td>10</td>
<td>5 5</td>
<td>36–80 (58)</td>
<td>61 ± 13</td>
<td>3</td>
<td>Bicarbonate (10)</td>
<td>Cellulose Acetate (6) Cuprophane (3) Polyacrylonitrile (1)*</td>
<td>3.9</td>
</tr>
<tr>
<td>Experimental</td>
<td>8</td>
<td>5 3</td>
<td>35–84 (62)</td>
<td>46 ± 8</td>
<td>3</td>
<td>Bicarbonate (8)</td>
<td>Cellulose Acetate (5) Cuprophane (3)</td>
<td>3.7</td>
</tr>
</tbody>
</table>

* There was no significant difference in the age, months on dialysis, dialysis session per week or hours on dialysis between the control and experimental groups in both studies.

* The figures in parentheses are the mean ages of the patients at the time of study.

* One experimental patient was dialyzed twice a week; all other patients were dialyzed three times a week.

* The figures in parentheses are the numbers of patients.

* This high-flux dialyzer was used with conventional dialysis prescription.
tivity were determined once in both groups before supplementation and after 4 wk of pyridoxine. Plasma ascorbate, predialysis, was determined in both groups at the beginning and end of the study. Plasma creatinine, predialysis and postdialysis, was determined at all stages in both studies as a measure of the adequacy of dialysis.

Sample Collection and Analyses

Plasma Oxalate and Creatinine. Blood (12 mL) was withdrawn from HD patients into sodium heparin vacutainer tubes, predialysis or predialysis and postdialysis. The separated plasma was analyzed for oxalate as previously described (24) and for creatinine by the Jaffe reaction (25) on an Abbott Biochromatic Analyzer 100. Plasma, 1.5 mL, was removed for ascorbate analysis and was treated with an equal volume of 10% wt/vol trichloroacetic acid. The supernatant was assayed for ascorbate by the method of Denson and Bowers (26).

Dialysate Oxalate. The entire hemodialysis was collected in 3.5 N HCl, which was added to give a final pH of <3.0 and to prevent in vitro ascorbate-to-oxalate conversion. Dialysate oxalate was determined on a representative sample taken from the entire dialysate as previously reported (24).

Urinary Oxalate. A 24-h specimen was obtained from all nonanuric patients and collected in 40 mL of 3.0 N HCl. Urine collections from HD patients were made in the 24-h period before dialysis treatment. Oxalate determination was carried out as previously described (27). Our 24-h urinary oxalate excretion value for normal subjects on an unrestricted diet was determined in an earlier study (27) and shows excellent agreement with several published values (28, 29).

EGPT Activity and Index. Heparinized blood was centrifuged immediately after withdrawal, 1,000 g for 20 min. The plasma and buffy coat were quickly removed. A volume of water twice that of the packed red blood cells was added to induce hemolysis. The contents were frozen at −80°C and analyzed within 1 month.

Basal and stimulated (pyridoxal phosphate added) EGPT activity was determined as described by Kopple et al. (14) and expressed as micromoles of pyruvate formed per milliliter of packed erythrocytes per hour. EGPT index was calculated as the ratio of stimulated-to-basal activity as follows:

\[
\text{stimulated EGPT activity} / \text{basal EGPT activity}
\]

An EGPT index of 1.25 or less was considered normal.

Calculation of the oxalate removal rate per 24 h is as described (24).

The oxalate distribution volume (ODV) per kilogram body weight of HD patients was calculated from the preplasma and postplasma dialysate oxalate values obtained on the same day, as follows:

\[
\text{ODV (L/kg body wt)} = \frac{\text{Total oxalate removed on dialysis (mmol)}}{\text{Decrease in plasma oxalate by dialysis (mmol/L)}} + \text{kg body wt}
\]

The body weight used was a mean of predialysis and postdialysis values. Nonanuric patients were omitted from these calculations.

Statistics

Statistical analyses of the results were performed by the Student's t test and linear regression analysis. All values are reported as mean ± SE.

RESULTS

B₆ Study, 0.59 mmol/day (100 mg/day)
Over 6 Months

The prestudy plasma creatinine of the B₆-supplemented group (0.94 ± 0.1 mmol/L) (mean ± SE) was similar to that of the controls (1.09 ± 0.1 mmol/L) (P > 0.05). The mean percent reduction in plasma creatinine in patients on HD over the four periods studied was similar in both groups: 50.9% in the controls and 51.9% in the experimental group (data not shown). The mean percent reduction in plasma oxalate in patients on HD at the 6-month stage was not significantly different between the groups: controls, 56%; experimental, 62%.

Only one patient in the experimental group had an EGPT index greater than 1.25, indicative of B₆ deficiency, before beginning B₆ supplementation, whereas none of the control group was deficient. EGPT basal activity of the experimental group was significantly higher than that of normal subjects at 1 and 2 months and higher than the control group at 1 month, P < 0.005, 0.05, and 0.025, respectively (Table 2). The activity of the unsupplemented control group was not significantly different from that of normal subjects at any stage of the study (Table 2). Plasma oxalate did not decrease in patients supplemented with B₆ but rather showed an upward trend that did not reach significance, whereas unsupplemented patients showed no change (Table 2). The oxalate removal rate, dialysis plus urinary excretion expressed as millimoles per 24 h, increased in the experimental group from 0.39 to 0.49 mm/day but did not reach significance (Table 3). The predialysis plasma ascorbate was significantly higher in the controls (211.2 ± 26.8 μmol/L) than in the B₆-supple-
TABLE 2. EGPT activity and plasma oxalate of patients on HD unsupplemented and supplemented with vitamin B6, 0.59 mmol (100 mg)/day

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>EGPT Basal and Stimulated Activity Unsupplemented</th>
<th>Plasma Oxalate Unsupplemented</th>
<th>Plasma Oxalate Supplemented</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EGPT activity and plasma oxalate of patients on HD unsupplemented and supplemented with vitamin B6, 0.59 mmol (100 mg)/day</td>
<td></td>
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<tr>
<td></td>
<td>Supplemented</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basal (µmol of pyruvate/ml of red blood cell hemolysate/h)</td>
<td>Stimulated (µmol of pyruvate/ml of red blood cell hemolysate/h)</td>
<td>Index</td>
</tr>
<tr>
<td>0</td>
<td>5.5 ± 1.5</td>
<td>5.8 ± 1.7</td>
<td>4.09</td>
</tr>
<tr>
<td>1</td>
<td>4.2 ± 1.1</td>
<td>4.6 ± 1.2</td>
<td>1.11</td>
</tr>
<tr>
<td>2</td>
<td>3.5 ± 1.3</td>
<td>3.8 ± 1.2</td>
<td>1.18</td>
</tr>
<tr>
<td>6</td>
<td>5.0 ± 1.4</td>
<td>5.2 ± 1.3</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Values are mean ± SE. "Basal" refers to activity in the absence of added pyridoxal phosphate. "Stimulated" refers to activity in the presence of added pyridoxal phosphate. There were eight patients in the unsupplemented group and nine in the supplemented group. EGPT basal activity of normal subjects, 1.25 ± 0.47 mmol/L (30). Plasma oxalate of normal subjects, 1.25 ± 0.47 mmol/L (30).

* Differs from normal subjects, P < 0.005 for 1 and 2 months, respectively.

** Differs from unsupplemented group for same period, P < 0.025.

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** Differs from unsupplemented group for same period, P < 0.025.

** Differs from unsupplemented group for same period, P < 0.025.
TABLE 4. EGPT activity and index of HD patients unsupplemented and supplemented with vitamin B₆, 4.43 mmol (750 mg)/dialysis treatment

<table>
<thead>
<tr>
<th></th>
<th>Before Study</th>
<th></th>
<th>No. With EGPT Index &gt;1.25</th>
<th></th>
<th>No. With EGPT Index &gt;1.25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Basal</td>
<td>Stimulated</td>
<td>Index</td>
<td>Basal</td>
</tr>
<tr>
<td>Supplemented Group</td>
<td>8</td>
<td>7.6 ± 1.2</td>
<td>8.5 ± 1.4</td>
<td>1.11 ± 0.10</td>
<td>0</td>
</tr>
<tr>
<td>Unsupplemented Group</td>
<td>10</td>
<td>3.3 ± 0.6</td>
<td>4.3 ± 0.6</td>
<td>1.36 ± 0.22</td>
<td>7</td>
</tr>
<tr>
<td>Normal Subjects</td>
<td>7</td>
<td>3.5 ± 0.4</td>
<td>4.1 ± 0.5</td>
<td>1.18 ± 0.01</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are mean ± SE. EGPT activity is expressed as micromoles of pyruvate per milliliters of red blood cell hemolysate per hour. "Basal" refers to activity in the absence of added pyridoxal phosphate. "Stimulated" refers to activity in the presence of added pyridoxal phosphate. The supplemented group received B₆, 4.43 mmol, orally after each dialysis treatment for 4 wk. a Differs from normal subjects, P < 0.01, and control group (unsupplemented), P < 0.005. b Differs from unsupplemented group, before study (P < 0.01) and on week 4 (P < 0.05). c Differs from prestudy value, P < 0.020, and from control group (week 4), P < 0.005. d Is not different from normal subjects.

The values for normal subjects were determined in an earlier study (24).

determined by percent reduction in plasma creatinine, was not significantly different between the groups in both studies, and the percent reduction in plasma oxalate was also similar. Because plasma ascorbic acid concentrations did not change significantly in either group throughout the 750-mg study, it is reasonable to conclude that the lack of decrease in plasma oxalate did not result from changes in plasma ascorbate concentrations. Studies by Tomson et al. (22) also failed to find any decrease in plasma oxalate when dialysis patients were supplemented with B₆, 0.59 mmol/day over 4 months; however, they did not study higher doses (3.55 to 4.73 mmol/day). Our findings are in sharp contrast to those studies where B₆ supplements of 3.55 and 4.73 mmol/day for 1 month were reported to lower plasma oxalate by 46 and 35%, respectively (20, 21).

The validity of these latter findings is in doubt for the following reasons. Balcke et al. (20) reported plasma oxalate values for normal subjects that are dramatically higher than recent values (3, 30). Morgan et al. (21) ultrafiltered plasma at an acid pH and determined oxalate on the ultrafiltrate. No correction was made for the substantial protein binding of oxalate under these conditions (30, 31). In addition, both studies (20, 21) lacked a control group of dialysis patients unsupplemented with B₆ and the B₆ status of the patients was not determined at any stage of these investigations.

In contrast to the latter studies (20, 21), plasma oxalate was determined here by a method that gives plasma oxalate values for normal subjects that are virtually identical to those reported by in vivo isotopic dilution techniques (30). Furthermore, the recovery of oxalate from whole blood after dialysis was 99.9% (24). Finally, the ODV values, derived from the decrease in plasma oxalate concentration during dialysis and the total oxalate removed by dialysis, were

TABLE 5. Plasma oxalate and ascorbate and the oxalate removal rate in patients on HD unsupplemented and supplemented with vitamin B₆, 4.43 mmol (750 mg)/dialysis treatment

<table>
<thead>
<tr>
<th></th>
<th>Unsupplemented Group</th>
<th></th>
<th>Supplemented Group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Prestudy</td>
<td>At 4 wk</td>
<td>N</td>
</tr>
<tr>
<td>Plasma Oxalate (µmol/L)</td>
<td>10</td>
<td>78 ± 14</td>
<td>90 ± 10</td>
<td>8</td>
</tr>
<tr>
<td>Oxalate Removal Rate</td>
<td>9</td>
<td>0.53 ± 0.09</td>
<td>0.52 ± 0.04</td>
<td>7</td>
</tr>
<tr>
<td>(mmol/24 h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Ascorbate (µmol/L)</td>
<td>10</td>
<td>71.8 ± 14.6</td>
<td>85.6 ± 21.4</td>
<td>8</td>
</tr>
</tbody>
</table>

Values are mean ± SE. The supplemented group was administered 4.43 mmol of B₆ after each dialysis treatment over 4 wk. a Oxalate removal rate (in millimoles per 24 h) is based on the number of dialysis treatments per week and urinary oxalate excretion per 24 h. The oxalate removal rates per 24 h of both groups are significantly higher than the urinary oxalate excretion of normal subjects, P < 0.001, for all values. Urinary excretion of normal subjects (N = 22), 0.29 ± 0.2 mmol/24 h, mean ± SE (37).
338 ± 15 m/L/kg body wt (N = 15) and 317 ± 23 (N = 13) for the 0.59- and 4.43-mmol studies, respectively, and show excellent agreement with values derived by isotopic dilution in patients with impaired renal function (343 ± 28; mean ± SE) (32). In calculating the ODV, nonanuric patients were omitted. We believe that the above results confirm the validity of our procedures for oxalate determination in plasma and dialysate.

The plasma oxalate values of HD patients in the studies presented here are higher than those in other studies (1, 3, 4) and our own reported values (24). We found an increase in plasma oxalate concentration from 49.2 to 75.0 μmol/L in 15 HD patients studied over 2.3 yr (24). Twelve of these latter patients took part in both studies reported here. This may explain the higher plasma oxalate values of the studies presented here, whereas the oxalate concentrations of HD patients reported elsewhere have not been followed sequentially (1, 3, 4, 22, 33).

The oxalate removal rate of HD patients, in millimoles per 24 h, was significantly higher than the urinary excretion of normal subjects at every stage of the 100-mg B6 study (all patients combined, data not shown) and at both stages of the 750-mg B6 study (Table 5) (P < 0.001 for all), in agreement with our earlier findings (24). We believe that the increased oxalate removal rate may be due to increased oxalate biosynthesis as previously proposed (24).

The EGPT basal activity of three subjects in the supplemented group (0.59 mmol) decreased sharply between the 2- and 6-month values, suggesting that these patients failed to take the prescribed daily B6 supplementation dose regularly during this period (data not shown). Consequently, no definitive conclusions can be drawn from the 6-month oxalate values. Other published studies (20–22) also suffer from the uncertainty of patient compliance, except for a number of patients given B6 iv (20). This problem was overcome in the second B6 study, 4.43 mmol per dialysis treatment, by having a dialysis nurse administer the prescribed dose to the patients after dialysis. All patients supplemented with B6 showed an increase in EGPT basal and stimulated activity after 4 wk, despite their high activity values presupplementation (Table 4) (individual data not shown). However, even these high activities did not decrease plasma oxalate or the oxalate removal rate, suggesting that large supplements of the vitamin do not decrease oxalate synthesis in these patients. It is possible that higher supplements of B6, 3.55 to 4.73 mmol/day, used in other studies (20, 21), may decrease oxalate biosynthesis. These higher doses were not used in our studies because doses greater than 2.96 mmol/day can result in sensory nerve damage (34). Because none of the supplemented patients in this second study were B6 deficient, before or during the investigation, their massively raised plasma oxalate values cannot be due to B6 deficiency. Furthermore, it is noteworthy that their plasma oxalate values were similar to those of the control group, seven of whom were B6 deficient before the study and five of whom were after 4 wk (Table 4). No correlation was found between plasma oxalate and the EGPT index in either study, in agreement with findings from other investigations (22, 24). Although large supplements of B6 do not lower plasma oxalate in non-B6-deficient patients, further studies are required to determine if B6 supplementation decreases plasma oxalate in B6-deficient patients when the effect of plasma ascorbate is controlled.

We have seen one patient with a very high plasma oxalate, 180.9 μmol/L, with 2.32 mmol removed per dialysis treatment, who when supplemented with B6, 100 mg/day over 6 months, had a decrease in plasma oxalate to 91 μmol while oxalate removed on dialysis decreased to 1.04 mmol/treatment. This patient was not B6 deficient and had been on dialysis for only 2.5 months. Although there was no history of stone disease, a case of primary hyperoxaluria was suspected (unpublished data). This finding is in agreement with those from earlier studies (35, 36) where B6 supplements of 0.15 to 1.18 mmol/day decreased urinary oxalate excretion in some patients with primary hyperoxaluria. Results on this patient along with results from previous studies (35, 36) suggest that where B6 supplements are effective in reducing oxalate generation, patients respond to doses of 0.15 to 1.18 mmol/day. Other than in this one patient, we have found no evidence that large B6 supplements decrease plasma oxalate in HD patients. Further studies are required to identify the mechanism(s) responsible for the increased body burden of oxalate in patients on maintenance dialysis.

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