Abstract

Background. Dialysis patients with primary hyperoxaluria are exposed to risks and hazards associated with calcium oxalate salt deposition in body tissues, since regular dialysis treatment does not adequately correct hyperoxalemia. The purpose of this study was to evaluate oxalate mass removal using various dialysis modes in a patient suffering from primary hyperoxaluria type 1 (PH1).

Methods. Oxalate kinetics during daily hemodialysis was compared with that of standard hemodialysis (STD HD) and hemodiafiltration (HDF) using high flux dialysers (FB 170 H and FB 210 U, Transdial, Paris, France). All dialysis sessions lasted for 4 h. Blood was withdrawn and spent dialysate was collected in plastic bags every hour to evaluate mass removal. Oxalate concentration in plasma and in spent dialysate was determined by an enzymatic method. Oxalate generation, distribution volume and tissue deposition were calculated using single-pool models adapted from previous studies.

Results. Although no significant difference was found in mass removal per session between dialysis strategies and dialyser types, weekly mass removal with daily HD was about 2 times greater than with STD HD or HDF. Even when daily HD was performed, the oxalate generation rate-mass removal ratio (G/R ratio) remained at a value of approximately 2.

Conclusion. Although daily HD sessions led to a substantial increase in weekly oxalate removal, all three types of renal replacement therapy were insufficient to compensate for estimated oxalate generation. To eliminate sufficient amounts of oxalate generated in PH1 patients, at least 8 h of daily dialysis with a high-flux membrane would probably be required.

Keywords: daily dialysis; hemodiafiltration; hemodialysis; oxalate kinetics; primary hyperoxaluria type 1

Introduction

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disorder caused by deficiency of the liver-specific peroxisomal enzyme, alanine:glyoxylate aminotransferase (AGT) [1]. The decreased transamination of glyoxylate to glycine leads to subsequent increases of its oxidation to oxalate, a poorly soluble end-product. Because the kidneys are the main route of oxalate excretion, hyperoxaluria leads to the formation of calcium-oxalate stones and nephrocalcinosis, resulting in renal failure. A decline in renal function is then responsible for the accumulation of oxalate within various organs and tissues, such as the bones, heart, arteries, retina and nerves, leading to severe and sometimes lethal consequences [2]. Therefore, there is a need for an effective therapy for the removal of oxalate. Although it is generally agreed that standard hemodialysis (STD HD) does not control hyperoxalemia in PH1 patients [3], there have been a few reports demonstrating oxalate removal by dialysis. Moreover, complications in measuring tissue oxalate deposition, generation or both in PH1 patients have made it difficult to obtain accurate estimates of oxalate removal.

The purpose of this study was to evaluate oxalate mass removal by various modes of dialysis therapy, including daily haemodialysis (daily HD), in a PH1 patient using a direct dialysate quantification method. We also estimated tissue deposition and generation of oxalate according to simple models. Oxalate kinetics during STD HD were compared with values obtained...
during daily HD and haemodiafiltration (HDF) using high flux dialysers.

**Patient and methods**

**Patients**

Our female subject was born in 1934, and had been on STD HD since March 1985 due to PH1-induced end-stage renal disease. Renal transplantation was successfully performed in October 1985. Kidney graft biopsy in March 1986 demonstrated numerous oxalate crystals. Recurrence of the primary disease resulted in graft loss and the patient was returned to STD HD (4 h three times weekly) in April 1989. She underwent pretransplant liver biopsy which detected about 10% normal AGT activity, confirming the diagnosis of PH1.

At the time of the investigation, the patient was 59 years old and weighed 59 kg for 160 cm height. Oral administration of pyridoxin and vitamin C was discontinued during the study to exclude their effects on oxalate generation, accumulation or both.

**Sample handling and analysis**

Blood was withdrawn at the start of dialysis (Cᵢ), after every hour of dialysis, at the end of dialysis (Cᵢ₊₁), and at one (Cᵢ₊₂) and two (Cᵢ₊₂) hours after the end of dialysis. Blood samples were placed on ice and were centrifuged at 1000×g for 10 min at 4°C. Spent dialysate was collected into plastic bags every hour to evaluate oxalate mass removal. Sodium azide (0.02%) was added as a preservative. In order to prevent calcium salt precipitation, the spent dialysate was maintained at pH ≤ 5 by adding an appropriate amount of HCl. Plasma samples and ultrafiltrates were harvested and stored at −20°C until analysis.

The oxalate concentration in plasma and spent dialysate was determined by an enzymatic method based on the oxidation of oxalate by oxalate oxidase followed by the measurement of hydrogen peroxide (H₂O₂) produced using a peroxidase-catalysed reaction. Oxalate in dialysate, as in urine, was determined according to the method of Hallson et al. [4]. The plasma oxalate concentration in normal healthy subjects determined in our biochemistry laboratory was 20–40 μmol/l and daily urinary output was 100–450 μmol/24 h. Laboratory quality control for oxalate determination in dialysate was based on the assay of a 164 μmol/l specimen providing a variation coefficient of 9.5%.

**Dialysis strategies**

To compare oxalate removal efficiency, five protocols were followed using either FB 170 H or FB 210 U dialysers (1.7 or 2.1 m² triacetate membrane, Transodial, France). STD HDs were performed for 4 h during three sessions weekly in protocols I (with a dialyser FB 170 H) and II (with a dialyser FB 210 U). HDFs were performed for 4 h during three sessions weekly in protocol III (with a dialyser FB 210 U). Daily HDs were performed for 4 h during six sessions weekly in protocols IV (with a dialyser FB 170 H) and V (with a dialyser FB 210 U). Protocols I, IV, and V were performed for 1 week, while protocols II and III, were performed for 2 weeks. The blood flow rate was 250 ml/min and the dialysate flow rate was 500 ml/min. HDF was performed using post-dilution mode with an infusion rate of 50 ml/min.

**Calculations**

Oxalate generation, its volume of distribution, and its tissue deposition were calculated by single-pool models adapted from Marangella [5].

Oxalate distribution volume \( V \) (l) was calculated from the following formula:

\[
V = \frac{\text{Mass Removal}}{(C_i - C_{i+1}) + (G \times T_d)}
\]

where Mass Removal is the total mass removal of oxalate (μmol) calculated from the oxalate concentration in spent dialysate and the dialysate volume; \( C_i \) and \( C_{i+1} \) are pre- and post-dialysis plasma concentrations of oxalate (μmol/l), respectively; \( G \) is the oxalate generation rate (μmol/l × h); and \( T_d \) is the duration of dialysis session (h).

Tissue deposition of oxalate \( TD \) (μmol/24 h) was calculated from:

\[
TD = \frac{(G \times V \times T_{id} - \text{Mass Removal}) \times 24}{T_{id}}
\]

where \( T_{id} \) is the inter-dialytic duration (h).

Since the oxalate concentration in plasma increases linearly until it reaches the threshold of serum calcium oxalate supersaturation [5,6], the oxalate generation rate was estimated as follows:

\[
G = \frac{C_{i+1} - C_i}{t}
\]

where \( C_{i+1} \) is the plasma oxalate concentration at \( t \) (h) after the end of the dialysis session. Values were estimated from the slopes of the regression lines of time-concentration graphs of oxalate using plasma oxalate concentrations determined after the end of dialysis session.

The integrated clearance of oxalate, \( KI \) (ml/min), was calculated according to the following equation:

\[
KI = \frac{\text{Mass Removal}}{(C_i + C_{i+1}) \times T_d} \times \frac{1000}{60}
\]

All values are expressed as the mean and the standard error of the mean (M±SEM). Statistical analysis was performed using Student’s \( t \)-tests and \( P \) values < 0.05 were considered to be significant.

**Results**

**Oxalate plasma concentrations and mass removal by various dialysis strategies**

The predialysis and postdialysis plasma oxalate concentrations, mass removal and integrated clearance according to dialysis strategy and dialyser type are shown in Table 1. There was no significant difference in plasma concentration between the dialysis strategies. Of these, only postdialysis oxalate concentrations during daily HD using FB 210 U dialysers were significantly lower than when using FB 170 H dialysers. Although there were no significant differences in mass removal per session between dialysis strategies and dialyser types, weekly mass removal during daily HD was approximately 2 times greater than during STD HD or HDF. This difference was explained by the weekly dialysis duration, which was 24 h for daily HD and 12 h for STD and HDF.
Kinetic modeling of oxalate generation rate and tissue deposition

Plasma oxalate kinetics and hourly oxalate mass removal during protocols II and V, shown in Figures 1 and 2, illustrate calculated rates of oxalate generation, equilibration times and tissue deposition areas on time-concentration graphs. The mean equilibration time in the five protocols (∓SEM) was 8.2 ± 0.6 h (7.0–9.9 h range).

Table 2 shows the calculated oxalate distribution volumes, generation rates and tissue deposition in relation to dialysis strategy and dialyser type. Generation rates and tissue deposition of oxalate during STD HD with dialyser FB 170 H were significantly lower than during STD HD with dialyser FB 210 U. Tissue deposition of oxalate during HDF with dialyser FB 210 U was significantly lower than during STD HD using the same type of dialyser. Generation rates and tissue deposition of oxalate during daily HD with dialyser FB 210 U were significantly lower than during STD HD and HDF with same type of dialyser.

Accordingly, the oxalate generation rate-mass removal ratio (G/R ratio) was approximately two times lower with daily HD than during 4-h STD HD or HDF given three times weekly.

Discussion

Renal transplantation has been considered the treatment of choice for PH1 because STD HD was thought to be ineffective in preventing systemic oxalate accumulation. However, data from the European Dialysis and Transplant Association have provided
disappointing results. The three-year graft survival rate for living-related donor kidneys was 23% and 17% for cadaver kidneys. Various manipulations have been attempted to improve both preventive therapy for the primary disease and the outcome of renal transplantation, including aggressive preoperative dialysis, such as daily HD, to deplete the systemic oxalate pool. However, there is little data documenting oxalate removal, and oxalate kinetics during dialysis are incompletely understood.

Our study patient developed end-stage renal disease at 51 years of age. This is rather uncommon because 28% to 50% of PH1 patients reach end-stage renal failure by 15 years of age and the median age at the start of renal replacement therapy is 25 years. Oxalate generation by the liver and from bone stores is variable among individuals and may depend on age, residual enzyme activity, pyridoxin sensitivity, and other factors. We estimated oxalate kinetics in the present PH1 patient not receiving pyridoxin during various dialysis therapy modes by using simple oxalate kinetic models.

Recently, Marangella et al. [5,6] reported that plasma concentrations of oxalate increased linearly and then reached a plateau in PH1 patients after HD, suggesting that tissue deposition of oxalate occurs when the plasma concentration exceeds the solubility coefficient of this compound. Oxalate generation rate, its volume of distribution, and its tissue deposition were estimated in the present study by using simple, single-pool models adapted from Marangella et al. [5,6]. Our PH1 patient produced 4–6 mmol of oxalate per day, and had a tissue deposition of 2–5 mmol and a mean volume of distribution of about 38% of dry body weight. These results are in fairly good agreement with most recent reports, and
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concurs especially well with the results of Watts et al. [10] who assessed oxalate generation rates using a radioisotope.

An adequate control of oxalate balance is necessary to prevent additional oxalate deposition in PH1 patients on HD. A previous report indicated that oxalate removal rate was higher during HDF than STD HD [11]. However, in the present study we found no significant difference in mass removal per session between STD HD and HDF using triacetate membranes. This discrepancy may be explained by the type of membrane since in the previous study [11] HD was performed with Cuprophan and HDF with AN 69, a high permeable membrane. This suggests that the dialysis removal rate of oxalate may be increased by the use of high-flux dialysers but not by HDF. Moreover, our study showed that a larger membrane surface area or HDF, which also involves convective mass transfer, did not improve oxalate removal. Daily dialysis was the most effective strategy indicating that oxalate removal by HD is time-dependent.

However, the oxalate generation rate in our patient was far higher than oxalate removal, even when daily HD was performed. The high G/R ratio demonstrated the difficulty in removing oxalate by any of the HD strategies. In order to eliminate the accumulation of oxalate in PH1 patients, at least 8 h of daily dialysis is needed using a high-flux membrane. Although 8 h of night-time dialysis could be performed per day, the burden on the patients would be very heavy.

In terms of compliance, it would be difficult for PH1 patients to achieve adequate oxalate removal by prolonged dialysis using current techniques. Combined liver and kidney transplantation may be the best way to eliminate oxalate generation, but it is far more difficult to perform this operation than isolated renal or liver transplantation [12]. Renal replacement therapy should be improved to eliminate hyperoxalaemia in PH1 patients.

References


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