THE RELATIONSHIP BETWEEN THE MAGNESIUM CONCENTRATION IN THE DIALYSIS FLUID USED AND IN THE PLASMA AND ERYTHROCYTES OF PATIENTS WITH CHRONIC RENAL FAILURE BEING TREATED BY REGULAR HAEMODIALYSIS

Ch. Heierli and A. V. L. Hill
Renal Unit, Department of Medicine,
Royal Victoria Infirmary, Newcastle upon Tyne
(Received 15 April 1972)

SUMMARY

1. Plasma and erythrocyte magnesium concentrations have been determined in fifty-five patients on regular haemodialysis and in thirty-two healthy subjects. The dialysis fluid magnesium concentrations of the former were 0.58, 0.9 and 1.73 mm.

2. There was a linear correlation between the plasma and erythrocyte magnesium concentrations of normal subjects and dialysed patients whose dialysis fluid contained 0.58 and 0.9 mm-magnesium and who were treated by dialysis for at least 3 months. This correlation was otherwise independent of the time the patients had been treated by dialysis.

3. There was a linear correlation between the dialysis fluid and the predialysis plasma magnesium concentrations in all dialysed patients, except that, when the dialysis fluid magnesium was increased, a certain period of treatment was necessary before the new equilibrium was reached.

4. An unusually high magnesium concentration in the dialysis fluid for regular haemodialysis may benefit such patients in view of the known effect of an increased plasma magnesium concentration upon the parathyroid function.

Key words: chronic renal failure, haemodialysis, plasma magnesium concentration, dialysis fluid magnesium concentration.

The plasma magnesium concentration has been shown in vitro (Sherwood, Herman & Basset, 1970; Targovnik, Rodman & Sherwood, 1971) and by experiments with animals (Care, Sherwood, Potts & Aurbach, 1966; Buckle, Care, Cooper & Gitelman, 1968; Massry, Coburn & Kleeman, 1968; Buckle, 1970) to influence parathyroid gland activity. The studies of Pletka, Bernstein, Hampers, Merrill & Sherwood (1971) indicate that variations in plasma magnesium induce comparable changes in man, elevation above the normal range suppressing parathyroid activity.

Secondary hyperparathyroidism is a universal complication of patients with end-stage chronic renal disease (O'Riordan, Page, Kerr, Walls, Moorhead, Crockett, Franz & Ritz, 1970; Goldsmith, Furszyter, Johnson, Fournier & Arnaud, 1971). Elevating the plasma

Correspondence: Dr Ch. Heierli, Medizinische Universitätsklinik, Bürgerspital, 4000 Basel, Switzerland.

779
magnesium above physiological concentrations may, therefore, benefit such patients. We describe the relationship between the magnesium concentrations of dialysis fluid, plasma and erythrocytes in patients with chronic renal failure undergoing regular haemodialysis.

**PATIENTS AND METHODS**

The patients in this study had been treated by regular haemodialysis in the Newcastle-upon-Tyne area for at least 3 months, the average duration being 24 months. Their diet contained 50–60 g of protein/day, and none was receiving phosphate-binding or magnesium-containing medicines or vitamin D supplements. They were treated for 27–30 h/week with a Watson-Marlow Kil dialyser. Dialysis fluid was prepared by mixing concentrate with softened water to ensure a constant calcium and magnesium concentration. All such fluids had the same composition except for magnesium, as explained below; the calcium concentration was 6.1–6.3 mg/100 ml.

The patients are reported as three groups. Group 1 was composed of eleven patients treated at the main centre and nineteen in the home; the dialysis fluid magnesium concentration was 0.9 mm. Group 2 consisted initially of twenty-three, later twenty-five, patients treated at an affiliated centre where the dialysis fluid contained a magnesium concentration of 0.58 mm. This concentration was later changed to 1.73 mm for a period of 3 weeks, and the same patients are reported as group 3. Group 4 consisted of thirty-two healthy subjects. Blood samples were taken before dialysis from the arterial limb of the shunt or fistula or from a forearm vein of the healthy subjects without the use of a tourniquet. The informed consent of patients and subjects was obtained.

Magnesium concentrations were measured by atomic absorption spectrophotometry using a Hilger Watts atomic absorption spectrophotometer (Dawson & Heaton, 1961). Plasma was diluted 1:40 with 0.75% aq. EDTA (dipotassium salt). Erythrocytes were obtained as follows: 10 ml of fresh heparinized blood was centrifuged in a 1 cm diameter plastic tube for 40 min at 3000 g. The plasma, white cell and platelet layer and then the upper 30–50% of the packed erythrocytes were carefully removed by aspiration. A sample (0.1 ml) of the remaining packed erythrocytes were then taken with a 0.1 ml-wash-out-pipette and mixed with 8.0 ml of 0.75% aqueous EDTA (dipotassium salt). Samples were duplicated and left for 0.5 h to haemolyse. A thin grey sediment was produced after centrifuging for 10 min at 3000 g, and the magnesium concentration of the opalescent, red, supernatant fluid was determined. Recovery studies were performed after adding 0.06 mg/100 ml of magnesium to eight samples of this fluid. The mean recovery was 98.7%, 0.0592 mg/100 ml. Packed erythrocytes contain about 5% of trapped plasma (Leeson & Reeve, 1951). The magnesium content of the pure erythrocytes would therefore be about 4% higher than in the packed erythrocytes; but in accordance with other authors (Ginsburg, Smith, Ginsburg, Reardon & Aikawa, 1962; Boellner, Oleson, Fredrickson & Hughes, 1965; Schmidt, Kozzaurek, Zazgornik & Hysek, 1971), the magnesium concentration of the packed erythrocytes is reported uncorrected as ‘erythrocyte magnesium content’. Magnesium is probably unevenly distributed between cellular phases so the term content is used in preference to concentration wherever the distinction is possible.

**RESULTS**

*Normal values*

For the thirty-two healthy subjects the magnesium concentrations are shown in Table 1.
**Mg$^{2+}$ concentration in regular haemodialysis**

**Relation between plasma and erythrocyte magnesium concentration**

The relationship between the plasma and erythrocyte magnesium concentrations of groups 1, 2 and 4 is shown in Fig. 1. The regression equation is:

\[
[\text{erythrocyte Mg}^{2+}] = 0.56 + 2.14 \times [\text{plasma Mg}^{2+}], \quad r = 0.77, \quad P < 0.001
\]

where \([\text{ }]\) is the concentration (mM).

**TABLE 1. Plasma and erythrocyte magnesium concentration of thirty-two subjects (mm)**

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Erythrocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.87</td>
<td>2.44</td>
</tr>
<tr>
<td>SD</td>
<td>0.059</td>
<td>0.230</td>
</tr>
<tr>
<td>SEM</td>
<td>0.011</td>
<td>0.041</td>
</tr>
<tr>
<td>95% range (mean ± t 0.05 SD)</td>
<td>0.75-0.99</td>
<td>1.98-2.90</td>
</tr>
<tr>
<td>Observed range</td>
<td>0.75-0.95</td>
<td>1.95-3.0</td>
</tr>
</tbody>
</table>

**Fig. 1.** Correlation between plasma and erythrocyte magnesium concentration of normal subjects (○, \(n = 32\)) and of dialysed patients of group 1 (▲, \(n = 30\)) and group 2 (○, \(n = 23\)). The square outlines the normal range. Equation: \([\text{erythrocyte Mg}^{2+}] = 0.56 + 2.14 \times [\text{plasma Mg}^{2+}]; n = 85, r = 0.77, P < 0.001.

**Relation between magnesium concentration in dialysis fluid and plasma**

The relationship between the dialysate and plasma magnesium concentrations of group 1, 2 and 3 is shown in Fig. 2. The regression equation is:

\[
[\text{plasma Mg}^{2+}] = 0.69 + 0.81 \times [\text{dialysis fluid Mg}^{2+}], \quad r = 0.94, \quad P < 0.001.
\]
FIG. 2. Correlation between dialysis fluid and plasma magnesium concentrations of all patients subjected to dialysis. Equation: [plasma Mg\(^{2+}\)] = 0.69 + 0.81 × [dialysis fluid Mg\(^{2+}\)]; \(n = 103\), \(r = 0.94\), \(P < 0.001\), standard error of estimate = 0.134. The 95% range is enclosed between the two outer parallel lines.

FIG. 3. Alterations of plasma magnesium after increasing the dialysis fluid magnesium of the twenty-five patients of group 3. The hatched columns represent the mean plasma magnesium concentrations, the 95% ranges are shown by the vertical lines.
Fig. 4. Correlation between plasma and erythrocyte magnesium concentrations compared with other reports. The slope of Fig. 1 is drawn. ●, Observations on normal subjects; ○, uraemic and experimentally magnesium-depleted subjects reported by Hänze (1962), Wallach, Cahill, Rogan & Jones (1962), Boeliner et al. (1965), Dunn & Walser (1966), Losse, Zumkley & Wehmeyer (1966), Posen & Kaye (1967) and Schmidt et al. (1971).

Fig. 5. Correlation between dialysis fluid and plasma magnesium concentrations compared with other reports. The slope of Fig. 2 is drawn. The results reported are: ▲, Posen & Kaye (1967); ■, Coburn, Popovtzer, Massry & Kleeman (1969); ○, Pletka et al. (1971); and ●, Schmidt et al. (1971).
Effect of duration of dialysis

There was no association between the plasma or erythrocyte magnesium concentrations and the time the patients had previously been treated by regular haemodialysis; this period of treatment was at least 3 months.

Effect of changing the dialysis fluid magnesium concentration

Fig. 3 shows the effect upon the plasma magnesium of raising the dialysis fluid magnesium concentration from 0.58 to 1.73 mM. All plasma concentrations increased after two dialyses. This increase continued with even higher concentrations in the third week, the mean concentration of plasma magnesium reaching 2.09 mM. No side-effects from such concentrations were detected, even in a patient whose plasma magnesium concentration was 2.7 mM. Hypotension, nausea, vomiting, constipation and decreased tendon reflexes are early signs of magnesium intoxication (Randall, Cohen, Spray & Rossmeisl, 1964). Some of these features were present in a few patients, but they were not aggravated during the period of very high plasma magnesium concentrations.

<table>
<thead>
<tr>
<th>Method</th>
<th>Plasma</th>
<th>Erythrocytes</th>
<th>No. of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsburg et al. (1962)</td>
<td>P</td>
<td>0.87 (0.73–1.01)</td>
<td>2.34 (1.42–3.26)</td>
</tr>
<tr>
<td>Hänze (1962)</td>
<td>P</td>
<td>0.83 (0.75–0.91)</td>
<td>2.47 (1.93–3.00)</td>
</tr>
<tr>
<td>McIntyre (1963)</td>
<td>E</td>
<td>0.81 (0.60–1.03)</td>
<td>2.41 (1.03–3.68)</td>
</tr>
<tr>
<td>Schmidt et al. (1971)</td>
<td>E</td>
<td>0.87 (0.76–0.98)</td>
<td>1.83 (0.68–1.04)</td>
</tr>
<tr>
<td>Boellner et al. (1965)</td>
<td>A</td>
<td>0.90 (0.75–1.07)*</td>
<td>2.50 (2.18–2.75)*</td>
</tr>
<tr>
<td>Posen &amp; Kaye (1967)</td>
<td>A</td>
<td>0.82 (0.71–0.94)</td>
<td>* Observed range.</td>
</tr>
<tr>
<td>Heaton (1969)</td>
<td>A</td>
<td>2.34 (1.42–3.26)</td>
<td>2.47 (1.93–3.00)</td>
</tr>
</tbody>
</table>

DISCUSSION

This method of erythrocyte preparation has not been reported but the measured normal values of plasma and erythrocyte magnesium concentrations correspond well with the reported values given in Table 2.

Healthy persons maintain an even magnesium balance by excreting an appropriate amount of magnesium in urine. For patients undergoing regular haemodialysis magnesium is principally lost during the period of dialysis and the amount depends upon the differences between the ionized magnesium concentrations of plasma and dialysis fluid. Only if the intestinal absorption of magnesium during the period between dialyses is constant will the plasma magnesium concentration before dialysis be related to the dialysate magnesium concentra-
tion. Our data support this concept (Fig. 2). When the magnesium concentration in the dialysis fluid was increased, at least 1–3 weeks elapsed before a new balance was reached (Fig. 3). Schmidt et al. (1971) reported no significant change in the magnesium concentration before dialysis when they varied the dialysis fluid magnesium concentration in several stages from 0·18 to 0·81 mM; their dialysis fluid calcium concentrations were varied at the same time. Our study was performed by using dialysis fluid containing higher magnesium concentrations over a wider range, but the calcium concentration was constant and the period allowed for equilibration was longer. In general results of other workers tend to lie along the slope obtained in the present study (Fig. 5).

The magnesium concentrations in the plasma and erythrocyte are also correlated (Fig. 1) and the measurements of other workers lie along the slope, although they are mostly slightly below the regression line (Fig. 4); these other reports were of normal uraemic and experimentally magnesium-depleted subjects. Schmidt et al. (1971) reported an increase in erythrocyte magnesium content when the dialysis fluid magnesium concentration was raised from 0·18 to 0·29 mM. However, further increases to 0·75 and 0·81 mM were not associated with changes in erythrocyte magnesium content. We consider that the differences between the two studies as explained above are sufficient to explain the discrepancies. The relationship between erythrocyte and plasma magnesium concentrations require 3 or more weeks to be re-established when the plasma magnesium concentration is altered: Dunn & Walser (1966) showed that in experimental magnesium depletion there is an immediate decrease in plasma magnesium, but the erythrocyte magnesium concentration decreased only after 3 weeks, and Hänze & Hiller (1963) showed that in acute renal failure the erythrocyte magnesium content was normal despite an increased magnesium concentration in plasma.

Muscle has a much higher magnesium content than erythrocytes: 11 mmol/l of cell water (Dickerson & Widdowson, 1960) compared with 3·6–3·7 mmol/l of erythrocyte water (assuming that 100 ml of erythrocytes contain 71 ml of water) (Hänze & Hiller, 1963; Kessler, Levy & Allen, 1969). Most other cells have a magnesium content near that of the muscle. Patients with chronic renal failure, or who died as a consequence of the renal failure, have been reported as having a normal (Bergström & Hultman, 1969; Schroeder, Nason & Tipton, 1969) or a low (Lim, Dong & Khoo, 1969) content of magnesium in muscle. In contrast, all investigators have found that magnesium content of erythrocytes was increased in chronic renal failure. It is most likely that the muscle magnesium content is regulated by other factors such as acidosis, whereas the magnesium content of erythrocytes, with a certain delay, remains related to the extracellular magnesium concentration. This would explain the discrepancies between different reports.

It is concluded that the plasma magnesium concentration of patients on regular haemodialysis can be predictably varied by altering the dialysis fluid magnesium concentration, and the erythrocyte magnesium content will follow a similar trend. The magnesium content of other cells may not be affected in a similar way. Maintenance of above-normal plasma magnesium concentrations is therefore possible and in this study has not resulted in undesirable side effects. Such measures suppress parathyroid function and may benefit patients treated by regular haemodialysis who are known to have secondary hyperparathyroidism (O'Riordan et al., 1970; Goldsmith et al., 1971) without the hazard of metastatic calcification, which is inherent in the use of high concentrations of calcium in the dialysis fluid (Sokol, Gral, Edelbaum, Rosen & Rubini, 1967). A long-term clinical trial of this regime is clearly desirable.
ACKNOWLEDGMENTS

Ch. H. was supported by a grant from the M. and W. Lichtenstein-Frank-Stiftung of the University of Basel, Switzerland. A. V. L. H. was supported by the Scientific Research Committee of the Newcastle University Hospitals. The patients were under the care of Professor D. N. S. Kerr and Dr P. R. Uldall whom we thank for their support in this study. We are grateful to the staff and technicians of Rye Hill Hospital for their assistance during these studies.

REFERENCES


Mg$^{2+}$ concentration in regular haemodialysis


