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Hypercalcemia in patients treated with CAPD

Peritoneal dialysis is known as the recognized and prevailing method of substitution treatment in patients with terminal renal failure. Application to treatment of hyperphosphatemia calcium carbonicum as the phosphate binder is often complicated by the development of hypercalcemia. (10, 11, 15). Hypercalcemia is defined as the concentration of ionized calcium in serum above reference value or when concentration of total corrected calcium with current concentration of albumin is above 2.7 mmol/l. The quote of ionized calcium for non heparinised blood is 1.12–1.31 mmol/l (3, 5, 6). 46% of total calcium occurs in serum as ionized calcium, 44% of total calcium occurs as bind with albumin and about 10% as calcium binds with other anions: carbohydrate, citrate, phosphate, sulphate. In daily practice total calcium is estimated. In order to qualify the concentration of ionized calcium on the base of estimated total calcium the concentration changes of albumin in serum and sharp changes of blood pH should be considered.

Calcium homeostasis is influenced in patients treated with peritoneal dialysis by different factors: gastrointestinal absorption, which is affected by calcium carbonate, diet and vit. D; peritoneal transfer of calcium which depends on the concentration of calcium in serum, the concentration of calcium dialysate solution and the concentration of glucose in using solution. Renal osteodystrophy is often a complication which occurs in patients with end stage renal disease.

The aim of this study was to examine the frequency of the occurrence of hypercalcemia in patients treated with CAPD using dialysis solutions with the calcium concentration Ca 1.75 mmol/l and Ca 1.25 mmol/l.

MATERIAL AND METHODS

The study was performed on clinically stable patients treated with CAPD. The study was performed on 11 patients – 4 women and 7 men. The mean age was 54.18±13.03 ranging from 37 to 72 years. The mean time on CAPD was 36±12.82 months, ranging from 12 to 54 months. During the last three months they did not have peritonitis, did not receive vit. D, erthropoetin, steroids. Parathyreidectomy and kidney transplantation were not performed on these patients. They have no history of gastrointestinal and liver diseases. Patients were dialysed by following 4 exchanges per day using 2000 ml of solution per exchange. The study lasted 48 weeks. 11 patients were treated on the calcium dialysate solutions of 1.75 mmol/l for 24 weeks. Then they were switched to 1.25 mmol/l calcium dialysate solutions. The study was performed at the beginning (0) and after 2, 12, 24 weeks of treatment on each kind of dialysate solution.

Total calcium level was estimated by using Gilteman method modified by Kessler and Wolfman), which is based on colorimetric measurements of calcium-cresoloftalein complex in alcalic environment by using the apparatus Technicon RA 1000. Ionized calcium was estimated in whole blood by using

ionoselective electrode and the apparatus Ciba Corning 634 Diagnostics Ltd. Parathormon was measured by using the immunoradiometric assay Kit Cis Bio International. The range of the norm is 11–62 pg/ml. We did the statistical analysis by using t-Student test and regression correlation. Values are expressed as mean values ± standard deviation. Significance was accepted at the value $p < 0.05$.

RESULTS

While the treatment with the solutions with the level of calcium Ca 1.75 mmol/l was performed we observed a gradual increase in the concentration of total calcium, which at the 24th week of the treatment became significantly higher in comparison with baseline . The mean concentration of total calcium at the beginning of the treatment with the solution Ca 1.75 mmol/l was 4.76 mEq/l ± 0.30. After two weeks the level of total calcium was 4.82 mEq/l ± 0.37. After 12 weeks the concentration of total calcium increased to 4.93 mEq/l ± 0.36, while at the 24th week of the treatment the concentration was 5.11 mEq/l ± 0.48. The level was significantly higher after 24 weeks of the treatment than at the beginning ($p < 0.05$).

While the treatment with the solution with the level of calcium Ca 1.25 mmol/l was performed the concentration of calcium at the beginning was 5.11 mEq/l ± 0.48. Two weeks after switching the dialysate solution with the level of calcium from Ca 1.75 mmol/l to Ca 1.25 mmol/l we observed the highest decrease in the concentration of total calcium, which was 4.78 mEq/l ± 0.37. This decrease was statistically significant in comparison with the treatment in 24th week with the solution Ca 1.75 mmol/l ($p < 0.005$). After 12 and 24 weeks of the treatment the concentration of total calcium was slightly higher (respectively 4.9 mEq/l ± 0.57 and 4.83 ± 0.32) ($p < 0.05$) but significantly decreased in comparison with the baseline.

Based on the analysis of the concentration of ionized calcium we found that there was a tendency in increasing the level of ionized calcium while the treatment with the solution Ca 1.75 mmol/l was performed and the highest value of ionized calcium was achieved in the 24th week of the treatment. The mean concentration of ionized calcium with the solution Ca 1.75 mmol/l was at the beginning 1.24 mmol/l ± 0.08. After 2 weeks of performing the study the mean concentration was 1.28 mmol/l ± 0.1. After 12 and 24 weeks of the treatment the mean concentration of ionized calcium achieved respectively 1.29 mmol/l ± 0.06 and 1.31 mmol/l ± 0.1. While the treatment with the solution Ca 1.25 mmol/l was performing the mean concentration of ionized calcium was 1.31 mmol/l ± 0.1. After 2 weeks of the treatment with this solution we observed a statistically significant decrease of ionized calcium to 1.18 mmol/l ± 0.05 ($p < 0.001$). After 12 weeks the concentration of ionized calcium increased to 1.25 mmol/l ± 0.06 . After 24 weeks the concentration of ionized calcium was 1.25 mmol/l ± 0.05. After 12 and 24 weeks of the treatment with the solution Ca 1.25 mmol/l the concentration of ionized calcium was significantly lower in comparison with the analogical period of the treatment with the solution Ca 1.75 mmol/l ($p < 0.05$).

Based on the analysis of the concentration of total calcium while the treatment with the solution Ca 1.75 mmol/l was performed we observed 3 episodes of hypercalcemia – one in the 12th week and two in the 24th week. While the measurements of ionised calcium were performed we diagnosed 12 episodes of hypercalcemia (Fig. 1). Four in each examined period – in the 2nd, 12th and 24th week.

The concentration of ionized calcium above the normal range was investigated in 8 patients. In 4 patients the episode of hypercalcemia was observed more than once. We did not observe the episodes of hypercalcemia during the treatment with the dialysate solution Ca 1.25 mmol/l despite two patients who had the concentration of ionized calcium close to the normal range (Fig. 2).

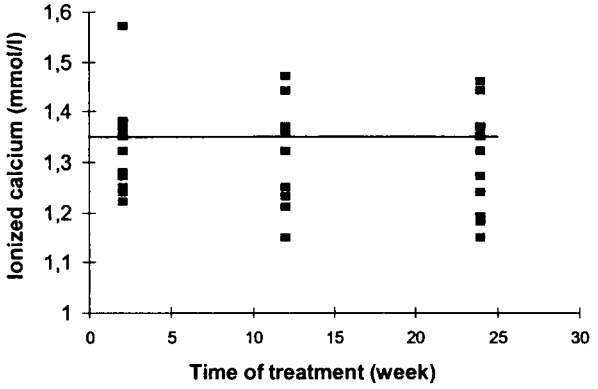

Fig. 1. Concentration of ionised calcium in serum patients treated CAPD with solution Ca 1.75 mmol/l

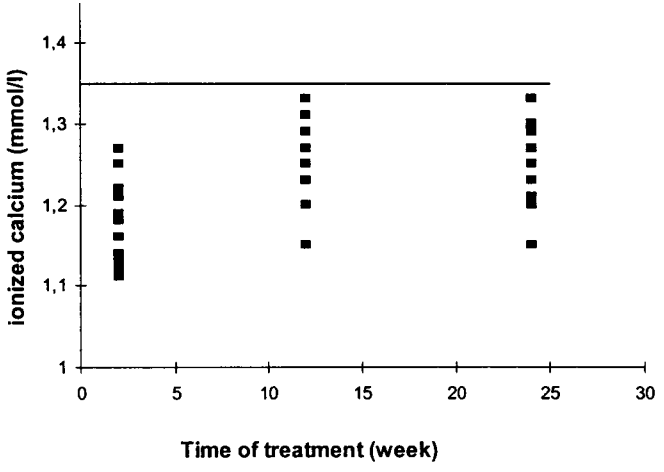

Fig. 2. Concentration of ionised calcium in serum patients treated CAPD with solution Ca 1.25 mmol/l

Doses of calcium carbonicum were similar in both periods of the study. They ranged from 1.0 to 4.0 g per day. The median values of albumin were similar in both periods of treatment and no significant differences were detected. While the treatment with the solution Ca 1.75 mmol/l was performed the concentrations of albumin were at the beginning 3.5g/dl ± 0.87; after 2, 12 and 24 weeks respectively 3.28g/dl ± 0.69; 3.53 g/dl ± 0.64 and 3.24 g/dl ± 0.42. While the treatment with the solution Ca 1.25 mmol/l was performed the concentrations of albumin were respectively after 2, 12, 24 weeks of the treatment – 3.24 g/dl ± 0.42; 3.51 g/dl ± 0.45; 3,53 g/dl ± 0.47.

The mean level of bicarbonate was significantly lower while the treatment with the solution Ca 1.75 mmol/l was performed in comparison with the solution Ca 1.25 mmol/l. At the beginning of the treatment with the solution Ca 1.75 mmol/l the mean value of bicarbonate was 26.1 mmol/l ± 1.91. After 2 weeks the concentration of bicarbonate decreased to 22.7 mmol/l ± 1.38 ($p < 0.01$). After 12 and 24 weeks the mean concentration of bicarbonate was respectively 22.5mmol/l ± 1.1 and 22.0 mmol/l ± 1.34.

While using the solution Ca 1.25 mmol/l at the beginning the mean concentration of bicarbonate was 22.0 mmol ± 1.34. After 2 weeks of the treatment with this solution the concentration of bicarbonate increased significantly to 25.3 mmol/l ± 2.4 ($p < 0.01$) in comparison to analogical periods of the treatment with the solution Ca 1.75 mmol/l. After 12 and 24 weeks the values were still significantly higher (respectively 25.1 mmol/l ± 1.5 $p < 0.005$ and 25.6 mmol/l ± 1.8 $p < 0.002$).

At the beginning of the treatment with the solution Ca 1.75 mmol/l the mean concentration of PTH was significantly lower in comparison to analogical periods of the treatment with Ca 1.25 mmol/l solution – 196 pg/ml ± 73.2. After 2 weeks of the treatment with this dialysate solution the mean value decreased significantly to 83.8 pg/ml ± 76.5 $p < 0.05$. After 12 and 24 weeks the mean value of PTH did not differ significantly and were respectively 79.1 pg/ml ± 72.1 and 112 pg/ml ± 85.4. With the solution Ca 1.25 mmol/l the concentration of PTH had a tendency to increase. At the beginning the treatment with the solution was 112 pg/ml ± 85.4. After 2 weeks the level increased significantly and was 146 pg/ml ± 99.4. After 12 weeks the value of PTH was the highest, 182 pg/ml ± 104 ($p < 0.003$). After 24 weeks the mean value of PTH was 158 pg/ml ± 112 ($p < 0.05$).

DISCUSSION

About 56% of patients treated with CAPD have hypoalbuminemia. The loss of albumin is caused by their undergoing to dialysate solutions which induces the reduction of the concentration of albumin in serum patients. It leads to the decrease in binding calcium in serum. This induces that the level of ionized calcium is higher than the indicated value of total calcium. This may make difficult diagnosis of hypercalcemia (1). That is why more favourable is to determine the level of ionized calcium. If we cannot determine the level of ionized calcium it is valuable to calculate corrected calcium.

The study of Morton et al. (8) showed that patients treated with CAPD have hypercalcemia 2.14 episodes per year. However, patients on hemodialysis have 0.45 episodes of hypercalcemia per year. Moreover, patients treated with CAPD developed more heavy episodes of hypercalcemia than patients on hemodialysis. CAPD patients develop hypercalcemia three times more frequently than hemodialysis patients dialysed with the same calcium concentration in dialysate solutions. Tsuchihashi et al. (13) suggest that hypercalcemia and hypoparathyroidism in conjunction with vitamin D_3 might play an important role in cardiovascular complications of chronic dialysis patients.

High frequency of hypercalcemia in patients treated with CAPD results not only from an oral supplementation of calcium carbonate, administration of vit. D_3, hyperparathyroidismus, the rate of bone turnover but also from the high mass transfer of calcium from dialysate solution. Daily calcium mass transfer for the solution Ca 1.75 mmol/l is from 84 mg to 358 mg (1, 9) Differences in the obtained results come from different concentrations of ionized calcium in serum among the examined patients, different concentrations of glucose in the dialysate solutions and from different volume ultrafiltration. Weinreich (14) underlines that net transperitoneal calcium transport is strongly depends on ionized serum calcium: i.e. median + 6.4 mg per exchange at Ca^{2+} greater than 1.29 mmol/l and median + 44 mg per exchange at Ca^{2+} below than 1.29 mmol/l in serum (14).

Depending on the relative proportions of diffusive and convective calcium transport calcium balance will thus be positive in most exchanges. Positive calcium balance will occur around the clock and this may explain why CAPD patients tolerated less calcium carbonate than hemodialysis patients intermittently exposed to similar calcium concentration in the dialysate. If the positive calcium balance gained from the solutions is additionally increased by about 700 g elementary calcium obtained from 6.25 g of calcium carbonate (12), which theoretically patients should receive for binding phosphorus. This may very often cause hypercalcemia. The concentration of ionized calcium also depends on pH of blood. An increase in pH, increases binding of calcium ions to albumins (8). This causes the decrease

in the concentrations of ionized calcium (7). The increase in pH by about 0.1 causes the decrease in ionized calcium by 0.042 mmol/l (14).

Patients with chronic renal failure reveal tendency to acidosis. Probable places of albumin fixation are less available because they bind hydrogen ions (8). Acidosis induces an increase in the concentration of ionized calcium ions. Based on observations it can be concluded that hypercalcemia appears more often when using calcium carbonate among patients with the low level of PTH. Chagnac (4) says that the decrease in the concentration of PTH may be a principal pathogenic factor, which increases the concentration of ionized calcium. An occurrence of hypercalcemia followed by low values of PTH is caused by the reduction of buffer surfaces for calcium ions. That is why calcium absorbed from intestines or from dialysate solutions cannot be correctly absorbed into bones.

Episodes of hypercalcemia in the examined group occurred in patients with low value of PTH. While the patients were treated with the solution Ca 1.25 mmol/l we did not observe episodes of hypercalcemia. We observed an increase in the concentration of PTH. One patient still had the low concentration of PTH. However, the level of ionized calcium was close to the upper limit. After two weeks of treatment with Ca 1.25 solution Brandi (2) observed a significant decrease of Ca^{+2} and a significant increase at PTH, too. A calcium count 1.25 in the CAPD dialysate made it possible to reduce the amount of aluminium containing phosphate binder, to increase the doses of $CaCO_3$ and to use pulse oral vitamin D_3 withaut causing severe hypercalcemia in the patients.

CONCLUSIONS

1. The estimation of total calcium is insufficient to diagnose hypercalcemia.
2. Using dialysate solutions with the level of calcium Ca 1.75 mmol/l more often induces episodes of hypercalcemia, particularly in patients with low concentrations of PTH.
3. An increased concentration of PTH was observed while dialysate solutions with the level of calcium Ca 1.25 mmol/l was used.
4. The reduction in the concentration of calcium in dialysate solutions allows the effective control of the concentration of phosphorus in serum with using calcium carbonate without episodes of hypercalcemia.

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SUMMARY

The aim of this study was to examine the frequency of the occurence of hypercalcemia in patients treated with CAPD using solutions with the calcium concentration Ca 1.75 mmol/l and Ca 1.25 mmol/l. The study was performed on 11 patients treated with CAPD and lasted 48 weeks. The patients were treated with the calcium dialysate solutions Ca 1.75 mmol/l for 24 weeks. Then they swiched to Ca 1.25 mmol/l. The study was performed at the begining (0) after 2, 12 and 24 weeks of treatment with each kind of dialysate solutions. The measurements of only total calcium revealed three episodes of hypercalcemia – one in the 12th week and two in the 24th week. While the measurements of ionised calcium were performed we diagnosed 12 episodes of hypercalcemia. Four in each examined period – in the 2nd, 12th 24th week. We did not observe the episodes of hypercalcemia during the treatment with the dialysate solution Ca 1.25 mmol/l.

Hyperkalcemia u pacjentów dializowanych CADO

Celem pracy było określenie częstości występowania hyperkalcemii u pacjentów leczonych CADO przy użyciu płynów dializacyjnych o stężeniu Ca 1,75 mmol/l oraz Ca 1,25 mmol/l. Badania przeprowadzono u 11 chorych leczonych CADO z powodu przewlekłej niewydolności nerek. Badania trwały 48 tygodni. Przez okres 24 tygodni pacjenci byli leczeni płynem o stężeniu wapnia 1,75 mmol/l, a następnie u tej samej grupy pacjentów w terapii stosowano płyn o stężeniu wapnia 1,25 mmol/l. Badania wykonywano w okresie wstępnym (0), po 2, 12 oraz 24 tygodniach leczenia danym rodzajem płynu. Oznaczanie tylko stężenia wapnia całkowitego pozwoliło na stwierdzenie trzech epizodów hyperkalcemii w czasie leczenia płynem dializacyjnym Ca 1,75 mmol/l, jeden w 12 tygodniu oraz dwa w 24 tygodniu leczenia. Natomiast oznaczanie wapnia zjonizowanego wykazało u tych pacjentów aż12 epizodów hyperkalcemii, po cztery w 2, 12 i 24 tygodniu leczenia. Nie obserwowano epizodów hyperkalcemii w czasie leczenia płynem dializacyjnym Ca 1,25 mmol/l.