CHAPTER V

DISCUSSION AND CONCLUSION

In this chapter, the following aspects of the investigation are presented :

1) discussion of the study result
2) conclusion
3) recommendation from the study
4) limitation of the study
5) recommendation for further research

Discussion of the study result.

At the beginning of the study , all of our patients had high plasma PTH (range 77 - 362 pg/ml : normal 13 - 54 pg/ml) .Radiographic findings found in all patients were normal in 2 cases , mild osteoporosis in 1 case , soft tissue calcification in 2 cases and combination of osteoporosis and soft tissue calcification in 2 cases (table 3.). However, these abnormal x-ray findings were not the typical features of secondary hyperparathyroidism. The typical features of secondary hyperparathyroidism such as subperiosteal resorption of the phalanges or sclerotic bone in high turnover bone disease and pseudofractures ,the typical form of osteomalacia in low turnover bone disease (Andress, and Sherrard, 1993) were not found in all of the patients during the study (table 3.) . Osteoporosis , the decreasing in bone density, may arise not only from secondary hyperparathyroidism but also from osteomalacia or aging. It

is also a common radiographic feature of advanced renal failure (Andress, and Sherrard, 1993).

Several areas of soft tissue calcification were detected in radiographic evaluation of the patients before the study , such as calcification of aorta, aortic knob , acetabulum and hip (table 3.) . The factors that predispose to such calcification include an increasing in plasma calcium- phosphate product , the degree of secondary hyperparathyroidism , the both high and low levels of blood magnesium, the degree of acidosis and the presence of local tissue injury (Andress, and Sherrard, 1993).
In conclusion only radiographic studies can not indicate the pathology of bone lesions in renal osteodystrophy.

Although the levels of PTH were high in all of the patients ,but the levels of alkaline phosphatase were low (table 2.) , and the x-ray features showed no typcial characteristic of osteitis fibrosa (table 3.). From these evidences, it suggested that the bone histology of all of the patients were less likely to be overt high turnover bone disease (Andress, and Sherrard, 1993). However, it is mentioned before that renal osteodystrophy will progress if the levels of PTH are high for a long period. The reduction of PTH will benefit in prevention of renal osteodystrophy.

Osteoporosis in some patients may come from aging, or mild osteomalacia from iron over load (Pierce-Myli, and Perides, 1984) . All patients in this study were anemia and had high serum ferritin (table 1.) .This evidence most likely came from impaired erythropoiesis and lacking of erythropoietin. Erythropoietin treatment will improve this condition. Unfortunately , because erythropoietin supplementation is very expensive ,only 2 cases received erythropoietin therapy. We think that erythropoietin

treatment should improve this condition. These patients were less likely to be aplastic bone disease because they had too high PTH levels and too low aluminium levels (Andress, and Sherrard, 1993).

In western studies, the distribution of bone lesions in CAPD patients was different in each studies. Ellis et al.,(1977) reported on bone biopsies from 276 dialysis patients . The majority of the patients had mixed uremic osteodystrophy, while pure osteitis fibrosa occurred in approximately one-third. A smaller number of cases had osteomalacia . In the period of using calcium carbonate as a phosphate binder instead of aluminium , Sherrard et al., (1993) reported the spectrum of bone disease in CAPD and hemodialysis patients showed the increase incidence of aplastic bone lesion , particularly in CAPD patients . The bone lesions in 142 cases of CAPD patients were found to be mild osteomalacia 21 %, osteitis fibrosa 9.1% , mixed type 3.5 % , osteomalacia 5.6% and aplastic lesion 60 % . The diabetic patients were not exclude in this study and the number of cases was as high as 30 % of CAPD patients.

In control group, the mean of PTH levels fell but still higher than normal (table 2.). It should be noted that one of them had normal PTH levels . From the falling trend of PTH levels it is possible that if the patients were followed for a longer period , there should be more patients who had normallized PTH levels. The exposure of sunshine may be the important factor for this phenomenon.However this factor seem to be inadequate in controlling of parathyroid hormone. To clarify the role of sunshine , many forms of vitamin D such as vitamin D3 (cholecalciferol) , 25 OH D3 , 1,25 OH2 D3 and 24,25 OH2 D3 need to be monitored. Our results were

similar to the study of Delmez et al., in 1986 . They followed 12 cases of CAPD for one year without vitamin D supplementation and evaluated many biochemical data including bone histology .They found that CAPD leaded to remove of iPTH , enhanced bone mineralization from the decline of prolong mineralization lag time and decreased osteoid production . They suggested that CAPD with good control calcium and phosphate was benefit. The PTH levels in this study were variable and the mean levels were still high, and higher than in our study.

The other factors that can be the inhibitors of PTH suppression are hypermagnesemia , H2 blocker (cimetidine) and beta-blocker such as propanolol (Herbener,J.F., and Potts, J.T.Jr., 1976) . All cases had normal levels of plasma magnesium . None in our patients received H2 blocker or beta-blocker except one in calcitriol group . He had received felodipine (beta-blocker) 6 months before the study . His PTH levels were still high at the beginning (133 pg/ml) and significantly decrease to normal (22.9 pg/ml) at 2 month treatment with calcitriol. There was no report about the effect of felodipine in suppression parathyroid hormone secretion and it was clearly confirmed that the suppression of parathyroid hormone in this case was from the effect of calcitriol.

In calcitriol group , we have demonstrated a significant suppression of parathyroid hormone with calcitriol therapy (table 2.). It was accepted that high turnover bone disease was mediated by a steady rise in serum PTH. This study showed that calcitriol was benefit in preventing high turnover bone disease in Thai CAPD people who had high levels of parathyroid hormone (table 2.).

The dosage of calcitriol 0.25 ug/day seem to be appropriate for correction of hyperparathyroidism in our patients who had mean body weights about 50 Kgs. This dosage was lower than in western study . Quarles et al., (1988) used oral calcitriol to suppress PTH levels in chronic hemodialysis and tritrated doses until the serum calcitriol concentrations exceeded 15 pg/ml (normal range 15 to 50 pg/ml). Calcitriol was taken orally in divided doses twice or thrice daily . They found the optimal dosage of calcitriol necessary to establish and maintain a normal serum calcitriol averaged approximately 0.6 ug / day. The optimal dosage from other studies was vary from 0.5 ug/day or 3-4 ug thrice weekly (Berl et al.,1978; Muramoto et al. , 1991). The study using radiolebeled 1,25 (OH)2D3 indicated the turnover rate of producing calcitriol was 1-2 ug / day (Seeman et al.,1980) . We found that calcitriol suppressed PTH levels only in 2 months (table 2.) . In other studies , PTH levels declined to normal range vary from 20 weeks to 9 months (Berl et al., 1978; Quarles et al., 1988; Muramoto et al., 1991) . The smaller dosage of calcitriol and the less time of administration to control PTH in our patients may come from lower body weights . The role of exposure to sunshine which lead to production vitamin D3 still to be questionable.

The administration of calcitriol leaded to development of hypercalcemia (plasma Ca = 11.2 mg/dl) , hyperphosphatemia (plasma phosphate = 6.1 mg/dl) and increase soft tissue calcification in one case at the last month of the study (table 3.). He received one capsule of calcitriol (0.25 ug) for 3 months without complication and plasma calcium and phosphate were 9 and 4.2 mg/dl respectively , after he received 2 capsules per day the complications occurred in the sixth month

(table 3.). Parathyroid assay during the study was done at the end of the study and it was found that his PTH levels fell from 112 to normal range of 7.87 pg/ml since the third month . In retrospective view it was clear that the increasing dosage was not necessary for him so that leading to develop complications. It will be better that plasma calcium and phosphate should be follow about 4-5 months before deciding to adjust doses of calcitriol. In western study , hypercalcemia was found infrequently in calcitriol treatment , its incidence varied from 0 to 50 % and it took from 1 to 3 months to develop (Berl et al. ,1978; Watson et al,, 1989; Quarles et al. , 1988). Because of the relatively short plasma half-life (12-16 hours) , episodes of hypercalcemia can be quickly recovered , usually within 1 week of stopping treatment.

Most of our patients had the same radiographic findings during the study except one case in calcitriol group who had increasing of calcification . The improving of x-ray findings may require longer follow up period.

Conclusion

1. Calcitriol statistically significant reduce the parathyroid hormone levels in CAPD patients by 91.9% in six months ($P < 0.05$). The mean levels were suppress to the normal range at 4th month ($P < 0.05$).

2. Hypercalcemia , hyperphosphatemia and increasing of soft tissue calcification developed in one case (25 % of the patients) .

3. In patients who did not received calcitriol treatment , the treatment with CAPD alone can suppress PTH levels by 45% (non significant), and the mean levels in the six months of the study were still higher than normal.

4. Except for PTH levels , the other parameters including radiographic features showed no evidences of progression of hyperparathyroid bone disease in CAPD patients with and without calcitriol treatment.

5. The treatment of CAPD without calcitriol treatment can suppress PTH levels but this suppression is not adequate to prevent hyperparathyroid bone disease . Calcitriol should be given in all cases of CAPD patients with high levels of parathyroid hormone.

Recommendation from the study

1. To prevent hypercalcemia , hyperphosphatemia and soft tissue calcification , plasma calcium and phosphate should be monitored monthly. The optimal time to adjust the dosage of calcitriol should be more than 3 months.

2. In CAPD patients PTH levels should be measured routinely , in cases of high PTH levels the administration of calcitriol should be considered ,

3. Calcitriol in the dosage of 1 capsule (0.25 ug) is appropriate in most patients and can suppress parathyroid hormone effectively without significant increasing of plasma calcium . It is unnecessary to increase dosage of calcitriol to tritrate plasma calcium to high normal levels because the incidence of hypercalcemia can easily develop in this situation. In hypocalcemia patients with calcitriol treatment , the increasing dosage of calcium carbonate should be done first if no improvement occur,then other parameters should be checked such as radiographic study , serum aluminium etc. to search for other causes.

4. Radiographic study should be done routinely in all CAPD patients every 6 or 12 months to search for bone disease or tissue calcification which are common in the CAPD patients.

Limitation of the study

The study should be more completed if we measured the level of vitamin D such as vitamin D3, 1,25(OH2)D3, 24,25(OH2)D3. Unfortunately, these laboratory tests were not available in Thailand.

Recommendation for further research

Other study about the renal osteodystrophy in CAPD or hemodialysis patients may include.

1. Monitoring of vitamin D and it's metabolite such as vitamin D3 , 25 (OH)D3 , 1,25 (OH)2 D3 , 24,25(OH)2D3 because these levels may be higher in Thai people.

2. Studying the optimal dosage and other forms in administration of vitamin D in CAPD and hemodialysis patients in Thailand.

3. Studying bone histology including other biological data such as radiographic features , bone mass measurement with single photon densitometry , dual beam photon densitometry , serum aluminum levels and parathyroid hormone.