Effect of percutaneous calcitriol injection therapy on secondary hyperparathyroidism in uraemic patients

Kazuhiro Shiizaki1, Shigeo Negi1, Masahide Mizobuchi1, Ikuji Hatamura2, Nobuhiko Narukawa1, Toshifumi Sakaguchi1, Yukiko Kitabata1, Shinji Sumikado1 and Tadao Akizawa1

1Center of Blood Purification Therapy and 2The First Department of Pathology, Wakayama Medical University, Wakayama, Japan

Abstract

**Background.** The impetus to develop percutaneous calcitriol injection therapy (PCIT) was the lack of therapeutic tools to treat secondary hyperparathyroidism (2HPT) resistant to medical therapy.

**Methods.** Nine dialysis patients resistant to intravenous calcitriol or calcitriol analogues underwent daily PCIT 5–10 times consecutively. The PCIT involved the injection of a volume of calcitriol equal to that of the enlarged parathyroid glands (PTGs) under ultrasonographic guidance. All patients had follow-up intravenous calcitriol after PCIT.

**Results.** The serum intact PTH concentration was markedly reduced following PCIT and was maintained for 12 weeks with intravenous calcitriol without significant changes in serum adjusted calcium and phosphorus concentrations. All patients tolerated PCIT without serious adverse events. Serum bone alkaline phosphatase concentrations and the volume of the enlarged PTGs were also significantly reduced.

**Conclusion.** PCIT is a safe and effective treatment, which may also suppress parathyroid hyperplasia and improve bone turnover for refractory 2HPT.

**Keywords:** calcitriol; end-stage renal disease (ESRD); interventional ultrasonography; renal osteodystrophy; secondary hyperparathyroidism

Introduction

New agents for the control of secondary hyperparathyroidism (2HPT), including calcium (Ca)-free phosphorus (P) binders, active vitamin D derivatives and calcimimetics, have been developed recently [1–4]. However, parathyroidectomy–autotransplantation (PTx–AT) is still necessary to control severe 2HPT resistant to medical therapy. General anaesthesia is necessary for PTx–AT, which can be dangerous for high-risk patients with pulmonary or cardiovascular disorders, especially as repeated operations may be needed in cases of recurrent or persistent hyperparathyroidism.

The development of ultrasonography has made it possible to perform percutaneous ethanol injection therapy (PEIT) in patients with refractory 2HPT, and this is now known to be as effective as PTx–AT [5]. However, there are some adverse side effects, such as laryngeal palsy, the difficulty of PTx–AT following failed PEIT and the necessity for specialists in all these techniques and procedures.

Calcitriol (1,25-dihydroxy vitamin D3), which is the most active metabolite of vitamin D, controls parathyroid gland (PTG) growth and suppresses the synthesis and secretion of parathyroid hormone (PTH) [6,7]. It has been reported that intravenous administration of calcitriol suppresses PTH dose dependently [3] but, for the many patients with advanced 2HPT that is resistant to intravenous calcitriol, effective and safe therapeutic tools, such as direct injection of calcitriol into the PTG (PCIT), are developed.

In the present study, the effects of PCIT on serum concentrations of PTH, Ca, P and bone markers, and on the volume of the PTG were investigated.

**Subjects and methods**

**Case studies**

Nine patients undergoing regular haemodialysis for end-stage renal disease (ESRD) participated in the present study (Table 1). All patients had severe 2HPT resistant to more than 3 months of intravenous administration of vitamin D derivatives. The study was approved by the local medical ethics committee, and informed consent was obtained from each patient.
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Data are means ± SD.
CGN, chronic glomerulonephritis; BAP, bone alkaline phosphatase; i-BGP, intact bone Gla protein; DXA, dual energy X-ray absorptiometry.

Percutaneous calcitriol injection therapy (PCIT)
The enlarged PTGs were examined by ultrasonography (SSD 5500, Aloka, Tokyo, Japan) and their sizes were estimated by 3D measurement (π/6 × a × b × c) [8]. Calcitriol injection was performed using the same type of needle as used for PEIT (KM-N type, Hakko, Tokyo, Japan) [5]. Under ultrasonographic guidance, the needle was inserted into the centre of the PTG. If the volume of the PTG was > 0.5 cm³, we made several insertions in different sites of the PTG in order to saturate it with calcitriol solution.

The PCIT was performed once a day for 5–10 consecutive days (6.56 ± 1.51) (mean ± SD). The injected volume of calcitriol solution (1 µg/ml) was estimated to be same as the volume of each gland (mean dose of calcitriol: 2.33 ± 1.00 µg per one injection, 15.7 ± 8.29 µg per total injections). There was good correlation between dosage and the total volume of the PTG (r² = 0.838, P < 0.01) (Figure 1). In patients with multiple enlarged PTGs, all detectably enlarged glands were treated by PCIT at the same time, even if they existed bilaterally.

After PCIT, all patients were treated with intravenous calcitriol at the end of every haemodialysis session. The initial dose, 1 µg per session, was altered according to the serum Ca and intact PTH (i-PTH) concentrations, which were measured periodically (dose of calcitriol 4 and 12 weeks after PCIT: 0.86 ± 0.48 and 0.86 ± 0.63 µg per haemodialysis session, respectively).

Laboratory measurements and radiological examinations
Concentrations of serum i-PTH, adjusted Ca (calculated by Payne formula) [9], P, bone alkaline phosphatase (BALP) and intact bone Gla protein (i-BGP) were obtained for all patients before and after the series of PCIT. In seven of the patients, these data were also obtained 12 weeks after PCIT.

Serum i-PTH concentration was measured by the two-antibody method using Allegro® i-PTH (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Serum BALP and i-BGP levels were measured by precipitation with wheat germ lectin using an Iso-ALP test kit (Roche Diagnostics GmdH, Mannheim, Germany) and by immunoradiometric assay using a BGP-IRMA kit (Yuka-Medias, Tokyo, Japan), respectively. Concentrations of serum Ca, P and albumin were determined with an automated analyser (TBA-200FR, Toshiba, Tokyo, Japan). Total PTG volumes were calculated using ultrasonography before and, in seven patients, at 12 weeks after PCIT. Bone mineral density was measured by dual-energy X-ray absorptiometry (DXA) (DPX-L, GE Lunar, Madison, WI, USA). Technetium-99m methoxyisobutylisonitrile imaging (99mTc-MIBI) or thallium-201-technetium-99 m subtraction scintigraphy (TI-Tc) of the PTG was carried out for all patients in order to rule out the existence of ectopic PTG.

Statistical analysis
Data were expressed as mean ± SD. Data were analysed by simple correlation or Student’s t-test, and a P value < 0.05 was considered statistically significant.

Results
Patient characteristics
Table 1 shows relevant laboratory data of the patients before PCIT. The mean serum i-PTH concentration was 716 ± 311 pg/ml, indicating severe 2HPT in spite of intravenous vitamin D therapy. The mean adjusted Ca and P concentrations were 10.8 ± 0.61 and 6.11 ± 1.76 mg/dl, respectively, so these patients were diagnosed as refractory 2HPT resistant to medical treatment. In addition, the high concentrations of bone metabolic markers (mean serum BAP and i-BGP levels were 161 ± 74.5 IU/l and 178 ± 108 ng/ml, respectively) and low bone mineral content by DXA (mean Z-score: −1.11 ± 0.68) suggested bone mineral loss because of high turnover bone disease resulting from the 2HPT.

Ectopic PTG was not detected by 99mTc-MIBI or TI-Tc in any of the patients.

Changes in the laboratory data after PCIT
The PCIT series significantly reduced serum i-PTH concentrations (177 ± 112 pg/ml; P < 0.01); the mean reduction rate was 74.3 ± 14.0%. In contrast, serum adjusted Ca and P concentrations did not change significantly throughout the study period (adjusted Ca
and P concentrations after PCIT were 11.6 ± 1.06 and 5.84 ± 1.11 mg/dl, respectively (Figure 2). Increased concentrations of serum BALP and i-BGP did not change significantly as a result of PCIT (BALP and i-BGP concentrations after PCIT: 177 ± 78.5 IU/l and 248 ± 210 ng/ml, respectively).

**Serum i-PTH concentration 12 weeks after PCIT**

Twelve weeks after PCIT, serum i-PTH concentrations in seven patients showed a significant reduction compared with values before PCIT (761 ± 340 vs 474 ± 223 pg/ml; *P* < 0.05) (Figure 3); however, serum adjusted Ca and P concentrations did not change significantly (10.8 ± 0.67 vs 10.6 ± 0.88 mg/dl and 6.14 ± 1.88 vs 5.69 ± 1.12 mg/dl, respectively).

**Effects of PCIT on bone metabolic markers**

In seven patients, bone markers tended to decrease as a result of PCIT and subsequent intravenous calcitriol treatment. The reduction in serum BALP concentration was significant 12 weeks after PCIT (176 ± 78.2 vs 127 ± 67.0 IU/l; *P* < 0.05) (Figure 4).

**Effect of PCIT on PTG volume**

Total PTG volumes were significantly reduced 12 weeks after PCIT compared with volumes before PCIT (1.78 ± 0.96 vs 1.31 ± 1.20 cm³; *P* < 0.05) (Figure 5).

**Discussion**

Secondary hyperparathyroidism from chronic renal failure causes many complications, including uraemic bone disease [10,11], which are detrimental to quality of life and prognosis; therefore, control of 2HPT is essential for such patients.

In Japan, intravenous calcitriol and 22-oxacalcitriol are used to suppress parathyroid function in patients with mild or moderate 2HPT [2]. However, some patients with 2HPT become resistant to these conventional therapies because of their poor effect on PTH reduction and/or complications of hypercalcaemia, so PCIT was developed to treat severe 2HPT resistant to medical therapies.

Kitaoka et al. reported the efficacy and safety of direct injection of calcitriol into the PTG three times a week for 2 weeks [12]. However, the follow-up period...
of their study was only 6 weeks and the changes in bone markers caused by PCIT were not investigated. In the present study, injection times for each patient were adjusted to suppress PTH concentrations sufficiently, so the mean serum i-PTH concentrations after PCIT were reduced to 177 ± 112 pg/ml (the mean reduction rate was 74.3 ± 14.0%). In contrast, serum adjusted Ca and P concentrations did not change significantly during the treatment with PCIT. Moreover, serum i-PTH concentrations 12 weeks after PCIT were significantly reduced compared with before PCIT, without significant changes in serum Ca and P. These results suggest that 2HPT was significantly suppressed by PCIT, and the response of the PTG cells to intravenous calcitriol therapy had recovered. This suppression of 2HPT might improve the high turnover bone disease caused by 2HPT as evidenced by a significant reduction in serum BALP concentrations.

We also confirmed a significant reduction of PTG volume 12 weeks after PCIT, which is another finding supporting its ability to suppress 2HPT. Fukagawa et al. reported a significant decrease in PTG volume after 12 weeks of oral calcitriol pulse therapy and hypothesized that the apoptosis was induced in PTG cells by the high concentration of calcitriol [8]. The in vivo induction of apoptosis in parathyroid cells by percutaneous maxacalcitol injection therapy (PMIT) has also been reported [13]. The regression of enlarged PTG after PCIT is presumed to result from the decreased number of parathyroid cells by apoptosis; however, the precise mechanism for this process remains under investigation. It was reported that the level of vitamin D receptors (VDRs) in PTG was significantly reduced in advanced nodular hyperplasia, and this is considered to be the pathogenesis of the PTG resistance to vitamin D therapy [14]. Bolus oral or intravenous calcitriol administration is reported to improve resistance to calcitriol by up-regulation of the VDR in PTG cells [15–17]. Thus, up-regulation of VDR by PCIT may be another mechanism of the suppression of 2HPT.

In summary, we clarified that PCIT and subsequent intravenous calcitriol administrations suppress 2HPT, high turnover bone disease and PTG hyperplasia without remarkable adverse events, including hypercalcaemia.
PCIT is another therapeutic option for severe 2HPT and an alternative to PEIT or PTx–AT.

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References