Efficacy of direct injection of calcitriol into the parathyroid glands in uraemic patients with moderate to severe secondary hyperparathyroidism

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Abstract
Introduction. Secondary hyperparathyroidism (2HPT) is a common complication in uraemic patients. When medical therapy, including high doses of intravenous calcitriol, fails to suppress the pathological secretion of parathyroid hormone (PTH), one of the newly developed interventional techniques, such as percutaneous ethanol injection therapy (PEIT), is an option before taking the surgical solution. A protocol for direct calcitriol injection therapy and a discussion of its effectiveness and limitations for an enlarged parathyroid gland(s) are presented.

Methods. Nine patients were selected according to the Japanese Guideline for Selective PEIT. Using the same technique as PEIT, a dose of calcitriol that was 200–300% of the calculated volume of the selected parathyroid gland was injected directly into the gland under ultrasonographic guidance.

Results. In six cases, the intact PTH concentration decreased to <360 pg/ml. The total volume of the enlarged parathyroid gland(s) also decreased to 54.7% of the initial volume. The blood supply to the treated glands, as evaluated by colour Doppler imaging, appeared to diminish transiently after injection, probably from the volume effect of this procedure. The number of enlarged parathyroid glands was not a limiting factor for this therapy; however, a grossly enlarged parathyroid gland (>2000 mm³) appeared to be resistant to this intervention and an intrathoracic parathyroid gland was found in a non-responsive case. None of the patients had any severe complications, such as nerve palsy or massive haemorrhage.

Conclusion. This new approach to the control of 2HPT is recommended as an alternative pharmacological parathyroidectomy to surgical therapy.

Keywords: direct calcitriol injection therapy; ectopic parathyroid gland; nerve palsy; percutaneous ethanol injection therapy; secondary hyperparathyroidism; ultrasonography

Introduction
Secondary hyperparathyroidism (2HPT) is a complication that develops in ~50% of patients with chronic renal failure (CRF), causing high turnover bone disease, ectopic calcification, bone fracture, anaemia and various types of cardiovascular complications, which all compromise the quality of life of these patients [1]. Parathyroidectomy (PTx) is the final treatment option when conservative medical management with vitamin D fails to suppress the disease activity, although it too can cause other complications. In the present report, the indication, efficacy and limitations of a new interventional therapy for 2HPT are discussed.

Inhibitory action of vitamin D on pathological parathyroid cells
Many researchers have demonstrated that 1,25-dihydroxyvitamin D₃ (calcitriol) can suppress parathyroid hormone (PTH) secretion, and inhibit the pathological growth of parathyroid gland(s) in patients with 2HPT [2]. A decreased density of vitamin D receptor (VDR) in enlarged parathyroid gland(s) has been demonstrated in patients with CRF, as well as in an experimental rat 2HPT model, which then requires a higher concentration of calcitriol to suppress PTH.
secretion, as well as parathyroid growth [3]. In addition, calcitriol has been shown to up-regulate the expression of VDR in parathyroid cells [4].

The extracellular calcium (Ca) concentration is another crucial factor in the control of PTH secretion and parathyroid growth. The inhibitory signal to parathyroid cells is transduced through the calcium-sensing receptor (CaR), the expression of which is also decreased in the enlarged parathyroid glands of uraemic 2HPT patients [5]. The decrease in the CaR causes less responsiveness to extracellular Ca, resulting in a shift of the dose–response curve of PTH secretion in pathological parathyroid cells [6]. This shift can be corrected by calcitriol [7], which is consistent with the fact that the expression of CaR is transcriptionally regulated by calcitriol in parathyroid cells [8,9]. Thus, vitamin D appears to regulate PTH secretion and parathyroid growth both directly and indirectly via the CaR.

Clinical use of calcitriol

The pathogenetic factors of 2HPT indicate that adequate administration of calcitriol should resolve the abnormal secretion of PTH and parathyroid growth in patients with CRF; however, uraemic patients with severe 2HPT can become refractory to conservative medical treatment with oral calcitriol. In the 1980s, intravenous high-dose calcitriol therapy at each dialysis session was introduced to suppress PTH secretion [10], and today in Japan, intravenous calcitriol and a vitamin D analogue, maxacalcitol (22-oxacalcitriol; OCT), are used to control moderate to severe 2HPT [11,12]. However, this therapy is self-limiting because the high dose of intravenous calcitriol, in addition to OCT, result in hypercalcaemia and hyperphosphataemia with decreased responsiveness of bone tissue to PTH, leading to an increased risk of ectopic calcification.

Two new interventional management strategies for enlarged parathyroid gland(s) have been reported recently [13]. One technique is ultrasonography-guided (USG) selective percutaneous ethanol injection therapy (PEIT), which leads directly to cell death, mainly by coagulation [14], and the other technique, using the same procedure, directly injects calcitriol into the pathological parathyroid gland(s) (i.e. direct calcitriol injection therapy), which has been shown to suppress PTH secretion effectively in 2HPT patients. A reduction of parathyroid volume has also been observed after direct calcitriol injection therapy, although the mechanism(s) for this remain to be clarified [15]. These two interventional methods must also be combined with intravenous high-dose calcitriol therapy to achieve and maintain an appropriate PTH concentration [15,16].

Technical procedure, outcome and limitations of direct calcitriol injection therapy

We selected uraemic 2HPT patients for direct calcitriol injection therapy according to the Guideline for Selective PEIT in Japan (Fukagawa et al., this issue). Enlargement of parathyroid gland(s) to >1.0 cm in diameter or 500 mm³ in volume is considered to be the safe selection criterion for direct calcitriol injection therapy. After ascertaining these parameters of the selected parathyroid gland(s), we performed direct calcitriol injection therapy in an outpatient clinic under high-resolution USG guidance (>7.5 MHz), with 1 μg/ml of calcitriol (Rocaltril®, Kirin Brewery Co. Ltd., Tokyo, Japan) for intravenous therapy. The amount of calcitriol used for injection is ∼200–300% of the calculated volume of the parathyroid gland. To evaluate the efficacy, we define one course as the time at which all parathyroid glands are injected. In effective cases, the intact PTH concentration decreased to <360 pg/ml within three courses of the corrected physiological concentration of calcium. The total volume of the enlarged parathyroid gland(s) also decreased to 54.7% of the initial volume (Figure 1).

Fig. 1. Representative case showing the ultrasonographic appearance of the parathyroid glands. (A) Before direct calcitriol injection therapy. (B) Immediately after direct calcitriol injection therapy. (C) Six months after direct calcitriol injection therapy. Note that the blood supply inside the parathyroid gland decreased immediately after direct calcitriol injection therapy, and that a dramatic size reduction was seen after 6 months.
The blood supply to treated glands, as shown by a colour Doppler imaging, appeared to diminish after direct calcitriol injection therapy, probably from the volume effect of this procedure (Figure 1B), which has often been seen after PEIT.

The number of enlarged parathyroid glands is not a limiting factor for direct calcitriol injection therapy in most cases; however, a grossly enlarged parathyroid gland (e.g. > 2000 mm³ before initial calcitriol injection) in one of the present patients appeared to be resistant to the intervention. Among the patients who underwent direct calcitriol injection therapy, there were three non-effective cases: one patient had an ectopic parathyroid gland in the thorax, and technetium-99m MIBI imaging failed to detect it prior to intervention [18]; one patient who had complained of severe pain due to the injection selected total PTx; and the other patient had a longer interval than normal (> 4 weeks) between calcitriol injections. None of the patients had any severe complications, such as nerve palsy or haemorrhage, which have been reported as adverse side effects of PEIT [19]. Only one patient had hypercalcaemia on the day following direct calcitriol injection therapy.

**Conclusion and future direction**

Our findings indicate that direct calcitriol injection therapy is useful and safe for the control of moderate to severe 2HPT in patients with CRF. It is noteworthy that direct calcitriol injection therapy reduced the parathyroid volume, possibly by inducing apoptosis of the parathyroid cells [20], and that may provide an insight into pharmacological PTx. However, the therapy has several clinical limitations, such as the size of the gland. If direct calcitriol injection therapy is useful and safe for the control of moderate parathyroid volume, possibly by inducing apoptosis of the gland. If direct calcitriol injection therapy is evaluated as being ineffective after three courses, PEIT or PTx are recommended before serious complications such as ectopic calcification or fractures occur.

**References**