Pharmacodynamic effects of cinacalcet after kidney transplantation: once- versus twice-daily dose

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Abstract

Background. In the setting of kidney transplantation, cinacalcet has been given, mainly, once daily, but also twice daily. The aims of this prospective study were to assess the acute pharmacodynamic effect of cinacalcet administered once or twice daily to kidney transplant patients with normal renal function and persisting hypercalcaemia due to hyperparathyroidism and to evaluate 1-year efficacy and tolerance of cinacalcet given at a dose of 30 mg b.i.d.

Methods. Eleven patients, who received a transplant 6–59 months previously, were included in the study. A first kinetic was done after administration of 60 mg of cinacalcet at 8 a.m. After a washout period of 1 week, the second kinetic was performed with cinacalcet at 30 mg b.i.d. within a 12-h period.

Results. During both kinetics, serum calcium (sCa), ionized calcium (sCa²⁺), albumin-corrected Ca and parathyroid hormone (PTH) levels decreased significantly. At 24 h after the second kinetic, sCa²⁺ was significantly lower. After 1 year of cinacalcet treatment, given at the dose of 30 mg b.i.d., there was a significant decrease in sCa, sCa²⁺, PTH levels and calcium × phosphorus (Ph) product. In contrast, Ph levels increased significantly. There was no significant change in renal function.

Conclusion. Once- or twice-daily acute administration of cinacalcet to kidney-transplant patients has similar efficacy. One-year administration of cinacalcet, given as two daily doses, is safe and efficient.

Keywords: cinacalcet; daily dose; hyperparathyroidism; renal function; renal transplantation

Introduction

Hyperparathyroidism is a common problem after successful kidney transplantation. At 1 year after transplantation, 10–20% of kidney transplant patients have developed hyperparathyroidism despite normal renal function [1]. Lobo et al. previously found that only 23% of kidney transplant patients with a serum creatinine level below 2 mg/dL had a normal serum parathyroid hormone (sPTH) level [2]. Hyperparathyroidism alone, or via induced hypercalcaemia, is harmful to both bone metabolism [1,3] and renal allograft function and histopathology [4]. Indeed, studies have shown that systematic allograft biopsies performed at 6, 12 and 26 weeks after kidney transplantation found nephrocalcinosis in 6, 12 and 17.6% of cases, respectively [5]. Nephrocalcinosis has been identified as a strong predictive factor for chronic allograft nephropathy [4]. Hence, persisting hypercalcaemia should be avoided after kidney transplantation.

Cinacalcet, a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor and, consequently, suppresses both serum calcium and parathyroid hormone levels, has been successfully used in dialysis patients [6] and in patients with primary hyperparathyroidism [7]. This has prompted transplant physicians to treat kidney transplant patients with persisting hyperparathyroidism with cinacalcet therapy [8–13]. In patients with primary hyperparathyroidism and normal renal function, cinacalcet has been given twice daily [7]. In the setting of kidney transplantation, cinacalcet has been given, mainly, once daily [8–10,12–16]. In only a few studies and case reports, it has been used twice daily [15,17]. The aims of this prospective study were to, first, compare the evolution of parathyroid hormone, vitamin D, calcium and phosphorus concentrations after once- or twice-daily cinacalcet intakes in kidney transplant patients with normal renal function, and second, to evaluate 1-year efficacy and tolerance of cinacalcet given at the dose of 30 mg b.i.d to kidney transplant patients with persisting hypercalcaemia.
Patients and methods

Patients

Eleven consecutive kidney-transplant patients, with persisting hypercalcaemia (e.g., serum ionized calcium > 1.4 mmol/L) due to hyperparathyroidism at least 6 months after transplantation, were included in this study after having given their informed consent. There were six men and five women, ranging in age from 29 to 65 years (mean 50.5). The median time since transplantation was 6 (6–59) months. Initial nephropathy was IgA nephropathy (n = 2), interstitial nephropathy (n = 2), polycystic kidney disease (n = 2), focal segmental glomerulosclerosis (n = 1), lupus nephritis (n = 1) and undetermined nephropathy (n = 3). All patients had been previously treated by haemodialysis for 117.5 ± 33 months and had received a kidney from a deceased donor. Four patients were receiving a second transplant, whereas all others were receiving a first transplant. The mean cold and warm ischaemia times were, respectively, 21 (±8) h and 64 (±10) min. None of the patients experienced delayed graft function as defined by the need for dialysis within the first week following transplantation. The time to reach a serum creatinine level below 220 µmol/L after transplantation was 7 ± 2 days. At inclusion, serum creatinine levels and calculated creatinine clearance according to the Cockcroft–Gault formula were 119 ± 48 µmol/L and 56 ± 17 mL/min, respectively. Three patients presented with acute rejection before starting the study. In all patients, immunosuppressive therapy was based on calcineurin inhibitors [tacrolimus: (n = 8) or cyclosporine A (n = 3)], with mycophenolic acid (n = 6), sirolimus (n = 2) or everolimus (n = 2), with (n = 8) or without (n = 3) steroids.

Methods

A first kinetic was done after administration of 60 mg cinacalcet at 8 a.m. After a washout period of 1 week, the second kinetic was performed with cinacalcet given at 30 mg b.i.d within a 12-h period. All patients were instructed to fast overnight; only water was allowed until 1-h post-dose. All patients took the same meals and at the same time during both kinetics. For the second kinetic, blood sampling started before the first 30 mg of cinacalcet were given.

At each kinetic, we measured different parameters. Serum parathyroid hormone and cyclosporine A/tacrolimus levels were measured before the cinacalcet intake and at 1, 2, 3, 4, 6, 9, 12, 18 and 24 h later. Cyclosporine A and tacrolimus 24-h area-under-the-curve (AUCA0–24h) data were calculated using the trapezoidal rule. Serum calcium (sCa), ionized calcium (sCa2+), phosphorus (sPh) and albumin levels were measured before the cinacalcet intake and at 2, 4, 6, 12 and 24 h later. At each time point, albumin-corrected calcium was calculated using the following formula: albumin-corrected calcium = sCa (mmol/L) + 1-albumin (g/L)/40. 25-Hydroxy vitamin D3 (25(OH)D3), 1,25-dihydroxy vitamin D3 [1,25-(OH)2-vit D3], and fibroblast growth factor 23 (FGF-23) were also measured before the cinacalcet intake and at 6, 12 and 24 h later. After the second kinetic, patients were given cinacalcet at 30 mg b.i.d. Thereafter, the following parameters were assessed at 1, 3, 6, 9 and 12 months after starting cinacalcet therapy: sCa, sCa2+, sPh, sPTH, serum creatinine and cyclosporine/tacrolimus levels, as well as urine calcium/creatinine levels. Blood samples were always obtained 12 h after the last intake of cinacalcet.

Measurement of sPTH. Serum intact PTH (i-PTH, Cobas®) was measured by an Elecsys® automated analyser using a two-site chemiluminescent enzyme immunoassay (Roche Diagnostics, Mannheim, Germany).

Measurement of vitamin D. For 1,25-dihydroxy vitamin D (1,25-(OH)2-vit D) analysis, patient samples were first delipidated. Then, 1,25-(OH)2-vit D was extracted from potential cross-reactants by immunoextraction with a highly specific solid phase monoclonal anti-1,25-(OH)2-vit D2 kit and followed by quantitation by 125I radioimmunoassay (Immunodiagnostic Systems Limited (IDS Ltd), Bolton, UK).

Measurement of FGF-23. The human FGF-23 (C-Term) kit (Immunotopics, Inc. San Clemente, CA, USA) was used to assay sera for FGF-23 according to the manufacturer’s instructions. It is a commercially available two-site enzyme-linked immunosorbent assay (ELISA) kit that detects epitopes within the carboxyl-terminal portion of FGF-23.

Measurement of cyclosporine A and tacrolimus. For the measurement of cyclosporine A and tacrolimus levels, both cyclosporine A and tacrolimus were determined using the Flex®-Dimension® validated automated immunoassay (Newark, NJ, USA).

Statistical analyses

Reported values represent either means ± SE or medians (ranges). Proportions were compared by the χ2-test or Fisher’s exact test. Quantitative variables were compared by the non-parametric Mann–Whitney test. During each kinetic and treatment follow-up, quantitative variables were compared by the non-parametric Friedman test for serial measurements and the Wilcoxon test. A P-value < 0.05 was considered to be statistically significant.

Results

Patient characteristics

Before transplantation, 10 out of the 11 patients were treated for hyperparathyroidism. Three had a parathyroid adenoma. Calcium phosphorus and parathyroid status before and at inclusion are summarized in Table 1.

Acute effect of once- or twice-daily dose of cinacalcet on serum parathyroid hormone

Serum parathyroid hormone levels decreased significantly during both kinetics (P < 0.0001; Figure 1A). After administration of cinacalcet, sPTH decreased to a nadir that occurred 2 h after dosing. At nadir, sPTH levels had decreased respectively by 76% (P < 0.0001) and 70% (P < 0.0001), as compared to pre-kinetic levels after
Acute effect of once- or twice-daily cinacalcet intake on calcium–phosphorus parameters

Before the cinacalcet intake, 25-(OH)-vit D$_3$ and 1,25-(OH)$_2$-vit D$_3$ levels were within the normal ranges in all patients. 25-(OH)-vit D$_3$ levels did not change significantly within the 24-h study period, i.e., 15.9 ± 1.34 at T0 versus 15.7 ± 1.8 ng/mL at T24 after the once-daily dose and 16.1 ± 1.55 at T0 versus 16.1 ± 2.3 ng/mL at T24 after the twice-daily dose.

Overall, there was a trend towards a decrease in 1,25-(OH)$_2$-vit D$_3$ levels, but this was not statistically significant. However, when comparing 1,25-(OH)$_2$-vit D$_3$ levels at T0 and T24, it decreased from 33.9 ± 5.4 at T0 to 25.4 ± 3.6 pg/mL at T24 (P = 0.02) after the once-daily dose and from 34.2 ± 3.6 at T0 to 26 ± 3.4 pg/mL at T24 (P = 0.05) after the twice-daily dose.

Finally, serum FGF-23 levels decreased slightly during the study period, from 145 ± 57 at T0 to 102 ± 32 IU/mL at T24 (P = 0.2) after the once-daily dose and from 163 ± 61 at T0 to 116 ± 59 IU/mL (P = 0.08) after the twice-daily dose. No significant difference was observed in 25-(OH)-vit D$_3$, 1,25-(OH)$_2$-vit D$_3$, and serum FGF-23 levels at any time point between both kinetic profiles.

Acute effect of once- or twice-daily dose of cinacalcet on vitamin D and FGF-23 levels

Before the cinacalcet intake, 25-(OH)-vit D$_3$ and 1,25-(OH)$_2$-vit D$_3$ levels were within the normal ranges in all patients. 25-(OH)-vit D$_3$ levels did not change significantly within the 24-h study period, i.e., 15.9 ± 1.34 at T0 versus 15.7 ± 1.8 ng/mL at T24 after the once-daily dose and 16.1 ± 1.55 at T0 versus 16.1 ± 2.3 ng/mL at T24 after the twice-daily dose.

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Acute effect of once- or twice-daily dose of cinacalcet on tacrolimus and cyclosporine levels

Tacrolimus AUC$_{0-24h}$ did not differ significantly when cinacalcet was given once (241 ± 35 ng h/mL) or twice daily (211 ± 27 ng h/mL). Cyclosporine A AUC$_{0-24h}$ was, respectively, 4944 ± 654 ng h/mL after cinacalcet was administered at the once-daily dose and was 4280 ± 163 ng h/mL after the twice-daily dose. Cyclosporine A AUC$_{0-24h}$ was not statistically compared because of the small number of patients receiving this in our study (n = 3).
One-year effect of cinacalcet given at the twice-daily dose

After both kinetic profiles, all 11 patients received cinacalcet at the dose of 30 mg b.i.d. None of the patients received any vitamin D analogue or phosphorus binder. Two months after having started the study, one patient presented with a BK virus nephropathy, which led to graft loss 6 months later. Hence, the results of the ten remaining patients are presented below.

Effect of 1-year therapy of cinacalcet, given at the twice-daily dose, on serum parathyroid levels and calcium-phosphorus parameters (Figure 2A–C)

After 1 year of cinacalcet therapy given at 30 mg b.i.d, sPTH decreased significantly from 319 ± 88 to 148 ± 25 µmol/L (P = 0.04). Serum calcium and serum ionized calcium levels also decreased significantly from 2.7 ± 0.04 to 2.42 ± 0.05 mmol/L (P = 0.01) and from 1.52 ± 0.02 to 1.34 ± 0.02 mmol/L (P = 0.008), respectively. Albumin-corrected calcium levels decreased from 2.68 ± 0.05 to 2.49 ± 0.07 (P = 0.06). Conversely, serum phosphorus levels significantly increased from 0.68 ± 0.07 to 1.01 ± 0.1 mmol/L (P = 0.04). The calcium–phosphorus product decreased significantly from 1.93 ± 0.13 to 1.35 ± 0.14 mmol²/L² (P = 0.008). Alkaline phosphate decreased significantly from 339 ± 34 to 144 ± 36 IU/L (P = 0.046).

Effect of 1-year therapy of cinacalcet, given at the twice-daily dose, on renal parameters (Figure 2D)

With respect (Figure 2D) to renal function, no significant change in either serum creatinine level or in calculated creatinine clearance was observed (119 ± 9 versus 118 ± 8 µmol/L, and 56 ± 5 versus 59 ± 7 ml/min, respectively). No significant change was observed in 24-h calciuria or in urine calcium/creatine, respectively [119.5 (37–237) vs 130.0 (44–263) µg/day, P = 0.33] and 1.44 (0.70–3.00) vs 1.60 (0.82–3.14) mmol/L (P = 0.56).
Serum PTH level (pg/mL) at baseline versus 114 (70–270) mg/day 12 months later and 0.19 (0.08–0.27) at baseline versus 0.16 (0.13–0.30). Systolic and diastolic blood pressure, as well as the number and dosage of antihypertensive therapy remained unchanged (data not shown).

**Safety profile**

None of the patients presented with acute rejection, experienced any gastrointestinal side effects or developed hypocalcaemia.

**Discussion**

Because of its harmful affect upon renal function and histology [4,5], as well as upon bone metabolism [3], hypercalcaemia should be avoided after kidney transplantation. For this reason, and in order to treat persisting hyperparathyroidism, subtotal parathyroidectomy has been previously the only option. However, this has been reported to be responsible, in many cases, for significant worsening of renal allograft function [18,19]. The efficacy and safety of using cinacalcet in dialysis patients with secondary hyperparathyroidism has prompted transplant physicians to use it in kidney transplant patients with persisting hyperparathyroidism. In this setting, the use of cinacalcet has not yet been approved and many questions remain unanswered, i.e., when should cinacalcet therapy be started and at what dosage should cinacalcet be given? Indeed, in patients with end-stage renal disease, cinacalcet is given at a once-daily dose [6]. Conversely, in patients with primary hyperparathyroidism and normal renal function, Peacock et al. administrated cinacalcet twice daily [7]. Finally, in kidney transplant patients who have nearly normal renal function, cinacalcet has been given both once [8–10,12–15] and twice daily [15]. Hence, in this prospective study, we assessed the acute pharmacodynamic effect of cinacalcet when given once or twice daily and evaluated the efficacy and tolerance of cinacalcet given twice daily in the setting of kidney transplantation. We found that the acute pharmacodynamic effect of cinacalcet was quite similar when given once or twice daily and that 1-year therapy of cinacalcet given at the dose of 30 mg b.i.d was efficient and safe.

Cinacalcet is cleared predominantly by oxidative hepatic metabolism and minimally by renal mechanisms. Renal impairment can cause changes in absorption, hepatic metabolism and plasma protein binding and distribution that could potentially impact on its pharmacokinetic and pharmacodynamic characteristics [20]. Previously, Padhi et al. assessed the effect of renal function and dialysis on the pharmacokinetics and pharmacodynamics of cinacalcet [21]. Following a single-dose (75 mg) administration of cinacalcet, the authors concluded that the increasing degree of renal impairment did not significantly modify either its pharmacokinetic profile, i.e., the area under the curve and maximal concentration, or its
pharmacodynamic effects. However, the percentage of decrease in sPTH concentrations from baseline to nadir was 56.6% in patients with normal renal function versus 67.9, 75.2 and 83.3% in patients with mild, moderate and severe renal function, respectively [21]. At steady state, Harris et al. showed that, in haemodialysis patients receiving 150 mg of cinacalcet once daily, nadir sPTH levels occurred at ~2 to 3 h after dosing, which corresponded with the maximal concentration of cinacalcet [22]. However, sPTH levels returned to nearly pre-dose levels at 8 h after dosing [22]. A similar finding was observed in patients with normal renal function treated by cinacalcet for primary hyperparathyroidism [7]. Very recently, Serra et al. compared the pharmacokinetic and pharmacodynamic effects of cinacalcet given at 30 mg and then 60 mg once daily in stable kidney transplantation. They found an inverse correlation between cinacalcet and parathyroid hormone levels. The nadir of PTH level occurred 3 h after cinacalcet dosing. At nadir, cinacalcet given at 30 and 60 mg lowered sPTH levels by 60 and 68% [23]. In the present study, after dosing cinacalcet at 60 mg once daily, sPTH decreased by 76% at 2 h and increased thereafter. Twenty-four hours after the cinacalcet intake at 60 mg once daily, sPTH level was 23% lower than at pre-dose. During the second kinetic, after dosing cinacalcet at 30 mg, sPTH level decreased by 70% at 2 h and increased thereafter. However, because of the second administration of 30 mg of cinacalcet at 12 h later, sPTH level decreased further, resulting in an overall decrease of 44% compared to pre-dose levels. Serum calcium, ionized calcium and albumin-corrected calcium concentrations decreased significantly independently of the number of cinacalcet intakes. However, when cinacalcet was given once daily, serum calcium, ionized calcium and albumin-corrected calcium decreased until T12 and increased thereafter. This is probably related to the addition of sPTH due to the second dose of cinacalcet. At T24, serum ionized calcium level was significantly lower when cinacalcet was given twice than once daily. In studies by Harris et al. [22], Peacock et al. [7] and Serra et al. [23], serum calcium concentrations remained relatively constant during the 24-h dosing interval. With respect to phosphorus levels, it increased when cinacalcet was given once or twice daily. However, the increase was higher when cinacalcet was given twice daily. Finally, in the present study, serum phosphorus, 25-(OH)-vit D3, and serum FGF-23 levels, as well as the calcium–phosphorus product remained constant during the 24-h dosing interval. Compared to baseline, only 1,25-(OH)2-vit D3 decreased significantly, independently of the number of cinacalcet doses. Hence, in summary, even though sPTH decreased somewhat more when cinacalcet was given twice daily, the administration of cinacalcet once or twice daily was quite similar. In addition, given the known beneficial effects of sPTH for normal bone formation, the normalization of PTH does not seem to be a valid objective. Conversely, the variations of sPTH levels in patients receiving cinacalcet may lead to improved bone mineralization. Indeed, in an animal model, daily intermittent, but not sustained, decreases in PTH levels by a calcimimetic compound have an ‘anabolic-like’ effect on bones with a chronic renal insufficiency-related low-turnover lesion [24]. In dialysis patients, suppression of sPTH with cinacalcet reverses bone loss in the proximal femur, but does not affect bone mineral density of the lumbar spine [25]. The authors speculate that cinacalcet may have a different effect on trabecular and cortical bone [25].

Similar to previous published reports, 1-year cinacalcet therapy given twice daily was associated with a significant decrease in serum calcium levels [8–10,12,13,15,16]. Conflicting data regarding the effect of cinacalcet upon serum parathyroid, phosphorus level, renal function, and urine calcium excretion have been published (Table 2). In the present study, there was a significant decrease in the sPTH level and a significant increase in the serum phosphorus level without any renal side effects.

Subtotal parathyroidectomy has been incriminated by some authors to result in a significant worsening of renal allograft function [18,19] that does not however seem to be harmful on graft survival [26]. The mechanism of deterioration of renal function remains unknown. Several authors speculate that it is related to a haemodynamic mechanism [19] as sPTH has a vasodilatory effect on pre-glomerular vessels [27]. Similarly, after cinacalcet therapy, some authors have reported a decrease in renal function [8,15]. This was not observed in the present study. Finally, conversely to previous case reports that showed that high doses of cinacalcet induce hypercalcemia [17,28], we did not observe any increase in urine calcium excretion after 1 year of cinacalcet treatment. Despite the higher doses of cinacalcet used in our study, none of the patients presented with

### Table 2. Review of published reports on the use of cinacalcet after kidney transplantation

<table>
<thead>
<tr>
<th>Studies</th>
<th>Number</th>
<th>Follow-up (months)</th>
<th>Maximal daily dose</th>
<th>sPTH level</th>
<th>sCa</th>
<th>sPh</th>
<th>Renal function</th>
<th>Calciuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serra et al. [9]</td>
<td>11</td>
<td>2.5</td>
<td>60 mg</td>
<td>↓ (23%)</td>
<td>↓</td>
<td>↑</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Kruse et al. [8]</td>
<td>14</td>
<td>3</td>
<td>30 mg</td>
<td>→</td>
<td>↓</td>
<td>→</td>
<td>→</td>
<td>ND</td>
</tr>
<tr>
<td>Srinivas et al. [10]</td>
<td>11</td>
<td>6</td>
<td>30 mg</td>
<td>↓ (54%)</td>
<td>↓</td>
<td>↑</td>
<td>→</td>
<td>ND</td>
</tr>
<tr>
<td>Leca et al. [12]</td>
<td>10</td>
<td>6</td>
<td>60 mg</td>
<td>↓ (13.5%)</td>
<td>↓</td>
<td>→</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Szewczak et al. [13]</td>
<td>9</td>
<td>6</td>
<td>30 mg</td>
<td>↓ (42%)</td>
<td>↓</td>
<td>↑</td>
<td>→</td>
<td>ND</td>
</tr>
<tr>
<td>El-Amm et al. [15]</td>
<td>18</td>
<td>6</td>
<td>180 mg</td>
<td>↓ (13%)</td>
<td>↓</td>
<td>↑</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Bergua et al. [16]</td>
<td>13</td>
<td>6</td>
<td>60 mg</td>
<td>↓ (54%)</td>
<td>↓</td>
<td>↑</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Present study</td>
<td>10</td>
<td>12</td>
<td>60 mg</td>
<td>↓ (54%)</td>
<td>↓</td>
<td>↑</td>
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</tr>
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</table>

sPTTH, serum parathyroid hormone; sCa, serum calcium; sPh, serum phosphorus; ND, not determined.

*Cinacalcet given twice daily.
hypocalcaemia or complained of gastrointestinal disorders. Finally, recently Falck et al. have reported that cinacalcet induces a significant decrease in tacrolimus, but not in cyclosporine A [29]. In the present study, we did not find a difference in tacrolimus area under the curve in patients receiving cinacalcet once or twice daily. However, we did not compare the tacrolimus area-under-the-curve before and after cinacalcet therapy.

The main limitations of our studies were the small number of patients enrolled and the lack of dosage of cinacalcet during both kinetics. In addition, we do not know whether the similar efficacy observed after once or twice-daily dose of acute administration of cinacalcet will remain unchanged after once or twice-daily dose of chronic administration. Indeed, we did not compare the long-term effect of once or twice-daily chronic administration of cinacalcet. Further studies are required to respond to this issue. A reduced compliance may be higher when cinacalcet is administrated twice daily and this possible reduced compliance should be considered when evaluating both strategies. Finally, the acute pharmacodynamic effect of cinacalcet observed in our patients who had a mild to moderate persistent hyperparathyroidism, may be different in those who have severe hypoparathyroidism.

In conclusion, once or twice-daily acute administration of cinacalcet to kidney-transplant patients with persisting HPT may be different in those who have severe hyperparathyroidism. One-year administration of cinacalcet, given as two daily doses, is safe and efficient.

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Conflict of interest statement. None declared.

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